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Metabolic Bone Disorders - Part II

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"Acta Orthopaedica Et Traumatologica" is the official journal of the Hellenic Association of Orthopaedic Surgery and Traumatology, first published in 1948. This revived edition of Acta Orthopaedica Et Traumatologica, published in English, aspires to promote scientific knowledge in Orthopaedics and Traumatology worldwide. It is a peer-reviewed Journal, aiming at raising the profile of current evidence-based Orthopaedic practice and at improving the scientific multidisciplinary dialogue. Acta Orthopaedic Et Traumatologica Hellenica presents clinically pertinent, original research and timely review articles. It is open to International authors and readers and offers a compact forum of communication to Orthopaedic Surgeons and related science specialists.

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or

Papaioannou NA, Triantafyllopoulos IK, Khaldi L, et al. Effect of calcitonin in early and late stages of experimentally induced osteoarthritis. A histomorphometric study. *Osteoarthritis Cartilage* 2007; 15(4): 386-95.

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LETTER FROM THE GUEST EDITOR

Dear Colleagues,

For one more time, I would like to thank the Senior Editor, Professor Nikos Papaioannou and the hardworking Assistant Editor, Ass. Professor Ioannis Triantafyllopoulos, for their invitation and collaboration issuing this second part of the Special Issue – Metabolic Bone Diseases.

After the successful publication of the first part (Issue 2023-2) and its wide warm acceptance in our scientific community, the second part (Issue 2023-3) is handed to you with further topics related to bone metabolism.

It is also a great chance to share with all of you my intimate thoughts on a hot topic. I had the privilege to be the first Editor of the Orthopaedic Journal of North Greece as well as Member of the Editorial Board of ACTA Orthopaedica et Traumatologica Hellenica. Time has come and the two journals (ACTA Orthopaedic et Traumatologica Hellenica and Orthopaedics) should be merged into one. The conditions are mature enough and in this small country with this great orthopaedic community there is no need to have two scientific journals on the same scientific field.

The current two Editors, Professor N. Papaioannou and Mr. J. Bischiniotis have worked hard all these years offering their best to keep both journals alive. But I think that the time has come to unite our powers for one Scientific Journal on the field of Orthopaedics and Traumatology. Therefore, my suggestion is that the two current presidents of the two Greek Orthopeadic Societies, Professor Z. Dailiana (HAOST) and Professor G. Drosos (OTEMATH) should collaborate with the two Editors and find the best solution. I believe that some issues considering the final name of the Journal and the keeping of the history of both could be easily solved.

George Kapetanos

Professor of Orthopaedics

The Orthopaedic view of Transient Osteoporosis of the Hip in Pregnancy.

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ABSTRACT

Scope. The analysis of Transient Osteoporosis of the Hip, which invades the 3rd trimester of pregnancy (TOHP) and arouses the interest of the Orthopedist in its treatment. It is a rare, unknown disease that presents with localized osteoporosis in the neck and femoral head, often bilateral and resolved spontaneously after 4-8 months. The reduction of the mechanical strength of the femoral neck carries the risk of fragility fracture. The diagnosis is made with the information from the history and the objective examination and is documented with Magnetic Resonance Imaging (MRI).

Material and Methods. During the last 25 years (1998-2023), out of a total of 85,000 deliveries, 18 cases of TOHP were diagnosed (0.021%). The symptoms of the onset of the disease were pain in the affected hip with lameness that limited daily activities.

Results. Treatment was conservative and included rest, discharge of the affected hip, analgesics and anti-osteoclastic drugs after childbirth. After 6-8 months, there was a complete remission of the manifestations of the disease, and only in one woman, the diagnosis was made after a fracture of fragility of the femoral neck that was treated surgically.

Conclusions. This rare disease (TOHP) has a benign progression and requires early diagnosis, with awareness of Obstetricians Gynecologists and Orthopedic Surgeons, for the immediate initiation of therapeutic measures. Protection from a possible femoral neck fragility fracture, as well as surgical repair if it occurs, are critical issues for the successful final outcome of pregnancy.

KEYWORDS. Transient osteoporosis of the hip, Pregnancy, Orthopaedic.

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1. TOHP an unknown syndrome

1.1. Generally-Causes TOHP

The first report of the disease was made about 65 years ago, when 3 cases of pregnant women were diagnosed, with hip pain, decalcification of the femoral head radiologically and the fact was attributed to neuromuscular causes [1]. Later, the basic features of the disease were established, summarized in pain, limitation of the range of motion of the hip and subsequent claudication. It is a disease that affects middle-aged men and women during pregnancy with radiological osteoporotic image of the upper end of the femur, without narrowing of the articular space. A key feature of this rare syndrome is the automatic restoration of both clinical and radiological manifestations, after 3-12 months [2]. The etiology of this disease is unknown, and initial opinions indicated that it is a form of Südeck-Lerisch's, algodystrophy [3].

Reference is also made to the similar picture as to this, in the early stages of aseptic necrosis of the femoral head, both in the clinical and radiological picture. This has sparked debate about the common etiology of these two hip diseases, involving injury history, inflammation, use of medications such as corticosteroids, metabolic and neurological disorders, neoplasias and vascular disorders. Alcoholism, smoking, hypothyroidism, hypophosphatasia, vitamin D deficiency, low testosterone levels and certain professional activities are also implicated [4].

Relatively recently, studies involving predisposing factors compared to control cases were reported in women with the disease, who gained more weight during pregnancy, presented dental problems and reduced athletic activity in childhood and immobilization for at least 1 month during pregnancy. A causal relationship has by no means been established and all considerations are directed to the multifactorial justification for [5].

Advanced reports with literature review indicate that the etiology remains unknown and the disease is not causally associated with aseptic necrosis of the femoral head. Conditions related to pregnancy, such as reduced activity, femoral head venous posture due to the increasing size of the pregnant uterus, thyroid nerve pressure and hormone disorders in pregnancy and lactation are implicated [6].

According to a theory about the etiology of the disease, the disorder in the synthesis of type I collagen is implicated. Since the basic solid components of the skeletal system are hydroxyapatite and collagen type I, its degradation during pregnancy, which can cause osteoporotic changes in the hip, is speculated [7]. This hypothesis is based on the case of osteogenesis imperfecta, where gene mutations associated with type I collagen, the risk of developing TOHP, is much greater.

It is known that in pregnancy, collagen I degradation changes occur to enlarge the cervical orifice, at the end of the second and third trimester of pregnancy, where body weight increases at the same time [8].

Collagenase derived from polymorphonuclei leukocytes, circulating with blood flow and settling in the bone tissue of the femur, with subsequent degradation of its mechanical strength. This theoretical view does not cover the cases of affected men and non-pregnant women, but in pregnancy the risk of fragility fracture in the hip area is clearly multiplied by weight gain and induced loads on the affected area, even with minimal strain on daily activities.

1.2. Radiological image

The radiological image is decisive in any case and is recommended for postpartum monitoring. The osteoporotic image of the femoral head and neck is characteristic, with extension in some cases to the acetabulum, as well as its restoration to normal after about 4-8 months. The preservation of interarticular space is always evident and this image resembles "ghost Joint" [9].

1.3. Magnetic Resonance Imaging (MRI)

The advent of MRI offered new possibilities for the early diagnosis of the disease, given the absence of radiation with this method and its clear applicability during pregnancy. It also can distinguish other pathological conditions, such as malignancy, septic arthritis, and stress fractures, that occur with a similar clinical picture.

MRI has proven from the beginning of its application in diagnosis, to be a sensitive, accurate and safe

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diagnostic imaging test. Hip imaging gives clear evidence, where it shows reduced intensity of the bone marrow signal, corresponding to bone marrow edema in the initial stage [10]. In contrast, in aseptic necrosis of the femoral head, this edema follows as a reaction to the microfractures caused by the collapse of the femoral head in the final stage. Familiarity with the distribution of lesions in the MRI picture offers safe conclusions about the nature of the disease and is a crucial tool for diagnosis [11], [12]. There have been cases that were diagnosed early, with documentation of the radiological picture, with differential diagnosis from aseptic necrosis of the femoral head and unnecessary surgical interventions. The opportunity was also given to understand pathological lesions, by correlating the images with biopsies that had unfortunately been performed to investigate the disease, to investigate possible causes with a greater approach [13].

1.4. Laboratory tests

The hematological and biochemical investigation in this disease does not offer substantial assistance to the diagnostic process since in the cases of measurements of hematological and biochemical parameters no pathological value was found.

Relatively recently it was reported that pregnancy can cause danger to the skeleton, with fluctuations in calcium metabolism and it is possible to activate monogenic bone disorders, resulting in the appearance of a disease like this, during pregnancy where increased calcium supply is required [15].

1.5. DEXA examination

The characteristic radiological osteoporotic image of the affected pregnant women led to an investigation of the Bone Mass Density (BMD), with the Dual, Energy, X-ray, Absorptiometry (DEXA) method, where a decrease of up to 20% in the bone density of the hip was found. Restoration of BMD to normal levels occurred over a one-year period, while the same measurement in the lumbar spine decreased, even without symptoms, by up to 31%. The restoration in this area took place 2 years after the cessation of lactation [16]. This test has no place in the diagnostic process, but it can be used to assess the effectiveness of the anti-osteoclastic treatment that may be administered to the patient after delivery.

1.6. Type of Delivery Recommended

Usually, this condition resolves spontaneously and no recurrence has been observed in the future, even in a subsequent pregnancy and it has been fully clarified that the delivery procedure with Normal Vaginal Delivery (NVD) is indicated and Cesarean Delivery (CD) is not required for prophylaxis the manipulations of possible musculoskeletal damage of the hip, in female sufferers during NVD. This is documented by many opinions that have been recorded in the relevant protocols by the WHO and the Academy of Gynecologists of the USA [17], [18].

1.7. Conservative treatment

The therapeutic measures proposed from the first diagnosis of this patological entity were conservative with immediate unloading of the affected hip and rest from all physical activity. The administration of analgesic preparations mainly during pregnancy but also after delivery with additional administration of NSAIDs, aimed at relieving physical discomfort. After delivery, the treatment administered was anti-osteoclastic anti-osteoporotic preparations, with an initial application of calcitonin which also provided an analgesic effect.

The administration of bisphosphonates after pregnancy is indicated because it did not gather the required safety guarantees for the fetus, for its administration in the first place. Supplements with calcium and vitamin D preparations complemented every medicinal effort. The administration of anticoagulation is not recommended if the patient needs immobilization for pain relief because the osteoporotic effect of these drugs has been demonstrated, which will likely worsen the already existing osteoporotic condition of the hip [6].

1.8. Surgical intervention

1.8.1. Preoperative assessment

Regarding the case where an undisplaced subcapital fracture occurs during pregnancy, immediate healing is required and in case of displacement, a

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total arthroplasty of the affected hip is required [6].

In these unfortunate situations, the cooperation of the orthopedic surgeon, the patient's gynecologist and the anesthesiologist is necessary.

The preoperative gynecological and fetal assessment is a primary factor for the health of the pregnant woman and the fetus. Intraoperative monitoring of the heart function of the fetus is recommended, and if the rate drops below 100 per minute, an emergency Cesarean Delivery (CD) is recommended for fetuses older than 26 weeks. Knowledge of the changing physiological changes in physiology and anatomy in pregnancy is critical to the management of these cases.

The main ones are the following:

The relaxation of the sacroiliac joints and pubic symphysis resulting in a loss of balance and an increase in falls.

The increase in blood volume predisposes to hemorrhagic status and anemia.

The increase in the size of red blood cells and the number of white blood cells, predisposing to disseminated intravascular coagulation.

The increase in cardiac output resulting in an increase in metabolism.

The increase in the volume of blood filtered to the kidneys with consequent increase in pulse volume which increases the possibility of causing pulmonary edema.

The blood pressure is reduced, thereby camouflaging the possible early shock.

The increase in the volume of the uterus in advanced pregnancy can possibly cause hypotensive syndrome in the prone position because of the pressure of the aorta and inferior vena cava.

1.8.2. Intraoperative management

The problems faced by the orthopedic surgeon, in this rare case of TOHP fracture, concern the preparation of the operation, the surgical planning and the surgery itself with the appropriate anesthetic method and the post-operative rehabilitation care. It is important to position the patient during the operation on her left side to avoid compression of the inferior vena cava and the aorta. The choice of the surgical method must be made with the criterion of saving time and minimal surgical intervention, with the least cost of radiation. Antibiotics to be used in the same way as outside pregnancy according to the protocols followed and prophylactic anticoagulation are considered fundamental in dealing with the increased possibility of venous thrombosis from pregnancy [19], [20].

1.8.3. Radiological assessment

Surgical planning requires the use of radiation to diagnose the nature of the fracture in order to select the appropriate method. The National Council on Radiation Protection and Measurements has established that the maximum possible safe limit of radiation that the fetus can accumulate during pregnancy should not exceed 50 mGy. However, depending on the age of the pregnancy and indeed in the last trimester, it is safely calculated that an exposure of 0.1 mGy is needed for the hip, which is in line with the protection measures. Practically in every single X-ray the use of radiation does not exceed 0.7 mGy, which ensures the protection of the fetus in every fetal period. When using the C-arm intraoperatively, the radiation source is under the operating table and there is relative protection. However, it is necessary to protect the other parts such as the pelvis and abdomen if this is possible during surgery. In general, however, it is preferable to avoid exposure of the fetus and the surgical techniques chosen do not require exposure to large amounts of radiation [21].

1.8.4. Anaesthetic intervention

The choice of anesthesia method is preferable to be made by a specialist doctor with experience in pregnancy anesthesiology, because there is familiarity with the changing physiology and pharmacokinetics of the pregnant woman and the fetus. The type of anesthesia is chosen according to the needs of the operation and there are no data documenting the influence of the type of anesthesia on the final outcome of the delivery. In any case, however, regional anesthesia is preferred, when it is possible to administer it [20].

2. Material and Methods.

During the time period 1998-2023, in 84,000 deliv-

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eries that took place, 18 (0.02%) cases of pregnant women, with an average age of 33.5 years (26-41 years), were counted, who presented with pain, reduced functionality and lameness from the hip. These symptoms appeared in the 3rd trimester of pregnancy and in a single case at the end of the 1st trimester.

Bilateral location was observed in 2 (11.1%) cases, in 12 (66.6%) cases the disease was located in the left hip, while in the right hip it was located in 4 (22.2%) cases. In bilateral cases, the disease was not presented at the same stage by MRI imaging and the milder forms were asymptomatic. This fact raised the suspicion of the existence of cases with slight or non-existent symptoms, which escape diagnosis.

Regarding the gender of the newborn, boys predominated with 15 (83.3%) cases, against 3 (16.6%) cases of girls.

Phenotypically all the women were small with normal body weight and MO, BMI=22.1 and during pregnancy their weight increased by 12-16 (MO 14) kgr, a value that is considered greater than that desired by Obstetricians and Gynecologists.

In all cases, the diagnosis, treatment and follow-up were done by the same Orthopedic Surgeon in collaboration with the respective Gynecologist, who referred the patients when they presented the symptoms of the condition. The opinion they sought mainly after the diagnosis was related to the type of delivery that would follow. In all affected women, delivery was by Cesarean Delivery (CD), due to insecurity during delivery, to prevent a possible hip fracture. We note that until 2015 when the relevant WHO protocols were announced, the relevant literature did not take a clear position on the type of treatment required in case of TOHP. After 2015, CD was chosen for reasons independent of the condition.

Affected women had no history of osteogenesis imperfecta or chronic disease, no history of alcoholism, history of injury, or chronic medication, except for calcium and vitamin D supplements given at the onset of pregnancy.

Smoking was reported in 14(80%) cases and all women were not involved in sports activities, not even at a young age and had an unclear family history of postmenopausal osteoporosis.

In terms of occupation, this was sitting in private or government services, with additional standing in some cases.

The symptoms of the material patients reported were sudden onset of hip pain, worsening over the next 2-3 weeks with walking, which in some cases was difficult or impossible. The pain was located in the femoral-inguinal fold, in the abduction of the adductor muscles, in their mass, and with extension to the anterior surface of the thigh. It was combined with pain at rest or at night and with difficulty in raising the leg of the affected hip, in a supine position. In one case, the diagnosis was made after a fragility fracture of the femoral neck, which occurred at the Leto Obstetrics, in 2002 at the visit for the routine ultrasound examination at the beginning of the third trimester of pregnancy.

During the clinical examination, we found in almost all cases pain produced in the hip flexion ("log roll" test), in passive hip rotation movements, with the knee extended on the examination bed, with the patient in a supine position and in the passive abduction and adduction movements of the hip with the knee in flexion. The neurological examination did not show any pathological finding and all affected women presented a feeling of insecurity and anxiety during the first assessment.

The hematological and biochemical examination showed no abnormal findings, except for a negligible increase in the sedimentation rate and CRP in 2 cases which were considered incidental findings.

The documentation of the condition was done in all cases with an MRI check during the pregnancy and after the delivery was followed by a complementary radiological check that informed us about the recovery of the disease, with intervals every two months.

The treatment we followed during the pregnancy was the immediate unloading of the affected hip with armpit bacteria or walker, rest and in some cases, paracetamol was administered with pain at rest. Symptom resolution was gradual in all cases and required 7-10 days. Vitamin D and calcium were additionally administered in increased doses, beyond those administered by the Obstetrician dur-

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ing pregnancy.

In the case of the interclavicular fracture (Garden III), reduction and union with ASNIS cannulated screws was performed immediately on the same day, followed by total arthroplasty of the affected hip, due to necrosis of the femoral head after 2 years.

After delivery, we also recommended unloading of the affected hip, calcitonin was administered in 5 cases and bisphosphonates per os and iv in the other 13 cases. calcium and vitamin D supplements were additionally administered.

3. Results

The follow-up of our material was done for up to 5 years, with clinical examination and radiological control every year, while full recovery was done in 4-8 months with an average of 6 months. No recurrence occurred even in a subsequent pregnancy that followed in 8 cases.

In the 1st case, 32-year-old woman (Picture 1a,1b,1c), pharmacist, with onset of the disease in the 9th month of pregnancy. Duration of disease 6 months. In the radiograph (Picture 1) in the left hip, femoral head is invisible ("ghost joint") from the obvious osteoporotic image. MRI lesions in the left femoral head (Picture 1b), and X-ray after 66 months (Picture 1c) reveals, full recovery.

In the 2nd case, 28-year-old woman (Pictures 2a, 2b), private employee, with sudden pain and lameness from the right hip, in the 8th month of pregnancy. The x-ray (Picture 2a) shows both hips with an osteoporotic picture. On MRI, the lesions are present in both hips (Picture 2b), with the left being lighter, without symptoms. Recovery in 8 months.

In the 3rd case, an 31-year-old woman, diagnosis of the disease, after a spontaneous fragility fracture of the left hip (figure 3a). She reported pain and lameness in the past 6 weeks. This was followed by arthrosis and after 3 years, due to necrosis of the femoral head, he underwent Total Hip Replacement (THR), as shown in figure 3b.

4. Discussion

TOHP is a rare disease that occurs in women during pregnancy and can affect both hips. The symptoms of this condition are characteristic and Obstetricians and Gynecologists have become aware of the existence of this condition which is often confused with manifestations of back pain and pelvic pain. The physiology and anatomy of the pregnant body are subject to significant changes, which an Orthopedic Surgeon should always be aware of. In the case of our material, the awareness of fellow gynecologists resulted from informative scientific lectures and mainly from the incident of the hip fracture that happened in the Obstetrics "Leto" during the patient's visit for a standard examination of the beginning of the 3rd trimester of pregnancy. On that day, after the fracture, an x-ray check was done immediately, after being supervised by a specialist Radiophysicist and Radiologist. The surgical restoration followed immediately after the appropriate preparation in collaboration with the Obstetrician Gynecologist and the patient after about 2 months with CV, had a healthy boy weighing 2450gr. Since then there have been clinical examinations of 1-2 women every year, with similar symptoms, but no TOHP, and MRI was needed to prove the absence of the disease. Colleagues Obstetricians and Gynecologists, alarmed by the case of hip fracture, chose CV, for delivery, although they had been encouraged by the literature and Orthopedic information with special counseling lectures. TOHP, as a disease of pregnancy, needs the cooperation of many medical specialties for a successful therapeutic effect aimed at a successful outcome of childbirth as well as saving the functionality of the mother's hip. This issue is an Orthopedic challenge and we should always be prepared to deal with this peculiar case of an orthopedic patient. We are more informed and prepared today than we were 20 years ago, with the establishment of protocols by world-renowned Orthopedic Societies, such as the American Academy of Orthopedic Surgeons (AAOS). Knowledge is constantly evolving at a rapid pace and the awareness of clinicians has been achieved.

5. Conclusions

Medical Science requires constant vigilance and

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daily information, even in the rare syndromes that the therapist is called upon to deal with. Prevention in any case is therapeutically superior to surgical repair in the case of TOHP hip fracture.

Basic tips in the direction of prevention are:

- Awareness of Obstetricians and Gynecologists for Orthopedic assessment when lameness is reported by a pregnant woman.
- Hip pain that persists and worsens during pregnancy, should be evaluated with great care.
- The clinical assessment should be done in detail; the affected hip should be unloaded immediately and the possible existence of TOHP should be documented with an MRI.
- Great care is needed in the differential diagnosis in distinguishing TOHP from other serious conditions such as malignancy, osteonecrosis of the femoral head, and septic inflammation.
- Prevention of a possible fragility fracture of the femoral neck is the main therapeutic goal.

Conflict of interest

The authors declare no conflicts of interest.

REFERENCES

1. Curtiss P. and Kincaid W., 1959: "Transitory Demineralization of the Hip in Pregnancy, A Report of Three Cases". The J.B.J.S. 41(7):p 1327-1333, October 1959. Departments of Orthopaedic Surgery and Radiology, University Hospitals, Western Reserve University School of Medicine, Cleveland.
2. Beaelieu J. et al, 1976: "Transient osteoporosis of the hip in pregnancy", Clin Orthop Relat Res. 1976 Mar-Apr;(115):165-8.
3. Lequensne M., 1968: "Transient Osteoporosis of the Hip", Ann. Reum. Dis. (1968), 27, 463. Title name: given at a meeting if the Heberden Society in November 1967.
4. Asadipooya K. Et al, 2017: "Transient osteoporosis of the hip: review of the literature", Review, Osteoporos, International Osteoporosis Foundation and National Osteoporosis Foundation 2017.
5. Hadji P. et al, 2017: "Pregnancy-associated transient osteoporosis of the hip: results of a case-control study", Arch. Osteoporos, International Osteoporosis Foundation and National Osteoporosis Foundation 2017.
6. Quaresima P. et al, 2021: "Pregnancy associated transient osteoporosis of the hip (PR-TOH): A non–obstetric indication to caesarean section. A case report with literature review", European Journal of Obstetrics & Gynecology and Reproductive Biology. Review article, ELSEVIER.
7. Takanobu A., et al, 2012: "Transient Osteoporosis of the Hip in Pregnancy Associated with Generalized Low Bone Mineral Density – A Case Report", School of Nursing, Faculty of Medicine, University of Oita, b Angelic Clinic Urata, and Okamoto Clinic, Oita, Japan. Gynecol Obstet Invest.
8. Uldbjerg N., et al 1983: "Ripening of the human uterine cervix related to changes in collagen, glycosaminoglycans, and collagenolytic activity. Am J Obstet Gynecol 1983;147: 662–666.
9. Bruinsma B., LaBan M., 1990: "The ghost joint: transient osteoporosis of the hip", Arch Phys Med Rehabil, Apr;71(5):295-8.
10. Hayes C., et al, 1993: "MR Imaging of Bone Marrow Edema Pattern: Transient Osteoporosis, Transient Bone Marrow Edema Syndrome, or Osteonecrosis", Radiografics, Vol 13, No 5.
11. Curtis W. et al, 1993: "MR Imaging of Bone Marrow Edema Pattern: Transient Osteoporosis, Transient Bone Marrow Edema Syndrome, or Osteonecrosis" Radio Graphics 1993; 13:1001-1011
12. Vante Berg B., et al, 2008: "Bone marrow edema of the femoral head and transient osteoporosis of the hip" Department of Radiology and Medical Imaging, Universit´e Catholique de Louvain, University Hospital, Brussels, Belgium, 2008, Journal of Radiology 67 (2008) 68–77.
13. Bloem J.L., 1988: "Transient osteoporosis of the hip: MR imaging", Radiology VOL. 167, NO. 3.
14. Schapira D., 1992: "Transient Osteoporosis of the Hip", Semin Arthritis Rheum, Oct;22(2):98-105.
15. Butscheidt S. et al, 2018: "Mutational analysis uncovers

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monogenic bone disorders in women with pregnancy-associated osteoporosis: three novel mutations in LRP5, COL1A1, and COL1A2". Osteoporos Int. 2018 Jul;29(7):1643-1651.

16. Janet L. et al, 1995: "Transient osteoporosis of the hip in pregnancy: natural history of changes in bone mineral density", Clinical Endocrinology.
17. Toussia S. et al, 2023: "Transient osteoporosis of the hip in pregnancy – a case series", The Journal of Maternal-Fetal & Neonatal Medicine, Published online: 08 Feb 2023, Available via https://doi.org/10.1080/tandf_crossmark_01.
18. WHO 2015: Health Organization Human Reproduction Programme. WHO statement on Caesarean section rates 10 April 2015. Reprod Health Matters 2015;23 (May (45)):149–50.
19. Tejwani N., 2017: "Treatment of Pregnant Patients With Orthopaedic Trauma", Review Article, NYU Hospital for Joint Diseases, New York, NY and the Philadelphia College of Osteopathic Medicine, Philadelphia, PA (Dr. K. Klifto). MDJ Am Acad Orthop Surg 2017; 0:1-12.
20. Smith M.W. 2008: "Orthopedic Issues in Pregnancy" Medical Education Program, Ft. Wayne, Indiana University School of Medicine, Indianapolis, Indiana, Obstetrical and Gynecological Survey, CME REVIEW ARTICLE 4, Vol 63, No 3.
21. Matzon JL. et al, 2015: "Considerations in the radiologic evaluation of the pregnant orthopaedic patient". J Am Acad Orthop Surg 2015;23(8):485-491.
22. Oqueh O. et al, 2009: "A longitudinal study of the effect of heparin thromboprophylaxis during pregnancy on maternal bone metabolism", Obstet Med. 2009 Dec; 2(4): 157–160.

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REVIEW

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An overview of molecular signaling pathways implicated in the progression of osteoarthritis

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ABSTRACT

Background. Osteoarthritis (OA) is the most prevalent joint disease worldwide, causing chronic disability in older people. Various factors are associated with its pathogenesis, including aging, obesity, joint instability, and joint inflammation.

Objectives. Since the establishment of experimental murine models with surgically induced knee joint instability many studies have revealed the major molecules or signaling pathways responsible for OA. The aim of our study is to summarize the most important molecular pathways and the growth factors that are implicated in the pathophysiology of OA.

Results. Several *in vitro* and *in vivo* studies demonstrated that neovascularization, Matrix Metalloproteinases (MMPs) secretion, sclerostin as well as TGF-β -Bone Morphogenetic Proteins (BMPs), Fibroblast Growth Factors (FGFs) and Notch signaling pathways play important role in chondrocyte and osteochondral unit homeostasis and in the development and progression of OA.

Conclusions. However, more *in vitro* and *in vivo* studies focusing on the investigation of interactions between the growth factors and cytokines involved into the specific molecular networks that regulate the homeostasis of articular cartilage and OA pathogenesis is deemed necessary.

KEY WORDS: Osteoarthritis, angiogenesis, Matrix Metalloproteinases, Sclerostin, Fibroblast Growth Factors, TGF-β, Bone Morphogenetic Proteins, Notch signaling.

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Introduction

Osteoarthritis (OA) is the major cause of disability in the adult population affecting more than 7% of the global population, corresponding to 500 million people worldwide. The prevalence of OA is high among the elderly (≈70%) and can lead to aggravated pain and progressive dysfunction. Although in the past it was considered as a primary disorder of articular cartilage, it is now generally considered a disease of the whole joint (panarthritis), including the calcified cartilage, subchondral cortical and trabecular bone, joint capsular tissues and the synovium [1]. It must be highlighted that the structural support and the biological cross-talk between bone and cartilage, make subchondral bone and cartilage become a closely functional unit that cannot be separated [2].

OA is characterized by abnormal neurovascularization at the osteochondral junctions, the regulatory mechanisms of which remain poorly understood. The invasion of nerves and vessels in the osteochondral unit is one of its hallmarks and is the primary reason for aggravated pain [3]. Many cytokines, including semaphorins [4], netrins [5], and growth factors, such as vascular endothelial growth factor (VEGF) and nerve growth factor [6], have been found to have significant contribution in angiogenesis process. Recently, several therapeutic strategies, such as platelet-rich plasma (PRP), hyaluronic acid (HA), and mesenchymal stem cells (MSCs), have been applied to improve OA-related symptoms, enhancing the regenerative potential of the osteochondral tissue. Additionally, molecular target therapy has demonstrated promising experimental results as it was associated with stabilization or delayed progression of the OA degeneration process and, in many cases, with restoration of the normal cartilage and subchondral bone, as observed by objective assessment methods like imaging techniques or histological and immunohistological examinations) [7 - 8]. Therefore, further *in vitro* and *in vivo* research on the molecular signaling pathways involved in the degeneration process during OA progression is deemed necessary.

Aim of the present study is to summarize the main molecular pathophysiological mechanisms that are implicated in cartilage and subchondral bone degenerative changes of OA and to unveil possible target therapeutic options that have potential restorative properties *in vivo*.

Extracellular Matrix (ECM) Degeneration and Angiogenesis

The cartilage ECM is mainly composed of collagen fibers polysaccharides, secreted enzymes and proteoglycan molecules. It serves as a protective structure for cartilage against elastic and shear loadings, but it also regulates the chondrocyte behavior via matrix–cell interactions [9]. Moreover, the collagenous proteins demonstrate crucial structural and mechanical role in the connective tissue, and in the bony tissues are mainly composed by types I, III and V. Collagen fragmentation is mediated by two distinct pathways. In the first, collagen degradation is mediated by secreted or membrane proteases. In the second, the collagen turnover occurs intracellularly through the urokinase plasminogen activator receptor-associated protein uptake (uPARAP/Endo180). After the uPARAP-induced turnover, collagen fragments are delivered to the lysosomes, where they are degraded by cathepsins B, L, N, and K under acidic conditions [10-11]. Matrix metalloproteinases (MMPs) are involved in both processes [12]. MMPs are a family of at least 24 zinc-dependent endopeptidases, capable of degrading all ECM components. In humans, the MMP family is consisted by 24 genes encoding 23 MMPs. MMP-23 is coded by two identical genes at chromosomal 1 (MMP-23A and MMP-23B). The classification of MMPs is based on a) their location in the ECM matrix (soluble) or on the cell membrane (insoluble), b) their structural appearance and substrate affinity. According to this classification they divided in six subgroups. The collagenases (MMP-1, MMP-8 and MMP-13), the gelatinases (MMP-2 and -9), the stromelisins (MMP-3, -10 and -11), the matrilysins (MMP-7 and -26), the membrane type ones (MMP-14, -15,,-16,-17 and -24) and finally the others (MMP-12, -18, -19, 20, -21, -22, -23, -27 and -28).c) their chronologically discovery. The MMPs -4, -5 and -6 are not included, because they have identical structural and functional similarities with other members of the list. Most MMPs

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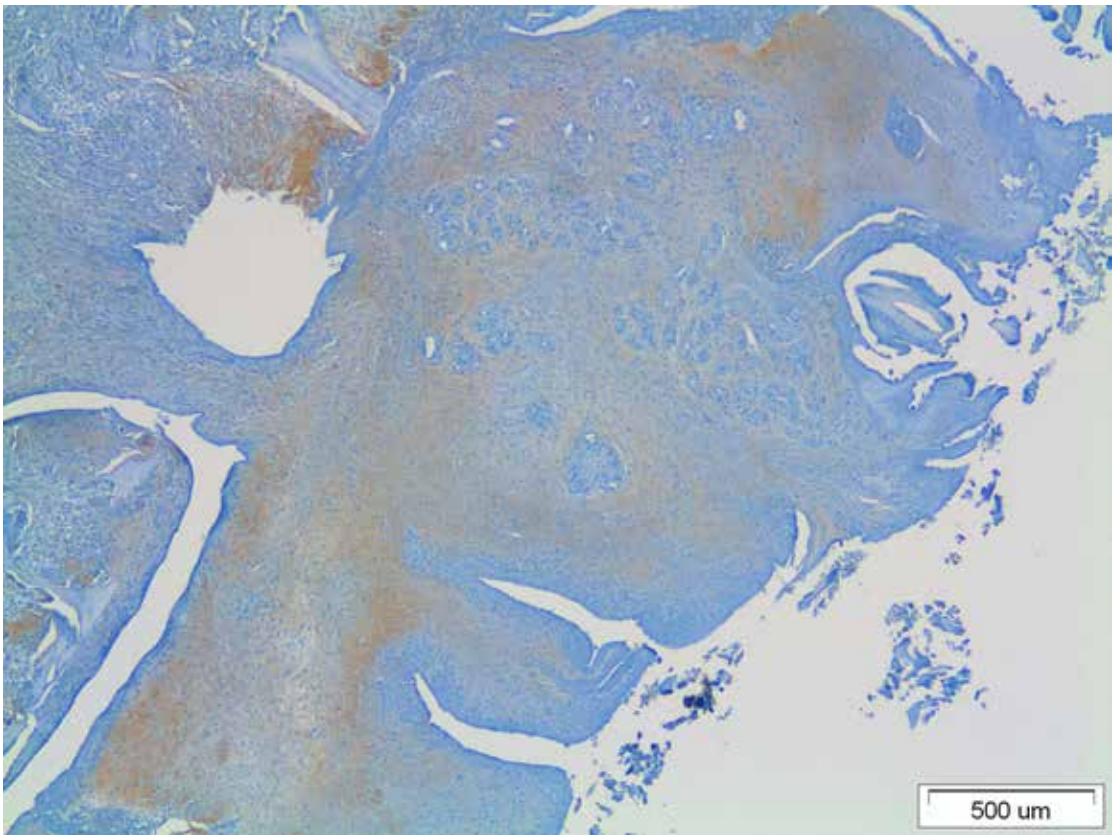

Figure 1: *Increased immunolocalization of MMP-1 in the cartilage and subchondral bone of a immunohistological section in OA patient with Mankin score 8 (Magnification 4X)*

are secreted into the extracellular space immediately after synthesis as proenzymes (pro-MMP) and are activated by proteolytic cleavage in the extracellular space. Specifically, the pro-MMPs are activated by proteolytic cleavage of the zinc-thiol interaction between the cysteine on the pre-domain and the Zn+2 on the catalytic domain by serine proteases or active MMPs, denominated as the "cysteine-switch mechanism" [13].

MMPs and a disintegrin and metalloproteinase production with thrombospondin motifs (ADAMTS) initiate ECM breakdown in OA **(Figure 1)**. Through the bone morphogenetic protein (BMP) pathway, the degradation of type II collagen (Col2A1) promotes the hypertrophy of chondrocytes, accelerating the degenerative alterations of OA [14]. Moreover, cartilage mineralization has also contributed to the OA development [15].

The activation of 2A-adrenergic receptor signaling pathway via the extracellular regulated protein kinases 1 and 2 (ERK1/2) and protein kinase A (PKA) pathways stimulate the synthesis of matrix degradation-associated enzymes, such as MMP-3 and MMP-13. Osteopontin, an inflammatory agent, also triggers the production of MMPs through the NF-κB signaling pathway [16].

The HTRA1–DDR2–MMP-13 axis is essential for ECM breakdown. This procedure begins after the increased expression of high-temperature requirement A1 (HTRA1) and the breakdown of pericellular matrix components, including type VI collagen. Col2A1 can also activate the transmembrane protein Discoidin Domain Receptor Tyrosine Kinase 2 (DDR2) in the absence of a pericellular matrix. DDR2 ultimately triggers MMP-13 leading to OA degenerative changes [17].

Healthy adult joint cartilage does not contain any blood vessels or nerves. Contrariwise, the osteoarthritic (OA) cartilage is invaded by blood vessels from the subchondral bone [18. In general,

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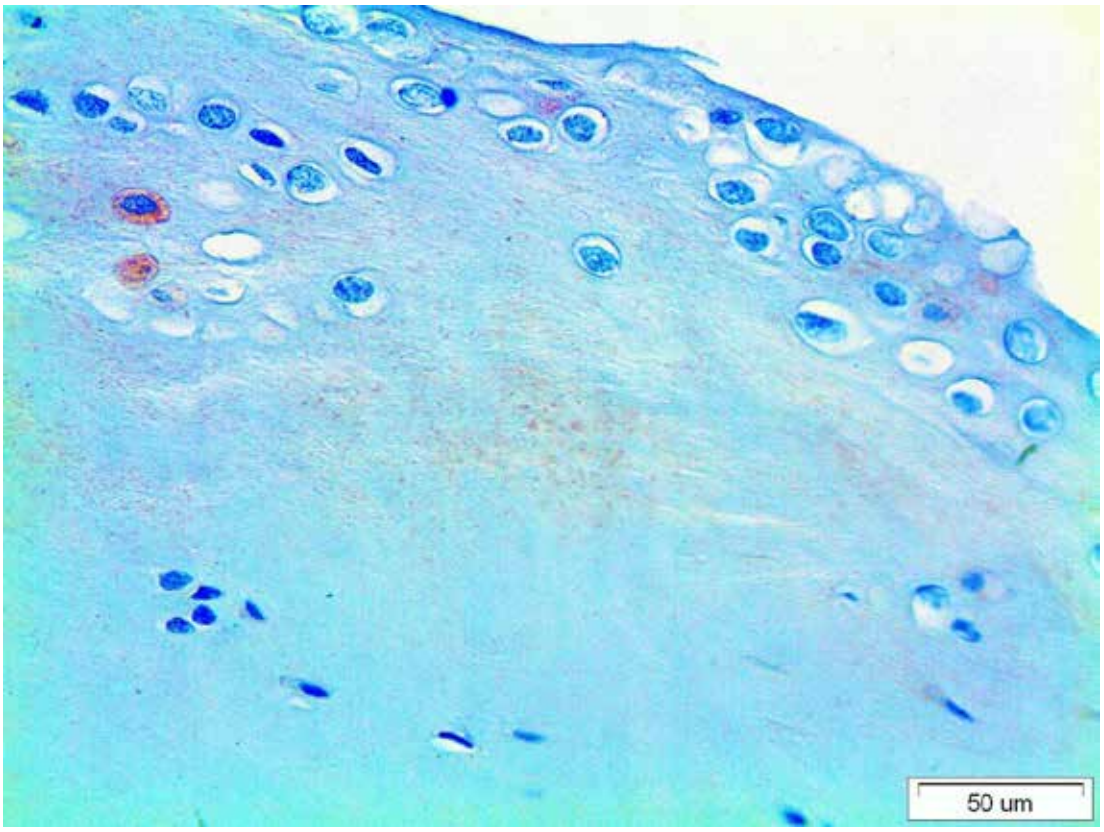

Figure 2: *Increased expression of the angiogenic growth factor Pleiotrophin (PTN) in the chondrocytes and Extracellular matrix of a immunohistological section in OA patient with Mankin score 7 (Magnification 40X)*

cartilage angiogenesis results from the imbalance between pro- and anti-angiogenic factors. The imbalance leads to increased production of pro-angiogenic factors and/or decreased production of anti-angiogenic factors [19]. VEGF-A, the best studied growth factor, is associated with MMP production, Additionally, inflammatory mediators induce angiogenesis and trigger MMP production. For example, TNF-α may contribute to the regulation of the expression of MMP-9 and MMP-14 that are crucial for vessel progression into the ECM [20. Many research studies have detected upregulation of MMPs in the osteoarthritic serum and joint tissues. Specifically, MMP-1 **(Figure 1)** and MMP-12 expression were increased in the osteochondral unit in patients with osteoarthritis (OA) and there was a positive correlation between their expression and OA severity [21,22] Furthermore, immunodetection of the collagenases (MMPs 1, 8, and 13) and stromelysin 1 (MMP-3) was demonstrated in a proportion of chondrocytes of human specimens that had OA-related degenerative matrix changes [23]. MMP-13, the collagenase with the strongest activity against type II collagen, seems to have a key-role in OA-associated joint destruction [335], while MMP-3 has been evaluated as a prognostic tool in prediction of the disease progression. Patients with increased plasma MMP-3 have increased possibility for OA progression over a 30-month period. Paradoxically, MMPs can decrease angiogenesis by cleaving the receptor binding sites of pro-angiogenic factors.

Additionally, several transcription factors, including hypoxia-inducible factor-1 (HIF-1), promote VEGF expression [24]. The protein dickkopf-related protein-1 (DKK-1) was detected in high concentrations in the synovial fluid of OA patients. It was suggested that DKK-1 and high-mobility group box 1 (HMGB1) led HIF-1 nuclear localization, and increase the expression of VEGF [24-25]. Inflammatory cytokines such as Interleukin-6 (IL-6) and IL-

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1, also, stimulate the expression of VEGF through the elevation of VEGF transcription in the nucleus. ERK1/2 stimulates the estrogen-related receptor γ (ERR γ). IL-1 which is a direct stimulus for NF-κB production [26].

VEGF belongs to a family that includes at least six members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and Placental Growth Factor (PIGF). VEGF-A or VEGF, which is the most abundant form, is playing a key-role in proliferation, migration and activation of endothelial cells and is a potent inducer of vascular leakiness. VEGF-B is important for new vessel development during embryogenesis] while VEGF-C and VEGF-D are involved in lymphangiogenesis. VEGF binds to the extracellular domains of two tyrosine kinase receptors, VEGF receptor I and VEGF receptor II . VEGF receptors also include VEGF receptor III, Neuropilin 1 (Npr1) and Neuropilin 2 (Npr2) [39]. VEGFR-II is the main VEGF signaling receptor and is considered the responsible receptor for VEGF-induced regulation of angiogenesis, vasculogenesis and vessels permeability [32]. VEGF is generated by articular cartilage chondrocytes and modulates autocrine levels of MMP-13 and tissue inhibitor of metalloproteinase-1 (TIMP-1). The reduction of TIMP expression and the overexpression MMPs disrupt the circulation of ECM components, collagen, and proteoglycans. VEGF may increase articular cartilage deterioration by activating osteoclasts and allowing blood vessels to penetrate the cartilage [27]. Moreover, VEGF appears to be involved in OA specific clinical pathologies including cartilage degeneration, osteophyte formation, subchondral bone cysts and sclerosis, synovitis, and pain. Moreover, a wide range of studies suggested that inhibition of VEGF signaling reduces OA progression.

The breakdown of hyaluronic acid (HA) and the increased activity of free radicals are correlated with reduced joint hydration. When the intra-joint pressure begins to overpass the capillary pressure, the accompanied transient hypoxia can result in joint degeneration defects. Reoxygenation is observed when the stress on the joint is decreased, and joint degeneration changes are halted.

Hypoxia and reperfusion cycles are closely related with the production of free radicals. Free radicals accelerate HA breakdown, lowering synovial fluid viscosity and increasing friction between joint surfaces [28]

Pleiotrophin (PTN) is a secreted growth factor with molecular weight of 18kDa which appears to have an important role in angiogenesis [29]. NMR studies have shown that PTN structure is consisted by two β-sheet domains containing three antiparallel β-strands, homologous to the thrombospondin type 1 repeat (TSR-1) [30] Thrombospondin is involved in bone development and remodeling, supporting the notion that PTN is a significant regulator in these biological processes [31] PTN binding to its receptors leads to its biological actions. N-syndecan, which contains, heparan sulfate chains, was the first PTN receptor to be detected [32]. N-syndecan is expressed by pre-osteoblastic cells and is implicated in the regulation of osteoblast recruitment [33]. The best studied PTN receptor is receptor protein tyrosine phosphatase beta/zeta (RPTPβ/ζ), which contains of a large glycosylated extracellular domain, a transmembrane region and a cytoplasmic portion that contains two repeated tyrosine phosphatase domains, which have a characterized role in PTN-induced cell migration. Another important PTN receptor that regulates the stimulatory or the inhibitory effect of PTN on cell migration is αvβ3 integrin, which forms a functional complex with RPTPβ/ζ on the cell surface of endothelial cells [33] Finally, anaplastic lymphoma kinase (ALK), a 220kDa receptor tyrosine kinase, has been also identified as PTN receptor, but current research studies demonstrated that ALK is not directly activated by PTN, but through PTN-dependent inactivation of RPTPβ/ζ. *In vitro* studies displayed that recombinant human PTN had chemotactic effects on both human osteoblastic and endothelial cells [350] whereas immunolocalization of PTN on both osteoblasts and endothelial cells was observed in the newly formed woven bone [34] Moreover, PTN induces hypertrophy during chondrogenic differentiation of human bone marrow stem cells, increasing the transcription of hypertrophic chondrocyte markers, such as MMP13, collagen 10 and alkaline phosphatase, and resulting in enhanced calcification and higher con-

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tent of collagen 10 [35]. PTN is also over-expressed in degenerative diseases like osteoarthritis, where increased PTN levels were identified in patient's synovial fluid [36] and serum, as well as in chondrocytes and subchondral bone osteocytes [36].

TGF-β and BMP Signaling

BMPs are members of the TGF-β (Transforming Growth Factor-β) family, a large growth factor family. More than thirty members of the BMP family have been identified and are categorized into several subgroups. Individually, the members of the BMP subfamily are called either BMPs, Osteogenic Proteins (OP-1, OP-2, OP-3 for BMP-7, BMP-8 BMP-8b respectively), Growth Differentiation Factors (GDF-1, GDF-2/BMP-9, GDF-3, GDF-5/BMP-14, GDF-6/BMP-13, GDF-7/BMP-12, GDF-8 to GDF-10 and GDF-11/BMP-11), or Cartilage-Derived Morphogenetic Proteins (CDMP-1/BMP-14 and CDMP-2/BMP-13) [216-225]. Based on their amino acid homology and structural similarities, BMPs are classified into several subclasses. Members of the first subclass are BMP-2 and -4, which have 80% amino acid homology and differ in the amino terminal region. BMP-2 contains an extra heparin-binding domain. The BMPs that constitute the second subclass are larger proteins having 78% amino acid similarity between the subgroups and involve BMP-5, -6 and -7. The BMPs of the third subclass are distantly related to the above molecules [37]. BMPs are synthesized intracellularly in a large inactive precursor form of about 50 – 100 amino acids that contains an amino-terminal signal peptide, a predomain and a mature peptide. After the signal peptide cleavage, the precursor polypeptide undergoes glycosylation and dimerization. Once secreted, the predomain is cleaved, allowing the mature and active BMP proteins to act as a dimeric biomolecule. Mature BMP is considered the BMP derived after the proteolytic cleavage of the carboxyl-terminal region and is secreted mainly as homodimer or as heterodimer [38].

Two different types of membrane serine/threonine kinases receptors for BMPs have been recognized: type I (BMPR-I) and type II (BMPR-II) [39]. Once BMP binds to BMPR-I, a ligand/receptor complex is formed, which connects with the BMPR-II receptor. This interaction in turn phosphorylates the cytoplasmic glycine/serine domain (GS domain) of BMPR-I, stimulating the BMP signaling cascade [40]. BMPs also, play remarkable role in bone metabolism and several studies have demonstrated the role of several antagonists and regulators of the BMP-induced pathways. The activities of BMPs are critical for a series of molecular events that result in angiogenesis, chondogenesis and osteogenesis [41]. The BMP-induced molecular signaling pathways can be regulated in three stages: through the extracellular signals, at the membrane or receptor level and through intracellular proteins and pathways.

The TGF-β signal pathway initiates intracellular signaling following the creation and activation of a heteromeric complex of types II and I serine/threonine kinase receptors, followed by the phosphorylation of particular Smad proteins, R-Smads. The phosphorylated R-Smads can heterodimerize with co-Smad, Smad4, ultimately translocating to the nucleus and activating the transcription of target genes [42].

In the TGF-β/Smad3 signaling pathway, sphingosine 1-phosphate (S1P), a bioactive lipid, is produced to function as an intracellular mediator or extracellular ligand for different receptors, resulting in inflammation, cell migration, and angiogenesis. The interaction between TGF-β/Smad3 and S1P/S1P3 and Smad3/S1P3 signaling in chondrocytes may play a role in the development of OA [43]. Additionally, it has been documented that overexpressing TGF-β1 causes aberrant subchondral bone remodeling that causes mice to develop OA and degrade articular cartilage [44]. Indeed, a recent study reported that the inhibition of TGF-β signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis [45]

Fibroblast Growth Factors (FGFs)

Along with the VEGF family, the FGF family of growth factors is one of the two best studied growth factor families in angiogenesis. The mammalian FGF family contains 22 members so far [46]. The FGF growth factors, except for FGF11-14 (which are intracellular) and FGF-21 and -23 (which act in an endocrine manner), facilitate their biological activ-

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ity by binding to the 4 transmembrane FGF Receptors (FGFR1-4) [47]. From the 4 FGFRs, FGFR1-3 are expressed in osteoblasts [46] and we have identified a similar expression pattern in endothelial cells (no detectable expression of FGFR4 in Human Umbilical Vein Endothelial Cells (HUVECs) leading to the hypothesis that the FGFR1-3 are mostly important for their biological activity in bone regeneration and angiogenesis. This is confirmed with data showing that mutations to FGFR1-3 are directly related with bone phenotypes, such as dwarfism and achondroplasia [47]. Among the 22 FGF ligands, FGF-2, FGF-4, FGF-7, FGF-8, FGF-9, FGF-10, FGF-17 and FGF-18 are expressed in the developing skeleton [48].

The most solid evidence on the role of the FGF family in angiogenesis has derived from skeletal phenotypes of mice deficient for FGF-2, -8, -9, -10, -18 and -23 [49], which clearly demonstrates the importance of each one of these growth factors on bone development and remodeling. Below we will mention key characteristics and properties of the ones that play significant role for the bone healing and regeneration process. FGF signaling may be increased in OA, as evidenced by the finding that ablation of FGRF1 in chondrocytes being associated with reduced OA development in particular OA models [50]. In particular, inactivated FGFR1 signaling ameliorates OA progression partially by promoting autophagic activity [50].

Notch Signaling

The recent identification and characterization of tip cell function during vessel sprouting in the retina [51] and the identification of the Notch signaling as the responsible mechanism for tip cell versus stalk cell physiology in the same model [52] have elucidated one pivotal signaling mechanism for angiogenesis. In every vessel sprouting process there is one endothelial cell invading, which is morphologically distinct, as it has extensive filopodia. The invading tip cell expresses high levels of the Notch ligand Delta-like 4 (Dll4) which activates Notch in the neighboring non-invading stalk cells. Activation of the Notch receptor leads to VEGFR2 downregulation and VEGFR1 upregulation impairing the response to VEGF signaling, and thus the tip cell behavior (no migration towards VEGF gradient levels) and promoting a stalk phenotype in these cells. Stalk cells proliferate more, produce less filopodia, migrate less and they are supposed to eventually form the lumen of the new vessel. It is considered that Notch expression defines the cell fate, since Notch presence will lead to a stalk cell behavior, whereas its absence is related to increased sprouting. Indeed, abnormal sprouting leads to a very dense vessel network, however poorly functional due to limited perfusion [53]

The Notch signaling system regulates the molecules involved in cartilage production and breakdown and hence plays a dual function in cartilage maintenance [54]. It is well known that Notch signaling is critical in the angiogenesis of condylar cartilage and disc, which is required to form OA [54]. Recent research has shown that changing Notch signaling may cause OA. Specifically, Notch 1 and 2 receptors are highly expressed in articular chondrocytes and are localized at the cell surface in normal mouse and human articular cartilage but are translocated into the nucleus in degenerated cartilage [54]. Inhibition of Notch signalling by Rbpj knockout in chondrocytes after skeletal development suppresses OA development in a murine surgical model, and injection of the γ-secretase inhibitor DAPT into the knee joints of the wild-type OA model mice results in a similar protective effect [54]. Mmp13 expression is increased by overexpression of Notch-ICD in mouse primary chondrocytes and chondrocyte cell lines and is decreased in Rbpj-knockout cartilage.

Sclerostin

Sclerostin is a soluble antagonist of canonical Wnt signaling and a strong inhibitor of bone formation, almost exclusively secreted by osteocytes [55]. It belongs to the cystine knot family and is a product of the sclerostin (SOST) gene [56]. Secreted Wnt inhibitors, such as sclerostin, are a group of proteins which facilitate their activity, binding extracellularly to the co-receptor LRP5/6 [55]. Sclerostin is a glycoprotein with a molecular weight of 24 kDa and is secreted almost exclusively by osteocytes and to a lesser extent by other cell types like osteoclasts, renal and vascular cells [57]. Sclerostin substantially regulates bone min-

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eralization processes and is a potent anti-anabolic agent in the skeleton. Osteocytes reduce the release of sclerostin after mechanical stimulation [57]. Reduced in vivo activity of sclerostin leads to increased bone mass and strength [58], while increased expression of sclerostin in experimental models is associated with reduced bone mass [59]. Moreover, many research studies reported that SOST is upregulated in OA acting as a rescue mechanism to prevent further degenerative changes of the joint. It antagonises inflammation-induced cartilage catabolism while it preserves chondrocyte anabolic activities. It also prevents abnormal bone mineralisation and osteophyte formation [60]. Specifically, chondrocyte SOST immunoexpression was remarkably elevated in the focal area of cartilage damage in surgically induced OA in sheep and mice models as well as end-stage in human OA. Contrariwise, the expression of SOST was decreased in the osteocytes of subchondral bone in sheep OA in association with bone sclerosis. SOST was biologically active in chondrocytes, inhibiting Wnt-β-catenin signaling and catabolic metalloproteinases MMPs and distintegrin or metalloproteinase with thrombospondin repeats (ADAMTS)] expression, but also decreasing the mRNA levels of aggrecan, collagen II and tissue inhibitors of metalloproteinases (TIMPs). Despite this mixed effect, SOST dose-dependently inhibited IL-1α-stimulated cartilage aggrecanolysis *in vitro* [60].

Conclusion

Recent clinical and experimental evidence demonstrated that many signaling pathways regulate the homeostasis of articular chondrocytes and OA development activating many growth factors and cytokines. Comprehensive understanding of the molecular networks including articular chondrocyte proliferation differentiation and the implicated molecules is needed for further elucidation of OA pathogenesis and progression.

REFERENCES

1. Goldring MG, Goldring SR. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. Ann NY Acad Sci 2010; 1192: 230 -237.
2. Zang LZ, Zheng HA, Jiang Y, Tu YH, Jiang PH, Yang LA. Mechanical and biological link between cartilage and subchondral bone in osteoarthritis. Arthritis Care Res (Hoboken) 2012; 64: 960-967.
3. Vincent TL Peripheral pain mechanisms in osteoarthritis. Pain. 2020;161 Suppl 1(1): S138-S146.
4. Chen DY, Sun NH, Chen X, Gong JJ, Yuan ST, Hu ZZ, Lu NN, Körbelin J, Fukunaga K, Liu QH, Lu YM, Han F. Endothelium-derived semaphorin 3G attenuates ischemic retinopathy by coordinating β-catenin-dependent vascular remodeling. J Clin Invest. 2021;131(4): e135296
5. Jiang W, Jin Y, Zhang S, Ding Y, Huo K, Yang J, Zhao L, Nian B, Zhong TP, Lu W, Zhang H, Cao X, Shah KM, Wang N, Liu M, Luo J. PGE2 activates EP4 in subchondral bone osteoclasts to regulate osteoarthritis. Bone Res. 2022; 10(1): 27
6. Qin Q, Lee S, Patel N, Walden K, Gomez-Salazar M, Levi B, James AW. Neurovascular coupling in bone regeneration. Exp Mol Med. 2022;54 (11):1844-1849.
7. Van Bellinghen, X.; Idoux-Gillet, Y.; Pugliano, M.; Strub, M.; Bornert, F.; Clauss, F.; Schwinté, P.; Keller, L.; Benkirane-Jessel, N.; Kuchler-Bopp, S.; et al. Temporomandibular Joint Regenerative Medicine. Int. J. Mol. Sci. 2018, 19, 446.
8. Haigler, M.C.; Abdulrehman, E.; Siddappa, S.; Kishore, R.; Padilla, M.; Enciso, R. Use of platelet-rich plasma, platelet-rich growth factor with arthrocentesis or arthroscopy to treat temporomandibular joint osteoarthritis: Systematic review with meta-analyses. J. Am. Dent. Assoc. 2018, 149, 940–952.
9. Shi, Y.; Hu, X.; Cheng, J.; Zhang, X.; Zhao, F.; Shi, W.; Ren, B.; Yu, H.; Yang, P.; Li, Z.; et al. A Small Molecule Promotes Cartilage Extracellular Matrix Generation and Inhibits Osteoarthritis Development. Nat. Commun. 2019, 10, 1914.
10. East L, McCarthy A, Wienke D, Sturge J, Ashworth A, Isacke CM. A targeted deletion in the endocytic receptor gene Endo180 results in a defect in collagen uptake.

EMBO Rep. 2003; 4(7): 710-6.

11. Engelholm LH, List K, Netzel-Arnett S, Cukierman E, Mitola DJ, Aaronson H, Kjøller L, Larsen JK, Yamada KM, Strickland DK, Holmbeck K, Danø K, Birkedal-Hansen H, Behrendt N, Bugge TH. uPARAP/Endo180 is essential for cellular uptake of collagen and promotes fibroblast collagen adhesion. J Cell Biol. 2003;160(7):1009-15

12. Lauer-Fields JL, Juska D, Fields GB. Matrix metalloproteinases and collagen catabolism. Biopolymers. 2002;66(1):19-32.

13. Paiva KBS, Granjeiro JM. Matrix Metalloproteinases in Bone Resorption, Remodeling, and Repair. Prog Mol Biol Transl Sci. 2017;148:203-303

14. Lian C, Wang X, Qiu X, Wu Z, Gao B, Liu L, Liang G, Zhou H, Yang X, Peng Y, Liang A, Xu C, Huang D, Su P. Collagen type II suppresses articular chondrocyte hypertrophy and osteoarthritis progression by promoting integrin β1-SMAD1 interaction. Bone Res. 2019;7:8

15. Yan JF, Qin WP, Xiao BC, Wan QQ, Tay FR, Niu LN, Jiao K. Pathological calcification in osteoarthritis: an outcome or a disease initiator? Biol Rev Camb Philos Soc. 2020 ;95(4):960-985

16. Jiao K, Zeng G, Niu LN, Yang HX, Ren GT, Xu XY, Li FF, Tay FR, Wang MQ. Activation of α2A-adrenergic signal transduction in chondrocytes promotes degenerative remodelling of temporomandibular joint. Sci Rep. 2016; 6:30085

17. Ge C, Mohamed F, Binrayes A, Kapila S, Franceschi RT. Selective Role of Discoidin Domain Receptor 2 in Murine Temporomandibular Joint Development and Aging. J Dent Res. 2018;97(3):321-328

18. Pesesse L, Sanchez C, Henrotin Y. Osteochondral plate angiogenesis: a new treatment target in osteoarthritis. Joint Bone Spine. 2011;78(2):144-9

19. Lehmann W, Edgar CM, Wang K, Cho TJ, Barnes GL, Kakar S, Graves DT, Rueger JM, Gerstenfeld LC, Einhorn TA. Tumor necrosis factor alpha (TNF-alpha) coordinately regulates the expression of specific matrix metalloproteinases (MMPS) and angiogenic factors during fracture healing.

20. Roberts S, Caterson B, Menage J, Evans EH, Jaffray DC, Eisenstein SM. Matrix metalloproteinases and aggrecanase: their role in disorders of the human intervertebral disc. Spine (Phila Pa 1976). 2000; 25(23): 3005-13

21. Kaspiris A, Khaldi L, Grivas TB, Vasiliadis E, Kouvaras I, Dagkas S, Chronopoulos E, Papadimitriou E. Subchondral cyst development and MMP-1 expression during progression of osteoarthritis: an immunohistochemical study. Orthop Traumatol Surg Res, 2013. 99(5): p. 523-9

22. Kaspiris A, Khaldi L, Chronopoulos E, Vasiliadis E, Grivas TB, Kouvaras I, Dagkas S, Papadimitriou E.Macrophage-specific metalloelastase (MMP-12) immunoexpression in the osteochondral unit in osteoarthritis correlates with BMI and disease severity. Pathophysiology, 2015. 22(3): p. 143-51.

23. Tetlow LC, Adlam DJ, Woolley DE. Matrix metalloproteinase and proinflammatory cytokine production by chondrocytes of human osteoarthritic cartilage: associations with degenerative changes. Arthritis Rheum. 2001; 44(3): 585-94

24. Feng Y, Ke J, Cao P, Deng M, Li J, Cai H, Meng Q, Li Y, Long X. HMGB1-induced angiogenesis in perforated disc cells of human temporomandibular joint. J Cell Mol Med. 2018;22(2):1283-1291

25. Jiang SJ, Li W, Li YJ, Fang W, Long X. Dickkopf-related protein 1 induces angiogenesis by upregulating vascular endothelial growth factor in the synovial fibroblasts of patients with temporomandibular joint disorders. Mol Med Rep. 2015;12(4):4959-66

26. Xu J, Cai H, Meng Q, Li Y, Chen G, Fang W, Long X. IL-1β-regulating angiogenic factors expression in perforated temporomandibular disk cells via NF-κB pathway. J Oral Pathol Med. 2016; 45(8): 605-12

27. Tanaka E, Detamore MS, Mercuri LG. Degenerative disorders of the temporomandibular joint: etiology, diagnosis, and treatment. J Dent Res. 2008; 87(4):296-307.

28. Landes CA, Goral W, Mack MG, Sader R. 3-D sonography for diagnosis of osteoarthrosis and disk degeneration of the temporomandibular joint, compared with MRI. Ultrasound Med Biol. 2006;32(5):627-32

29. Mikelis, C., M. Koutsioumpa, E. Papadimitriou Pleiotrophin as a possible new target for angiogenesis-related diseases and cancer. Recent Pat Anticancer Drug Discov, 2007. 2(2): p. 175-86

30. Lamprou M, Kaspiris A, Panagiotopoulos E, Giannoud-

VOLUME 74 | ISSUE 3 | JULY - SEPTEMBER 2023

is PV, Papadimitriou E. The role of pleiotrophin in bone repair. Injury. 2014 ;45(12):1816-23.

31. Hankenson KD, Sweetwyne MT, Shitaye H, Posey KL. Thrombospondins and novel TSR-containing proteins, R-spondins, regulate bone formation and remodeling. Curr Osteoporos Rep. 2010; 8(2):68-76

32. Raulo E, Chernousov MA, Carey DJ, Nolo R, Rauvala H. Isolation of a neuronal cell surface receptor of heparin binding growth-associated molecule (HB-GAM). Identification as N-syndecan (syndecan-3). J Biol Chem. 1994; 269(17):12999-3004

33. Imai S, Kaksonen M, Raulo E, Kinnunen T, Fages C, Meng X, Lakso M, Rauvala H. Osteoblast recruitment and bone formation enhanced by cell matrix-associated heparin-binding growth-associated molecule (HB-GAM). J Cell Biol. 1998;143(4):1113-28.

34. Petersen W, Wildemann B, Pufe T, Raschke M, Schmidmaier G. The angiogenic peptide pleiotrophin (PTN/HB-GAM) is expressed in fracture healing: an immunohistochemical study in rats. Arch Orthop Trauma Surg. 2004;124(9):603-7

35. Bouderlique T, Henault E, Lebouvier A, Frescaline G, Bierling P, Rouard H, Courty J, Albanese P, Chevallier N. Pleiotrophin commits human bone marrow mesenchymal stromal cells towards hypertrophy during chondrogenesis. PLoS One. 2014; 9(2):e88287.

36. Kaspiris A, Mikelis C, Heroult M, Khaldi L, Grivas TB, Kouvaras I, Dangas S, Vasiliadis E, Lioté F, Courty J, Papadimitriou E. Expression of the growth factor pleiotrophin and its receptor protein tyrosine phosphatase beta/zeta in the serum, cartilage and subchondral bone of patients with osteoarthritis. Joint Bone Spine. 2013;80(4):407-13

37. Wang EA, Rosen V, D'Alessandro JS, Bauduy M, Cordes P, Harada T, Israel DI, Hewick RM, Kerns KM, LaPan P. Recombinant human bone morphogenetic protein induces bone formation. Proc Natl Acad Sci U S A. 1990;87(6):2220-4

38. Guo J, Wu G. The signaling and functions of heterodimeric bone morphogenetic proteins. Cytokine Growth Factor Rev, 2012. 23(1-2): p. 61-7.

39. Rosenzweig BL, Imamura T, Okadome T, Cox GN, Yamashita H, ten Dijke P, Heldin CH, Miyazono K. Cloning and characterization of a human type II receptor for bone morphogenetic proteins. Proc Natl Acad Sci U S A. 1995 ;92(17): 7632-6

40. Miyazono K, Kamiya Y, Morikawa M. Bone morphogenetic protein receptors and signal transduction. J Biochem, 2010. 147(1): p. 35-51.

41. Carreira AC, Lojudice FH, Halcsik E, Navarro RD, Sogayar MC, Granjeiro JM. Bone morphogenetic proteins: facts, challenges, and future perspectives. J Dent Res. 2014; 93(4):335-45.

42. Yi JJ, Barnes AP, Hand R, Polleux F, Ehlers MD. TGF-beta signaling specifies axons during brain development. Cell. 2010;142(1):144-57

43. Li W, Zhao S, Yang H, Zhang C, Kang Q, Deng J, Xu Y, Ding Y, Li S. Potential Novel Prediction of TMJ-OA: MiR-140-5p Regulates Inflammation Through Smad/TGF-β Signaling. Front Pharmacol. 2019;10:15.

44. Lu K, Ma F, Yi D, Yu H, Tong L, Chen D. Molecular signaling in temporomandibular joint osteoarthritis. J Orthop Translat. 2021; 32: 21-27.

45. Zhen G, Wen C, Jia X, Li Y, Crane JL, Mears SC, Askin FB, Frassica FJ, Chang W, Yao J, Carrino JA, Cosgarea A, Artemov D, Chen Q, Zhao Z, Zhou X, Riley L, Sponseller P, Wan M, Lu WW, Cao X. Inhibition of TGF-β signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis. Nat Med. 2013;19(6):704-12.

46. Charoenlarp P, Rajendran AK, Iseki S. Role of fibroblast growth factors in bone regeneration. Inflamm Regen. 2017;37:10

47. Itoh N, Ornitz DM. Functional evolutionary history of the mouse Fgf gene family. Dev Dyn. 2008;237(1):18-27

48. Harada M, Murakami H, Okawa A, Okimoto N, Hiraoka S, Nakahara T, Akasaka R, Shiraishi Y, Futatsugi N, Mizutani-Koseki Y, Kuroiwa A, Shirouzu M, Yokoyama S, Taiji M, Iseki S, Ornitz DM, Koseki H. FGF9 monomer-dimer equilibrium regulates extracellular matrix affinity and tissue diffusion. Nat Genet. 2009 ;41(3):289-98.

49. Itoh N. The Fgf families in humans, mice, and zebrafish: their evolutional processes and roles in development, metabolism, and disease. Biol Pharm Bull. 2007; 30(10):1819-25.

50. Wang Z, Huang J, Zhou S, Luo F, Tan Q, Sun X, Ni Z, Chen H, Du X, Xie Y, Chen L. Loss of Fgfr1 in chondro-

cytes inhibits osteoarthritis by promoting autophagic activity in temporomandibular joint. J Biol Chem. 2018 ;293(23):8761-8774

51. Gerhardt H, Golding M, Fruttiger M, Ruhrberg C, Lundkvist A, Abramsson A, Jeltsch M, Mitchell C, Alitalo K, Shima D, Betsholtz C. VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. J Cell Biol. 2003;161(6):1163-77

52. Hellström M, Phng LK, Hofmann JJ, Wallgard E, Coultas L, Lindblom P, Alva J, Nilsson AK, Karlsson L, Gaiano N, Yoon K, Rossant J, Iruela-Arispe ML, Kalén M, Gerhardt H, Betsholtz C. Nature. 2007;445(7129):776-80.

53. Potente M, Gerhardt H, Carmeliet P. Basic and therapeutic aspects of angiogenesis. Cell. 2011 Sep 16;146(6):873-87

54. Saito T, Tanaka S. Molecular mechanisms underlying osteoarthritis development: Notch and NF-κB. Arthritis Res Ther. 2017;19(1):94.

55. Kramer I, Kneissel M, Kramann R, Weis D, D'Haese PC, Brandenburg VM. Sclerostin deficiency modifies the development of CKD-MBD in mice. Bone. 2018;107:115-123.

56. Pietrzyk B, Smertka M, Chudek J. Sclerostin: Intracellular mechanisms of action and its role in the pathogenesis of skeletal and vascular disorders. Adv Clin Exp Med. 2017; 26(8):1283-1291.

57. Poole KE, van Bezooijen RL, Loveridge N, Hamersma H, Papapoulos SE, Löwik CW, Reeve J. Sclerostin is a delayed secreted product of osteocytes that inhibits bone formation. FASEB J, 2005. 19(13): p. 1842-4.

58. Li X, Ominsky MS, Niu QT, Sun N, Daugherty B, D'Agostin D, Kurahara C, Gao Y, Cao J, Gong J, Asuncion F, Barrero M, Warmington K, Dwyer D, Stolina M, Morony S, Sarosi I, Kostenuik PJ, Lacey DL, Simonet WS, Ke HZ, Paszty C. Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength. J Bone Miner Res. 2008; 23(6): 860-9

59. Yao GQ, Wu JJ, Troiano N, Insogna K. Targeted overexpression of Dkk1 in osteoblasts reduces bone mass but does not impair the anabolic response to intermittent PTH treatment in mice. J Bone Miner Metab. 2011;29(2):141-8.

60. Chan BY, Fuller ES, Russell AK, Smith SM, Smith MM, Jackson MT, Cake MA, Read RA, Bateman JF, Sambrook PN, Little CB. Increased chondrocyte sclerostin may protect against cartilage degradation in osteoarthritis. Osteoarthritis Cartilage. 2011;19(7):874-85

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REVIEW

Femoral head osteonecrosis-imaging findings and differential diagnosis

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ABSTRACT

This review addresses the imaging features of femoral head osteonecrosis. Although the initial evaluation should include plain radiography in combination with thorough history and physical examination, MRI represents the method of choice for an early detection and correct diagnosis. It is also highlighted the imaging findings that enable differentiation of femoral head osteonecrosis from other pathological conditions including transient osteoporosis and arthritis.

KEYWORDS: Femoral head osteonecrosis, imaging findings , bone marrow edema, hip arthritis

Introduction

Osteonecrosis of the femoral head is a common disease caused by ischemia or disruption of the blood flow of the epiphyseal-subchondral bone [1], resulting in bone loss and weakening of the femoral head with complications such as fracture and osteoarthritis. It most often affects males, aged 30-50 years with bilateral involvement up to 72% [2]. The etiology is uncertain: idiopathic causes (37%), systemic diseases, trauma, corticosteroids and alcohol abuse [3].

Pathogenesis and Clinical Manifestations

Genetic predisposition, metabolic and local factors can compromise the microvascular circulation of the femoral head leading to bone necrosis that affects first the hematopoietic cells, then the bone cells and finally the fat cells [4]. The reparative process involves peripheral revascularization of the ischemic area with activation of osteoclasts and osteoblasts leading to osteopenia and new bone formation. Subsequently, cell migration takes place from the periphery of the lesion to the necrotic center to repair the damaged area [5,6]. The complications of the above procedure concern the formation of abnormal, mechanically weak bone, prone to subchondral fractures and subsequent osteoarthritis of the hip [7].

The most common symptom is acute hip pain located mainly in the groin radiating to the thighs

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Figure 1. *X-ray of pelvis and hip show a stage -II osteonecrosis of the left femoral head -crescent sign*

or buttocks, followed by functional impairment. Negative inflammatory markers and absence of fever help to differentiate femoral head osteonecrosis from inflammatory and septic arthritis .A normal plain hip radiography excludes hip arthropathy from the diagnosis at initial stages [8].

Classification

Among the multiple classification systems have been proposed for femoral head osteonecrosis the most commonly used are: 1) Ficat and Arlet, 2) University of Pennsylvania/Steinberg, 3) Association Research Circulation Osseous (ARCO) [9,10]. Ficat and Arlet is the simplest classification system developed in 1964. It was based on radiographic findings to stage the disease, without considering the size or location of the osteonecrotic lesion, two important factors which are used nowadays to predict the therapeutic outcome [11]. The Steinberg system and the Association for Research on Bone Circulation (ARCO) systems were designed in 1985 and 1994 respectively and included computed tomography (CT) and magnetic resonance imaging (MRI) findings to diagnose disease in early stage [12].

According to the classification systems, plain radiography has been shown to be inaccurate in assessing the degree of femoral head depression, overestimating ARCO stage II and underestimating ARCO stage III lesions [13]. Therefore, it is useful in assessing the degree of femoral head collapse after stage III of the ARCO classification system [14], MRI is useful for diagnosing disease in stages prior to collapse of the femoral head, distinguishing early from advanced disease, and quantifying the osteonecrotic lesion (location and size) [15].

Imaging findings

The plain radiograph findings according to the Ficat and Arlet system [11] include: stage 0: normal radiograph, stage I: normal radiograph and acute hip pain, stage II: sclerosis, osteopenia and cystic changes in the femoral head with preservation of its shape and the hip joint space, stage III: radiographic crescent sign - subchondral lucent line on the femoral head - with preservation of its shape and the hip joint space and stage IV: flattening of the femoral head and hip joint arthropathy (Fig.1). The same applies to CT, with the method being more sensitive in advanced stages, especially in stage III that can detect easily subchondral fractures and femoral head collapse. At CT a sclerotic line is seen, separating necrotic from viable bone [16].

Bone scintigraphy is used for diagnosis when plain radiography is normal and MRI is contraindicated. It has high sensitivity in detecting multifocal lesions, however due to low spatial resolution and low sensitivity it cannot be used for the quantification of the lesion [17].

MRI achieves excellent sensitivity and specificity for detecting the disease at early stages and is considered the method of choice for staging and quantification of the lesion, particularly when the plain radiography is negative, as well as for the follow up [15]. The Mitchell et al. [18] classification is commonly used for staging of the disease. The hall-mark of the disease is a sclerosing hypointense "band-like" lesion of the femoral head in axial MR-images. The pathognomonic finding is a serpentine rim on T2–weighted images, the "double line sign" (Fig.2). Its outer rim corresponds to reactive tissue of low signal intensity on T2–weighted images and the inner rim to hyperintensity vascular-regenerative tissue at the necrotic-viable interface of the lesion. The inner central area shows low, iso - and high signal intensity compared to normal

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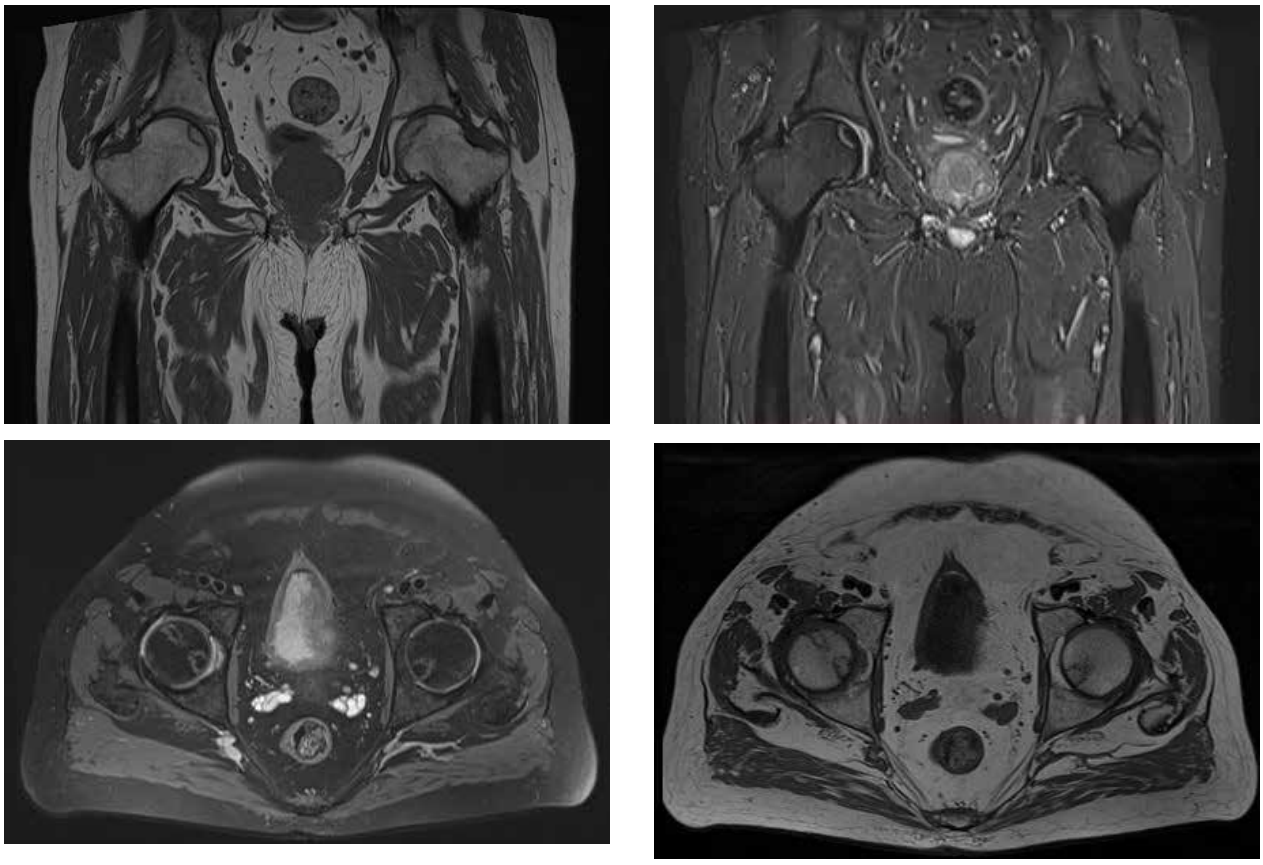

Figure 2. *Axial and Coronal T1 and STIR images show bilateral femoral head osteonecrosis-double line sign.*

bone marrow depending on the stage of the disease [16]. Paramagnetic contrast media administration can be used preoperatively to evaluate the contour of the femoral head and postoperatively to monitor the vascularized graft [19].

Joint fluid collection is seen in 50% of all cases. Bone marrow edema is not a finding in the early stages of the disease [20] and it is never seen before the presence of the band-like sign [21]. Its appearance correlates significantly with the onset and progressive worsening of the pain. It is a poor prognostic sign as it is related to subsequent collapse of the femoral head (Fig.3) [22]. The presence of subchondral fractures is a complication in femoral head osteonecrosis. They are seen as smooth low signal intensity areas on T1–weighted images, concave to articular surfaces extending along the whole necrotic region.

Staging and Quantification

The size of the necrosis is an important factor in determining disease prognosis and therapeutic management. Various quantification methods have been developed to characterize the size/location of the necrosis and at the moment three systems are widely used: Steinberg classification, Japanese Investigation Committee (JIC) classification and modified Kerboul classification [23]. In the Steinberg System the extent of involvement is estimated as a percentage of the articular surface or the femoral head area (< 15% of articular surface or head affected), moderate (15–30%), and severe (> 30%) [24]. In the JIC classification, the extent of femoral head involvement is estimated as the percentage of the weight-bearing area on the mid-coronal T1-weighted image: type A lesion < medial 1/3 of weight-bearing area, type B lesion < medial 2/3 of weight-bearing area, type C1 lesion > medial 2/3 of weight being area without exceeding the acetabular rim and type C2 lesion exceeding the acetabular margin [25]. In the modified Kerboul classifi-

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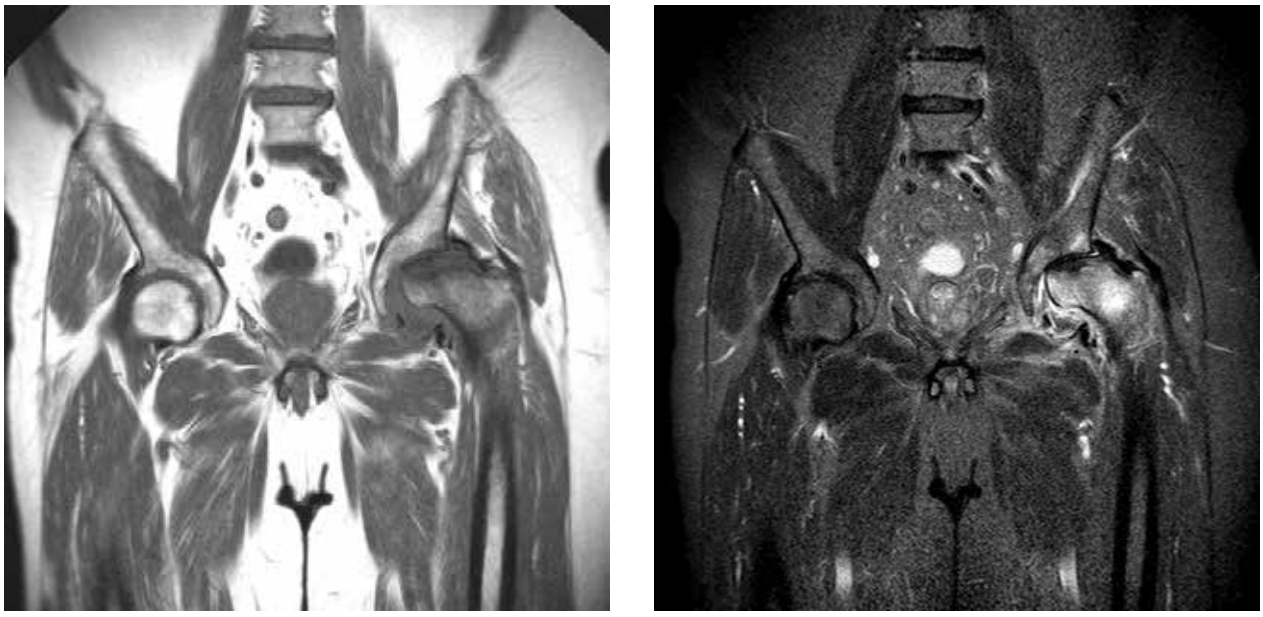

Figure 3. *Axial and Coronal T1 and STIR images show late- stage left femoral head osteonecrosis with femoral head flattening and hip arthropathy.*

cation system, the extent of necrosis is quantified by the combined angle of the necrotic portion on the mid-coronal and mid-sagittal MR images of the femoral head. The system distinguishes three categories: small lesions (combined necrotic angle < 190°), medium-sized lesion (combined necrotic angle between 190° and 240°), and large lesion (combined necrotic angle > 240°) with increased risk of femoral head collapse at the medium and large sized lesions [26,27].

The radiological report for the diagnosis of osteonecrosis and for treatment planning should include the following: 1) the site of necrosis, 2) the stage of necrosis, 3) the presence of a subchondral fracture, 4) the degree of collapse of the articular surface (critical point >2 mm) and 5) the quantification of necrosis (Table I).

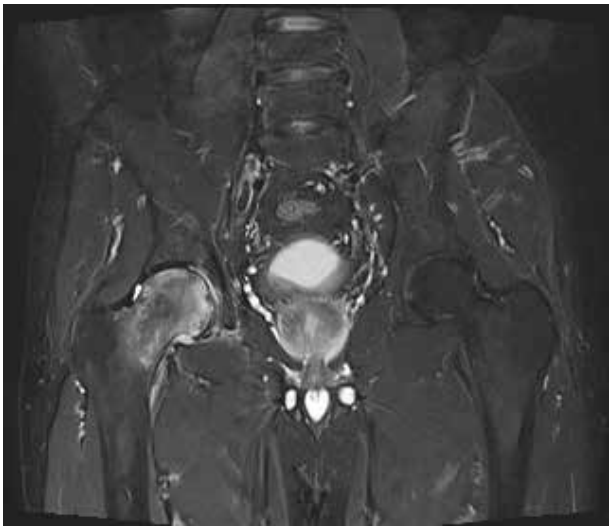

Figure. 4 *TOH. Coronal STIR image shows right femoral head and neck bone marrow edema-sparing sign*

Differential diagnosis

The differential diagnosis on MR imaging includes a) potential pitfalls (persistent red marrow, fovea centralis, synovial herniation pits) and b) pathological conditions (subchondral cysts, idiopathic transient osteoporosis, subchondral insufficiency fractures, stress injuries, arthritis) that can misinterpret as femoral head osteonecrosis.

Persistent red marrow: The presence of red marrow in the subchondral region of the femoral head is found more often in women. Normal red marrow signal intensity is higher than of adjacent muscle, whereas in femoral head osteonecrosis, T1-weighted signal intensity of the involved area is lower than that of adjacent muscle [28].

Fovea centralis: The central fovea represents the

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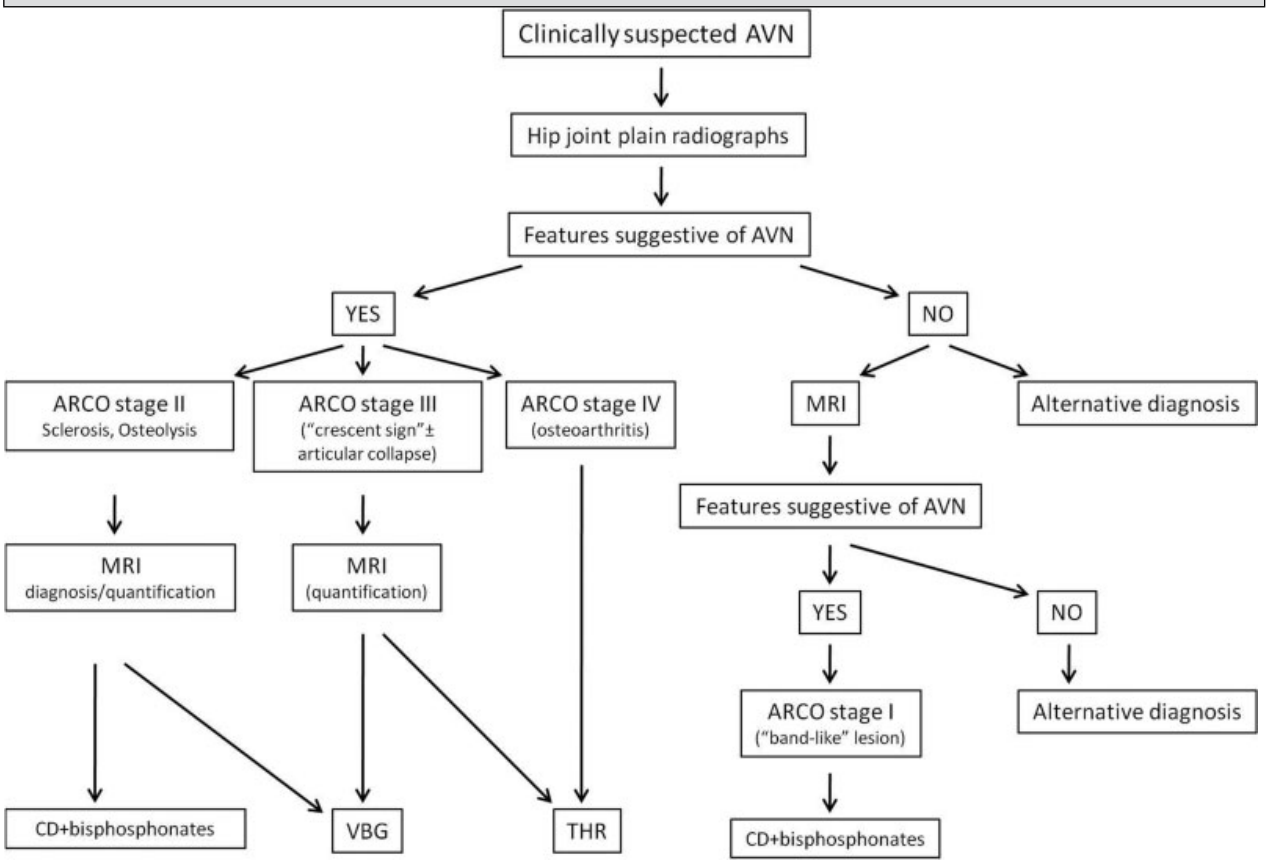
TABLE 1.

ARCO proposed algorithm about the correlation of imaging findings and treatment planning



normal anatomic attachment of the ligamentum teres and it is demonstrated as a low-signal indentation on the medial rim of the femoral head (3 o'clock on axial MR images) [28].

Herniation pits: It is a benign lesion that resembles a subchondral cyst. The lesion is typically located at the 10 and 2 o'clock position in the subchondral region of the femoral head, a fact that helps distinguish it from AVN [29].

Transient osteoporosis (TOH): It occurs more often in middle-aged men and women in the perinatal period, without a history of trauma, and it is always unilateral [30] in contrast to the more common bilateral involvement of femoral head osteonecrosis [31]. Radiography typically shows severe osteopenia and cortical bone loss in the femur within 5 weeks of the onset of symptoms. Constant finding on spinal and hip DXA is osteopenia or osteoporosis. MRI shows bone marrow edema in the early phase of the disease with imaging findings becoming apparent in about the first 48 hours. A pathognomonic sign (the "sparing" sign) is the presence of extensive bone marrow edema sparing the inferior medial part of the femoral head and the greater trochanter and is visualized in 90% of patients at approximately 4 to 6 weeks (Fig.4) [32]. After intravenous contrast injection there is marked enhancement of the hip joint due to reactive synovitis. In TOH, subchondral fractures are described in up to 49% patients and they are seen as irregular, thin lines deep in the articular surface, often discontinuous, with low signal intensity in all sequences. However MR signal characteristics of the necrotic area in femoral head osteonecrosis varies according to the stage of the disease. Finally, the imaging

findings of TOH resolve spontaneously within 6-9 months after weight-bearing restriction and analgesic therapy [30].

Stress injuries: They are stress fractures (more common in athletes) or insufficiency fractures (over the age of 60) [28]. Plain radiograph may initially be normal on MRI, bone marrow edema and periarticular tissue edema are initially visualized, and then a low-signal linear or curvilinear fracture line on all sequences appear in the medial subchondral region of the femoral head [31]. In equivocal cases a history of trauma and the presence of osteopenia may help in the differential diagnosis from femoral head osteonecrosis.

Infectious and inflammatory diseases: An unexplained monoarticular joint-fluid collection in high-risk individuals (immunosuppression, renal failure, DM, intravenous drug users) raises the suspicion of septic arthritis. MR imaging abnormalities present within the first 24 hours after the onset of symptoms (diffuse reactive bone marrow edema, joint fluid collection, periarticular edema, enhancement by paramagnetic substance, abscesses and myositis) [32]. In rheumatoid arthritis, the presence of bone marrow edema is an early MR finding. The presence of bone erosions and arthritis contribute to the differential diagnosis from femoral head osteonecrosis [33]. Early hip involvement in ankylosing spondylitis is depicted as subchondral bone marrow edema usually anteriorly in location, suggesting enthesopathy [34].

Conclusion

Early diagnosis and staging of osteonecrosis of femoral head is becoming increasingly important for early and effective treatment of the disease. History and predisposing factors combined with timely MR imaging contribute to the differential diagnosis from other pathologic mimickers.

REFERENCES

1. Mirzai R, Chang C, Greenspan A, Gershwin ME. Avascular necrosis. Comprehensive therapy 1998; 24: 251-5.
2. Assouline-Dayan Y, Chang C, Greenspan A, et al. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum 2002; 32(02): 94–124.
3. Murphey MD, Foreman KL, Klassen-Fischer MK, et al. From the radiologic pathology archives imaging of osteonecrosis: radiologic-pathologic correlation. Radiographics: a review publication of the Radiological Society of North America, Inc. 2014; 34: 1003-28.
4. Chang CC, Greenspan A, Gershwin ME. Osteonecrosis: Current perspectives on pathogenesis and treatment. Semin Arthritis Rheum 1993; 23(1): 47-69.
5. Mont MA, Pacheso IH, Hungerford DS. Non-traumatic osteonecrosis of the femoral head: part I. Demographics, pathogenesis, diagnosis and staging. Bombay Hospital Journal 1996;38.
6. Ohzono K, Saito M, Takaoka K, et al. Natural history of nontraumatic avascular necrosis of the femoral head. The Journal of bone and joint surgery. British volume 1991; 73: 68-72.
7. Seamon J, Keller T, Saleh J, Cui Q. The pathogenesis of nontraumatic osteonecrosis. Arthritis 2012; 2012: 601763.
8. Manaster BJ. From the RSNA Refresher Courses. Radiological Society of North America. Adult chronic hip pain: radiographic evaluation. Radiographics: a review publication of the Radiological Society of North America, Inc. 2000; 20 Spec No: S3-S25.
9. Mont M, Marulanda G, Jones LC, et al. Systematic analysis of classification systems for osteonecrosis of the femoral head. J Bone Joint Surg 2006; 88-A-(Supplement 3): 16–26.
10. Steinberg ME, Steinberg DR. Classification systems for osteonecrosis: an overview. Orthop Clin N Am2004; 35: 273–83.
11. Ficat RP. Idiopathic bone necrosis of the femoral head: early diagnosis and treatment. J Bone Joint Surg Br 1985; 67-B(1): 3–9.
12. ARCO (Association Research Circulation Osseous). Committee on terminology and classification. ARCO News 1992; 4: 41–46.
13. Zibis AH, Karantanas AH, Roidis NT, et al. The role of MR imaging in staging femoral head osteonecrosis. Eur J Radiol 2007; 63(01): 3–9.

14. Vassalou E, Spanakis K, Tsifountoudis I, Karantanas A. MR Imaging of the Hip: An Update on Bone Marrow Edema. Seminars in Musculoskeletal Radiology Vol. 23 No. 3/2019.
15. Karantanas AH. Accuracy and limitations of diagnostic methods for avascular necrosis of the hip. Expert opinion on medical diagnostics 2013; 7: 179-87.
16. Azzali E, Milanese GI, Martella I, et al. Imaging of osteonecrosis of the femoral head Acta Biomed 2016; Vol. 87, Supplement 3: 6-12.
17. Dasa V, Abdel-Nabi, Anders M, et al. F-18 fluoride positron emission tomography of the hip for osteonecrosis. Clin Orthop Relat Res 2008; 466: 1081–6.
18. Mitchell DG, Rao VM, Dalinka MK, et al. Femoral head avascular necrosis: correlation of MR imaging, radiographic staging, radionuclide imaging, and clinical findings. Radiology 1987; 162: 709–15.
19. Malizos KN, Karantanas AH, Varitimidis SE, et al. Osteonecrosis of the femoral head: Etiology, imaging and treatment. European Journal of Radiology 2007; 63: 16–28.
20. Kim YM, Oh HC, Kim HJ. The pattern of bone marrow oedema on MRI in osteonecrosis of the femoral head. J Bone Joint Surg Br 2000; 82B: 837–41.
21. Fujioka M, Kubo T, Nakamura F, et al. Initial changes of non-traumatic osteonecrosis of femoral head in fat suppression images: bone marrow edema was not found before the appearance of band patterns. Magn Reson Imaging 2001; 19: 985–91.
22. Ito H, Matsuno T, Minami A. Relationship between bone marrow edema and development of symptoms in patients with osteonecrosis of the femoral head. AJR 2006; 186: 1761–70.
23. Hines J.T. Osteonecrosis of the Femoral Head: an Updated Review of ARCO on Pathogenesis, Staging and Treatment. J Korean Med Sci. 2021; 36(24): e177.
24. Steinberg ME, Brighton CT, Steinberg DR, et al. Treatment of avascular necrosis of the femoral head by a combination of bone grafting, decompression, and electrical stimulation. Clin Orthop Relat Res 1984; (186): 137-53.
25. Nishii T, Sugano N, Ohzono K, Sakai T, Sato Y, Yoshikawa H. Significance of lesion size and location in the prediction of collapse of osteonecrosis of the femoral head: a new three-dimensional quantification using magnetic resonance imaging. J Orthop Res 2002; 20(1): 130-6.
26. Kerboul M, Thomine J, Postel M, Merle d'Aubigné R. The conservative surgical treatment of idiopathic aseptic necrosis of the femoral head. J Bone Joint Surg Br 1974; 56-B(2): 291-6.
27. Ha YC, Kim HJ, Kim SY, et al. Effects of age and body mass index on the results of transtrochanteric rotational osteotomy for femoral head osteonecrosis. J Bone Joint Surg Am 2010; 92(2): 314-21.
28. Jackson SM, Major MN. Pathologic conditions mimicking osteonecrosis. Orthop Clin N Am 2004; 35(3): 315-20.
29. Nokes SR, Vogler JB, Spritzer CE, et al. Herniation pits of the femoral neck: appearance at MR imaging. Radiology 1989; 172: 231–4.
30. Vande Berg BC, Malghem JJ, Lecouvet FE, et al. Idiopathic bone marrow edema lesions of the femoral head: predictive value of MR imaging findings. Radiology- 1999; 212(2): 527-35.
31. Khurana B, Okanobo H, Ossiani M, et al. Abbreviated MRI for patients presenting to the emergency department with hip pain. AJR Am J Roentgenol 2012; 198(06): W581-8.
32. Karchevsky M, Schweitzer ME, Morrison WB, Parellada JA. MRI findings of septic arthritis and associated osteomyelitis in adults. AJR Am J Roentgenol 2004; 182(01): 119–22.
33. McQueen FM. The use of MRI in early RA. Rheumatology (Oxford) 2008; 47(11): 1597–99.
34. Vander Cruyssen B, Muñoz-Gomariz E, Font P, et al; ASPECTREGISPONSER-RESPONDIA working group. Hip involvement in ankylosing spondylitis: epidemiology and risk factors associated with hip replacement surgery. Rheumatology (Oxford) 2010; 49(01): 73–81.

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REVIEW

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The Greek challenging reality of fragility fractures and inspirations for the future

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ABSTRACT

A different type of pandemic has been challenging the last decades the global health care systems. These are the fragility fractures, which are linked with increased morbidity, mortality and impairment of the quality of life of the elderly. National health care systems are burdened with treating these demanding patients, consuming large amounts of resources, financial and medical. This fact has led to the need for more optimal utilisation of the existing resources.

Patients with fragility fractures have multiple co-morbidities and optimally they need a multi-disciplinary approach for their management. For this a team of healthcare professionals has to be formed, involving orthogeriatricians, orthopaedics, physiotherapists, anaesthetists, nurses, dieticians and many more. Another important aspect of this problem is the primary and secondary prevention of the fragility fractures, mainly by diagnosing and treating the osteoporosis and preventing the falls of the elderly population.

The Fragility Fracture Network is a global organisation with the vision to create a society where the elderly receives high quality care and have improved quality of life. Its aim is to spread the information and the means to achieve this goal globally. In the present article we discuss all of these aspects focusing on the local challenges of the Greek health care system and present some inspirations for the future.

KEY-WORDS: Fragility fractures, Osteoporosis, Orthogereatrics, Falls prevention, multidisciplinary approach

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The Challenge

The challenge that the health care professionals face in the modern health care is the increasing number of patients with fragility fractures. These fractures are always associated with osteoporosis, recurrent falls and the increasing age of the global population.

Osteoporosis is a condition where the bone density is reduced and the micro-structure of the bones is disrupted, leading to increased risk of fracture (1) (2).

Fragility fractures are low energy fractures, usually caused by simple falls. The bone due to osteoporosis is mechanically weak and breaks with minimal force, force that under normal circumstances would not cause a fracture.

Older studies shown that in the developed world, one in three women and one in five men, aged over 50 years, will sustain at least one fragility fracture during their remaining lifespan (3). A recent study conducted in six different European countries, shown that during 2017, 2.7 million fragility fractures occurred. Two thirds of these fractures occur in women and through projections the total number of fragility fracture is expected to raise by 23% by 2030 (4). Fragility fractures can occur in several parts of the skeleton with most common site being the fractures of the femoral neck (19.6%), vertebrae (15.5%), distal radius and proximal end of the humerus (17.9%) (4).

Fragility fractures are linked with increased morbidity and mortality, hospital readmissions, further fractures which are linked with increased financial and social burden around the world.

Primary prevention of fragility fractures includes population screening, diagnosis and treatment of patients with osteoporosis associated with increased risk of fracture. International associations such as IOF (International Osteoporosis Foundation) are updating frequently their guidelines. In Greece similar associations such as ELIOS (Greek Institute of Osteoporosis) and EEMMO (Greek Association of Bone Metabolism), update regularly the guidelines for the Greek population (5,6).

The diagnosis of osteoporosis is established with the measurement of the bone density, but for the start of appropriate anti-osteoporotic therapy the health care professional has to consider also other parameters such as the vitamin D levels, other medical conditions which affect the bone quality or the tendency and frequency of falls and the possible co-existing sarcopenia. Consequently, all patients with osteoporosis alongside with the anti-osteoporotic medication need to receive guidance for good nutrition and physical activity. Their medication for other medical conditions has to be reviewed as well, as some medication could be the cause factors for frequent falls.

Despite the increasing awareness globally about the importance of osteoporosis prevention and the devastating effects of fragility fractures, many studies around the world have shown that a really significant presentence of patients with fragility fractures do not receive treatment for osteoporosis or even never tested for (4,7–9). This significant treatment gap is present in Greece as well, as similar conclusions were drawn from studies of the Universities of Larissa and Thrace (10,11). These facts illuminate the need to increase the awareness of the medical professionals and the public about the importance of the osteoporosis screening and treatment. For this goal the role of the general practitioners and the family doctors is of paramount importance to raise the awareness of the public.

Another layer of the present challenges is the secondary prevention of these fractures. The health care professionals who are treating these patients with fragility fractures have to be vigilant and not lose the opportunity to start the anti-osteoporotic therapy even after the first fracture, preventing a future one.

The biggest challenge is the treatment of patients with fragility fractures of the hip, as these fractures are the most frequent and need increased resources to treat. These patients have multiple comorbidities and they are usually frail. Only a small fraction of them are fit, well and independent (12,13). Consequently these patients are more likely to develop complications, delayed rehabilitation and even increased mortality (14–17). Similar are the results in the Greek literature, with fragility fracture patients being significantly impaired pre-operatively lead-

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ing to poor clinical outcomes (18,19).

Many of the hip fractures patients need readmission to the hospital following treatment for fragility hip fractures, either due to worsening of their medical conditions or due to a new fragility fracture (20–22). Unfortunately a second fragility hip fracture is linked with increased mortality (23). It is evident that there is a need of a multidisciplinary approach to the treatment of these patients, with the view of a holistic approach of their medical conditions.

Inspirations

The fragility fracture network (FFN) is a global scientific organisation with the vision to develop a community where patients sustaining a fragility fracture, receive high quality standard treatment for the fracture, have standardised enhanced rehabilitation and continue their life with high quality without new fractures.

The aim of this network is to organise and improve the health care systems across the globe and promote the multi-disciplinary approach of these frail patients. Another aim of the organisation is to draw the attention of the health care professionals to the secondary prevention of the fragility fractures.

The Greek chapter of the fragility fracture network has the same vision and aims of action. According to the recent global call to action, we are all asked to contribute to the improvement of the care of the patients with fragility fractures using a multi-disciplinary approach to their treatment, based on the four base pillars of the FFN (24).

Pillar I: Multi-disciplinary approach of the patients with fragility fractures combined with orthogeriatric management.

Pillar II: Good rehabilitation after the treatment of the fragility fracture with the view to return to as normal activity levels as possible, independence and high quality of life.

Pillar III: Secondary prevention of new fragility fractures following a fragility fracture, by preventing new falls and improving the bone health of the patients.

Pillar IV: National collaborations and change of politics.

Pillar I: Multi-disciplinary approach of the treatment of fragility fractures

The traditional approach of patients with a fragility fracture depends on the type of fracture. This includes fractures that are treated conservatively and they do not need to be admitted in the hospital or they need operative treatment with short in-hospital stay. Usually these are fractures of the distal end of the radius, the proximal end of the humerus and the vertebral fractures. These type of fracture have low morbidity but present an important 'opportunity' to the health care professionals which has not to be lost. In addition to the fracture treatment the treating doctors can act accordingly in order to reduce the risks of a new fragility fracture.

Fragility fractures of the hip are treated surgically either with internal fixation of the fractured bone or with replacement of the head of the femur. Both have the intention to allow immediate unrestricted mobilisation of the patients. After the arrival of this type of patient in the hospital they should not stay longer than needed in the emergency department for unnecessary investigations or laboratory tests. The patient should be transferred to the wards as soon as safely possible, and depending on the medical co-morbidities, physical examination, blood test and other investigation results, an effort for medical optimization should be made. At the same time important interventions should be made such as the administration of the necessary fluids, the appropriate analgesia, the control of the cognitive state and the prevention of delirium.

Patients with hip fractures should be treated surgically as soon as possible and ideally within the first 36 hours of hospital admission. Any delay of surgery is linked with increased morbidity and mortality (25). If this goal is not achieved, in some healthcare systems the ministry is removing the founding to the hospitals. In order to achieve this goal in Greece, it is obviously necessary to inform and raise awareness to all involved parties on the treatment of these patients.

The treatment team of these patients includes traditionally the orthopaedic surgeons, the anaesthetists, the nurses, the physiotherapists and doc-

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tors from other specialties only when called. This is the current situation in many countries and also in Greece, while during the last decade this has changed in other countries. Based on what was previously mentioned regarding the condition of these patients (co-existing diseases, multiple drugs, possible sarcopenia or malnutrition, cognitive disorders etc.) it is obvious that in the treatment team other specialties should be involved as well, such as pathologists, psychiatrists, physiatrists and other health care professionals such as psychologists and dietitians. Systematic geriatrician or ortho-geriatrician involvement in the management of these patients both pre- and post-operatively has been implemented in some countries the last few years with very good results. In countries where the geriatrics as subspecialty is practically non-existent, this role can be fulfilled by internal medicine doctors. Their role can be of paramount importance for treating and preventing complications.

Pillar II: Rehabilitation of patients with fragility fractures

The rehabilitation of the patients following a fragility fracture has the aim to help the patients achieve independent function and good quality of life. Unfortunately, this cannot be achieved in all the patients, as the functional status of the patients before the fracture is most of the times the intended goal of the rehabilitation. Especially for the patients with hip fractures the rehabilitation should start immediately after surgery with the view of long-term good outcomes.

Early rehabilitation is defined as the rehabilitation that happens during the hospitalisation in the acute hospital, but the rehabilitation does not stop there. Each patient should be included in an individualised long term rehabilitation program, according to the individual patients' needs. Of course, the rehabilitation of a patient following a hip fracture should not be focusing only on the mobilisation of the patient, but on an overall rehabilitation of the patient, according to their needs. The ultimate goal should always be a good functional outcome and a good quality of life. The lack of rehabilitation medicine physicians and physiotherapists in the Greek healthcare system and the community, is making the situation even more challenging. Also, sometimes the patients may need special arrangements inside their housing or even be treated in specialised rehabilitation centres, which unfortunately are not enough throughout the country.

Pillar III. Secondary prevention of fragility fractures

Patients who sustained a fragility fracture are at high risk of sustaining a new one. Especially the first two years after the first fracture the risk is significantly greater (4,9,22).

These patients after the treatment of the first fracture (operative or conservative), should be checked and treated for underlying factors that led to the fragility fracture in the first place, such as osteoporosis, recurrent falls or visual impairment. This is called the secondary prevention and it is evident that this will need a multi-disciplinary approach as well. Unfortunately, in most countries there is a significant deficit in this approach, causing a significant treatment gap (4,9).

The Fracture Liaison Service (FLS) aims to systematically implement the secondary prevention in all patients with fragility fractures (26). Different models of organising and operating these services have been introduced in different countries with the type A having the best results (27,28). This service aims to identify and register all patients who have sustained a fragility fracture. Then these patients are referred for testing and treatment, following with regular monitoring and continuation of treatment. Results from the implementation of such services have led to a reduction of a new fragility fracture (29).

Testing, monitoring and treating the osteoporosis should be as in the primary prevention, with special focus on the patients' compliance.

Emphasis should be given on the prevention of the falls, as a fall is what will eventually lead to the fracture. Therefore, it is necessary to control and intervene at the causes of the falls. The falls may be related to neurological diseases, vision problems, sarcopenia or specific medication. Pre-

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venting the unnecessary polypharmacy can be the first step of reducing the falls (removing unnecessary medication or replacing with others with less side effects).

Sometimes modifications in the patient's home micro-environment may be necessary, to make it safer for their daily living. Removal of obstacles, carpets or adjustments of steps may be needed, alongside with special exercise and strengthening rehabilitation programs (30,31).

Pillar IV. Change of national politics

It is evident that for the implementation of the above three pillars many changes in the national healthcare systems should be made. Especially in our country many changes have to be made in the core of the healthcare system, such as the implementation of the geriatric specialty, the establishment of the Fracture Liaison Service, the improvement of the community services and the education of physiotherapists.

As members of the national fragility fracture network, we have the obligation to inform and educate ourselves and our work partners in the healthcare structures. Ultimately, sooner or later the diffusion of the idea will bring the intended results locally. This will eventually raise the awareness to the government as well, to make the necessary changes in the system itself, with the ultimate goal being to create a community where the older people receive high quality care with less fragility fractures and overall, a better quality of life.

REFERENCES

1. Gallagher J, Riggs B, Eisman J. Diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med. 1994;90(90):646–50.
2. Organization WH. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO study group [meeting held in Rome from 22 to 25 June 1992]. World Health Organization; 1994.
3. Kanis JA, Oden A, McCloskey E V, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012;23(9):2239–56.
4. Borgström F, Karlsson L, Ortsäter G, Norton N, Halbout P, Cooper C, et al. International Osteoporosis Foundation, Fragility fractures in Europe: burden, management and opportunities, Arch. Osteoporos. 15 (1)(2020 Apr 19) 59.
5. Makras P, Anastasilakis AD, Antypas G, Chronopoulos E, Kaskani EG, Matsouka A, et al. The 2018 Guidelines for the diagnosis and treatment of osteoporosis in Greece. Arch Osteoporos. 2019;14(1):1–10.
6. Διονυσιώτης Ι, Καψοκούλου Α, Σαμλίδη Ε, Παπαθανασίου Ι. Αναθεωρήσεις στην αποκατάσταση του ηλικιωμένου ασθενούς με κάταγμα ισχίου. Arch Hell Med Ellenikes Iatrikes. 2019;36(2).
7. Harvey NCW, McCloskey E V, Mitchell PJ, Dawson-Hughes B, Pierroz DD, Reginster J-Y, et al. Mind the (treatment) gap: a global perspective on current and future strategies for prevention of fragility fractures. Osteoporos Int. 2017;28(5):1507–29.
8. Lems WF, Raterman HG. Critical issues and current challenges in osteoporosis and fracture prevention. An overview of unmet needs. Ther Adv Musculoskelet Dis. 2017;9(12):299–316.
9. Ross BJ, Lee OC, Harris MB, Dowd TC, Savoie III FH, Sherman WF. Rates of osteoporosis management and secondary Preventative treatment after primary fragility fractures. JBJS Open Access. 2021;6(2).
10. Bougioukli S, Kollia P, Koromila T, Varitimidis S, Hantes M, Karachalios T, et al. Failure in diagnosis and under-treatment of osteoporosis in elderly patients with fragility fractures. J Bone Miner Metab. 2019;37(2):327–35.
11. Drosos G, Kougioumtzis I, Tottas S, Titsi Z, Ververidis A, Tilkeridis K. Elderly patients with hip fractures, treatment for osteoporosis, evidence for sarcopenia and malnutrition. A preliminary report. Therapy. 8:0.
12. Penrod JD, Litke A, Hawkes WG, Magaziner J, Koval KJ, Doucette JT, et al. Heterogeneity in hip fracture patients: age, functional status, and comorbidity. J Am Geriatr Soc. 2007;55(3):407–13.

VOLUME 74 | ISSUE 3 | JULY - SEPTEMBER 2023

13. Ranhoff AH, Holvik K, Martinsen MI, Domaas K, Solheim LF. Older hip fracture patients: three groups with different needs. BMC Geriatr. 2010;10(1):1–7.
14. Nordström P, Gustafson Y, Michaëlsson K, Nordström A. Length of hospital stay after hip fracture and short term risk of death after discharge: a total cohort study in Sweden. Bmj. 2015;350.
15. Folbert EC, Hegeman JH, Gierveld R, Van Netten JJ, Velde D van der, Ten Duis HJ, et al. Complications during hospitalization and risk factors in elderly patients with hip fracture following integrated orthogeriatric treatment. Arch Orthop Trauma Surg. 2017;137(4):507–15.
16. Pioli G, Bendini C, Pignedoli P, Giusti A, Marsh D. Orthogeriatric co-management–managing frailty as well as fragility. Injury. 2018;49(8):1398–402.
17. Pan L, Ning T, Wu H, Liu H, Wang H, Li X, et al. Prognostic nomogram for risk of mortality after hip fracture surgery in geriatrics. Injury. 2022;53(4):1484–9.
18. Makridis KG, Badras LS, Badras SL, Karachalios TS. Searching for the 'winner'hip fracture patient: the effect of modifiable and non-modifiable factors on clinical outcomes following hip fracture surgery. Hip Int. 2021;31(1):115–24.
19. Molla Moustafa R, Tottas S, Karaglani M, Tilkeridis K, Ververidis A, Drosos G. 3 rd Panhellenic Conference of Fragility Fracture Network Greece (FFN GR) " Necessity of Interdisciplinarity and Networking ." 2022;22(1):142–50.
20. Lizaur-Utrilla A, Serna-Berna R, Lopez-Prats FA, Gil-Guillen V. Early rehospitalization after hip fracture in elderly patients: risk factors and prognosis. Arch Orthop Trauma Surg. 2015;135(12):1663–7.
21. Elkassabany NM, Passarella M, Mehta S, Liu J, Neuman MD. Hospital characteristics, inpatient processes of care, and readmissions of older adults with hip fractures. J Am Geriatr Soc. 2016;64(8):1656–61.
22. Johansson H, Siggeirsdóttir K, Harvey NC, Odén A, Gudnason V, McCloskey E, et al. Imminent risk of fracture after fracture. Osteoporos Int. 2017;28(3):775–80.
23. Sobolev B, Sheehan KJ, Kuramoto L, Guy P. Excess mortality associated with second hip fracture. Osteoporos Int. 2015;26(7):1903–10.
24. Dreinhöfer KE, Mitchell PJ, Bégué T, Cooper C, Costa ML, Falaschi P, et al. A global call to action to improve the care of people with fragility fractures. Injury. 2018;49(8):1393–7.
25. Morrissey N, Iliopoulos E, Osmani AW, Newman K. Neck of femur fractures in the elderly: Does every hour to surgery count? Injury. 2017;48(6).
26. Mitchell PJ. Fracture liaison services: the UK experience. Osteoporos Int. 2011;22(3):487–94.
27. Ganda K, Puech M, Chen JS, Speerin R, Bleasel J, Center JR, et al. Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. Osteoporos Int. 2013;24(2):393–406.
28. Walters S, Khan T, Ong T, Sahota O. Fracture liaison services: improving outcomes for patients with osteoporosis. Clin Interv Aging. 2017;12:117.
29. Barton DW, Piple AS, Smith CT, Moskal SA, Carmouche JJ. The clinical impact of fracture liaison services: a systematic review. Geriatr Orthop Surg Rehabil. 2021;12:2151459320979978.
30. Skelton DA, Rutherford OM, Dinan-Young S, Sandlund M. Effects of a falls exercise intervention on strength, power, functional ability and bone in older frequent fallers: FaME (Falls Management Exercise) RCT secondary analysis. J frailty, sarcopenia falls. 2019;4(1):11.
31. Sherrington C, Fairhall NJ, Wallbank GK, Tiedemann A, Michaleff ZA, Howard K, et al. Exercise for preventing falls in older people living in the community. Cochrane database Syst Rev. 2019;(1).

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REVIEW

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Male Osteoporosis

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ABSTRACT

Osteoporosis is a chronic condition characterized by impaired bone remodelling that results in reduced bone mineral density, excessive bone loss and increased fracture risk. Osteoporosis in men is a fairly common condition, affecting 2-8% of men worldwide and more than 30% by the age of 85. Despite these compelling figures, the condition is under-estimated, under-diagnosed and under-treated. As a result and since the condition is almost always a "silent disease", the first presentation is often a fragility fracture. Although the mechanisms and conditions that cause osteoporosis in men are similar to those in women, male osteoporosis has some unique features. Risk factors in men are very heterogenous and hypogonadism represents a common underlying cause. Other common aetiological factors are poor vitamin D and calcium levels, chronic underlying haematological, gastroenterological and rheumatological conditions and use of offending drugs or substances. The evidence for diagnosis, screening and treatment of male osteoporosis is quite poor and most of the current knowledge is extrapolated from the female counterpart. Identification and prompt therapy of underlying conditions leading to osteoporosis is essential before additional anti-resorptive or anabolic treatment is considered. This review discusses the current evidence on pathophysiology, aetiology, diagnosis, screening and treatment of osteoporosis in men.

KEYWORDS: Male osteoporosis, osteoporosis, fracture risk, hypogonadism, pharmacological treatment

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Introduction

Osteoporosis is a common disease characterized by low bone mass with microarchitectural disruption and skeletal fragility, resulting in an increased risk of fracture. It is a leading cause of morbidity and mortality in older people as well as a significant financial burden to health systems worldwide.

Although the mechanisms and conditions that cause osteoporosis in men are similar to those in women, male osteoporosis has some unique features. Furthermore, epidemiological data and clinical experience suggest that osteoporosis in men is overlooked and often diagnosed late when an osteoporotic fracture has already occurred. Epidemiological surveys show that causes or contributing factors for osteoporosis can be identified in a significant percentage of men who have sustained an osteoporotic fracture, a finding illustrating the importance and value of early diagnosis and treatment in order to prevent the fracture.

The epidemiology, aetiology, clinical evaluation and treatment of osteoporosis in men will be reviewed in this chapter.

Epidemiology

In the developed world, 2% to 8% of males are affected by osteoporosis (1, 2). By the age of 85 years, over 30 percent of men will have a femoral neck T-score at or below -2.5 (3).

Although the fracture risk for men is lower compared to women, it remains significant: A 60-year-old man has a 25% risk of fracture (compared to 44% for a woman of the same age) (4). Furthermore, 1 in 5 men over the age of 50 will sustain an osteoporotic fracture (5).

Pathophysiology

The underlying mechanism in all cases of osteoporosis is an imbalance between bone formation and bone resorption. Low bone mass density can occur either when pubertal bone accretion is reduced resulting in suboptimal peak bone mass or when the rate of bone resorption is accelerated after peak bone mass is achieved: that takes place when osteoclasts are degrading the bone matrix faster than the osteoblasts are rebuilding the bone (6).

Pubertal bone accretion – achievement of peak bone mass

Peak bone mass is defined as the amount of bony tissue present at the end of the skeletal maturation and represents the maximum amount of bone an individual can attain during his life. The exact age of peak bone mass is unclear and can be affected by a number of factors (genetic, ethnic, hormonal, environmental). However, it probably occurs around the mid-thirties in most people.

In men, there is a dramatic increase of bone mass during puberty and the peak bone mass seems to be skeletal site-specific: it occurs around the age of 20 in the spine but later on in life in femur and radius (7).

One major factor is the *timing of onset of puberty*. The evidence suggests that there is a critical time window during which adequate concentrations of sex steroids is essential in order to achieve the optimal bone mass. Adult men with a history of constitutionally delayed puberty have decreased radial and spinal bone mineral density (8) as well as femoral bone density (9). Furthermore, this bone deficit does not seem to be corrected with age even when the steroids' levels are restored (8, 9).

Another major determinant of peak bone mass is intact production of *gonadal steroids*. The findings suggest that men with idiopathic hypogonadotrophic hypogonadism have lower cortical and trabecular bone mass (10) which is improved after correction of the hormonal deficit (11). Interestingly, *both androgens and oestrogens* have profound effect on peak bone mass in men.

Age-related bone loss

The imbalance between bone resorption and bone formation is responsible for bone loss after the peak bone mass is achieved. In men, trabecular bone loss appears to start prior to cortical bone loss and typically soon after the peak bone mass is achieved (12).

Aetiology

Male osteoporosis has historically been classified into two main categories, primary and secondary. Furthermore, primary osteoporosis can be further

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TABLE 1. Causes of osteoporosis in men

Endocrine conditions	Haematological conditions	Other conditions	Drugs and substances
Hypogonadism - delayed puberty	Multiple myeloma	Rheumatoid arhritis	Alcohol Tobacco
Diabetes mellitus (type 1, 2)	Mastocytosis	Renal and hepatic disease	Overreplacement with levothyroxine
Estrogen deficiency	Chronic anemia	Immobilisation	Glucocorticoids
Hypercortisolism (Cushing's)	**Gastrointestinal conditions**	Osteogenesis imperfecta	Heparin
Hyperthyroidism	Coeliac disease	Homocystinuria	Anticonvulsants
Hyperparathyroidism	Inflammatory bowel disease	Ehlers-Danlos syndrome	Chemotherapy Immunotherapy
Vitamin D deficiency	Malabsorption	Marfan syndrome	Protein pump inhibitors
Growth hormone deficiency	Cirrhosis	Eating disorders (anorexia nervosa)	Cyclosporine Anti-retrovirals Lithium

divided into i) involutional (or senile) osteoporosis, which occurs in men older than 70 years old with no other risk factor present, and ii) idiopathic osteoporosis, which occurs in patients younger than 70 years old without risk factors (13).

It should be noted however that, even though the underlying conditions that cause osteoporosis in men are similar to those in women, diagnostic search is often less vigorous and active in men, especially when no apparent risk factors are presents. Epidemiological surveys suggest that secondary causes can be identified in 40-60% of men who have severe osteoporosis or have sustained osteoporotic fractures (14, 15).

The medical conditions and risk factors for osteoporosis are summarised in Table 1. Some of these conditions and risk factors have been shown to be most predictive of osteoporotic fractures in men (16, 17, 18):

- Hypogonadism
- Low calcium and vitamin D levels
- Alcohol and tobacco use
- Low bone mineral density (BMD)
- Advancing age
- Prior history of fragility fracture
- Chronic glucocorticoid use and
- Parental history of hip fracture

Hypogonadism, both primary and secondary, is a common of osteoporosis in men. As previously discussed in this chapter, sex steroids play a key role in attainment of peak bone mass. Testosterone levels are also pivotal for maintenance of bone mass: the balance between bone formation and disruption is affected when testosterone levels fall < 200ng/dL as it seems that bone turnover increases at this point probably due to a parallel fall of serum oestrogen <15 pg/mL (19). It is well documented that low levels of oestradiol can increase the risk of fractures in men (20, 21) and this is probably be due to a deficit of testosterone transformation into oestradiol secondary to an aromatase enzyme dysfunction. Furthermore, hypogonadism lead to muscular atrophy, muscle mass loss and sarcopenia, factors further contributing to the risk of fractures.

Low serum vitamin D levels and poor calcium intake. The negative impact of low vitamin D levels on skeletal health is well-documented (22, 23). It is estimated that around 15% of male osteoporosis is caused by vitamin D deficiency (24). Suboptimal calcium intake (less than 1.200mg) is fairly common in el-

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TABLE 2. Diagnostic criteria for osteoporosis and osteopenia in men ≥ 50 years based upon DXA measurements (33, 34)

Category	Bone mass
Normal	BMD value within 1.0 SD of the young adult female reference mean (T-score ≥ -1.0)
Osteopenia	BMD more than 1.0 but less than 2.5 SD below the young adult female reference mean (−2.5 < T-score < −1.0)
Osteoporosis	BMD value 2.5 or more SD below the young adult female reference mean (T-score ≤ −2.5)
Severe osteoporosis	T-score ≤ −2.5 and one or more fragility fractures

TABLE 3. Laboratory work-up

In all cases	In most cases
Full blood count	Testosterone
Calcium (corrected for albumin too)	Parathyroid hormone
Phosphorus	Serum/urine protein electrophoresis
Erythrocyte sedimentation rate	Thoracic-lumbar spine X-ray (Face/Profile)
Creatinine	**In selected cases**
Alkaline phosphatase	24hour urinary free cortisol
25 (OH) Vitamin D	Serum tryptase
TSH	Anti-Tissue Transglutaminase antibodies
24hour urinary calcium	Bone turnover markers (P1NP or CTx)

derly men. There is some evidence from trials supporting the role of calcium and vitamin D correction in men (25, 26) in terms of bone mass. However, the evidence is less clear for risk of fractures (27).

Cigarette smoking and excessive *alcohol consumption* are associated with accelerated bone loss and fracture risk (28, 29, 30) although the underlying mechanism is not entirely clear.

Glucocorticoid excess, either endogenous or iatrogenic has a negative impact on male skeletal health. This is primarily due to the direct impact on the bone, but also due to the secondary hypogonadism and sarcopenia the steroids' excess can induce.

Clinical manifestations

Osteoporosis is a silent disease. It doesn't give any symptoms until a fracture occurs. Even then, some of these fractures are incidental findings on imaging done for other purposes as they can be asymptomatic. However, it should be noted that these men often have symptoms of the underlying condition (endocrine, gastrointestinal, connective tissue) that predisposes to osteoporosis therefore there should be a high degree of clinical suspicion.

Typical fragility fractures occur in the vertebral column, the ribs, the hip and the wrist. Men sustain fewer fragility fractures than women but their mortality is higher than women following a fragility fracture (31).

Diagnosis

In all men, irrespective of age, a clinical diagnosis of osteoporosis can be made in the presence of a fragility fracture. In all other cases, bone mineral density (BMD) assessment by dual-energy x-ray absorptiometry (DXA) should be performed. DXA is considered the gold standard test to diagnose osteoporosis in men ≥50 years even though it is not as well standardised as in postmenopausal women. There has been some controversy regarding the reference database for the calculation of T-scores in men. This is because it is documented that at any

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skeletal site T-score men have a lower absolute risk for fracture than women (32). Nonetheless, both the World Health Organisation and the International Society for Clinical Densitometry (ISCD) recommend the use of a female reference database for men over the age of 50, rather than using healthy young males as reference (33, 34). The diagnostic cut-offs are summarised in Table 2.

For younger men, aged <50 years, the diagnosis should not be made on BMD measurements alone (34). In these individuals, a low Z-score ≤-2.0 alone is not necessarily suggestive of osteoporosis, unless there is a history of a fragility fracture or a secondary cause for osteoporosis is present.

Value of screening – who should be tested for osteoporosis

Routine male population screening for osteoporosis based solely on age has been a controversial issue. However, an increasing number of groups, institutions and societies such as the National Osteoporosis Foundation (NOF), International Society for Clinical Densitometry (ISCD), and the Endocrine Society recommend BMD testing for all men older than 65 or 70 as it is probably a cost-effective approach. This approach is reflected on the guidelines for diagnosis and treatment of osteoporosis in Greece (35), which recommend routine DXA measurement in all men above the age of 65. In younger men, under the age of 65, BMD testing should be performed when i) there is clinical evidence of possible low bone mass (fragility fracture, evidence of osteopenia in other forms of radiography) and/or ii) there are underlying conditions that predispose to osteoporosis (as summarised in Table 1).

Fracture Risk Assessment Tool (FRAX)

The FRAX score represents a diagnostic tool used to evaluate the 10-year probability of fracture. It integrates clinical risk factors and BMD at the femoral neck to calculate the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture and can be used in men as an aid to the clinician, although its intervention thresholds increase the proportion of older men who are candidates for therapy compared to the WHO criteria (36).

Diagnostic approach to the man with osteoporosis for secondary causes

Detailed history should be obtained and thorough clinical examination should be performed in any man diagnosed with osteoporosis as they can potentially point towards a possible underlying diagnosis. The laboratory work-up is summarised in Table 3. It should be noted, that, if a rarer underlying condition is suspected, the relevant investigations should be performed.

Treatment

The treatment of osteoporosis in men consists of a) non-pharmacological measures, b) calcium and vitamin D correction, c) treatment of potential underlying causes and d) pharmacological measures.

Non-pharmacological measures

Lifestyle measures and modifications should be encouraged for men with osteoporosis. Weight bearing exercise has been shown to be beneficial by a) increasing muscular strength, b) potentially increasing bone mass, c) improving co-ordination thus preventing falls (37, 38, 39).

Calcium and vitamin D

The estimated daily calcium requirements are 1000mg for men aged 19-70 and 1200mg for men over the age of 70. Suboptimal serum calcium concentrations is a fairly common problem in elderly men, predominantly due to poor intestinal absorption (mainly due to polypharmacy) and reduced glomerular filtration therefore oral supplementation of 500-1000 mg/day of calcium carbonate is typically suggested.

Poor serum vitamin D concentrations is another common problem, especially amongst older men residing in institutions. Various dosing regimens have been proven to treat vitamin D deficiency in men. Most groups and societies suggest a daily vitamin D supplementation of 600-800 I.U.

Treatment of underlying conditions

Secondary causes can be identified in 40-60% of men who have severe osteoporosis or have sustained osteoporotic fractures (14, 15). This under-

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lines the importance of prompt and appropriate management of the underlying cause for osteoporosis (see Table 1 for the various causes). Offending medications should be discontinued if that's possible or have their dose reduced. There are some special considerations for some of these underlying conditions:

Hypogonadism is a common cause for osteoporosis in men. Proper assessment of the hypogonadism, calculation of the bioavailable/active testosterone and the decision to treat with testosterone balancing the cardiovascular risk is an important aspect of treatment of osteoporosis in hypogonadal men. There are quite convincing data that correction of the hormonal deficit in younger men with clear aetiology for the hypogonadism (e.g. pituitary tumour, Klinefelter syndrome) increases bone mass (40, 41, 42, 43). The evidence is less clear for older men as only a few small trials (44, 45, 46) and the "Testosterone Trials" (47) have examined the efficacy of testosterone on bone mass. The improvement on bone mass following administration of testosterone in older men is similar to the one observed in the placebo groups. It is probably recommended that the decision to treat with testosterone in older men should be taken on an individualised basis taking into account the cardiovascular risk as well.

An area of debate is whether testosterone replacement therapy is adequate in a man with osteoporosis due to hypogonadism or whether additional anti-osteoporotic treatment is necessary. In the absence of any strong clinical data, the recommendation of the Endocrine Society is to add an anti-osteoporotic pharmacological agent to the hypogonadal men with high fracture risk alone (48). Risk factors include a previous fragility fracture, severe osteoporosis (defined as T-score ≤-3.0), treatment with high dose glucocorticoids and persistent osteoporosis despite successful correction of the hypogonadism for at least 2 years.

Osteoporosis due to gastrointestinal diseases (commonly celiac disease or inflammatory bowel disease) is characterised by the low, and often very low, calcium and vitamin D concentrations and secondary hyperparathyroidism therefore these patients often require higher doses of calcium and vitamin D.

Glucocorticoid-induced osteoporosis is a relatively common cause of osteoporosis in men and is observed even with relatively low doses of exogenous steroids (equivalent to prednisolone 5-7.5 mg). The bone loss is more aggressive in the first months of treatment with steroids therefore it should be treated aggressively, particularly in those already at high risk for fracture.

Pharmacological measures

With regards to the pharmacological approach to osteoporosis in men, there are two questions: which patient to treat and what the treatment options are.

Whom to treat?

For hypogonadal men, the indications for additional to testosterone treatment have been discussed earlier in this chapter (see "Treatment of underlying conditions" section).

For eugonadal men, the indication for pharmacological treatment are: a) history of fragility fracture, b) established osteoporosis, c) osteopenia (48, 49).

Treatment options

Bisphosphonates is the first line treatment for most men with osteoporosis. Most groups suggest oral alendronate or risendronate as initial therapy (48, 50, 51) since randomized trials (52, 53, 54, 55, 56) have proven the efficacy and safety of these medications (down to eGFR 30-35 ml/min). When oral bisphosphonate is contraindicated or not tolerated, zolendronate can be used (57, 58).

Denosumab is a potent anti-resorptive agent and has a role for treatment of osteoporosis in men especially when a) bisphosphonates are not tolerated or not effective and b) the patient's renal function is poor (eGFR < 30-35 ml/min). It should be noted that denosumab has been shown to improve bone mass in men (59), but there are no data about fracture risk reduction.

Teriparatide has been shown to be effective in improving the spinal and femoral BMD in men (60).

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Similar results have been shown for *abaloparatide* (61), but none of these trials assessed fractures. In most guidelines, these agents are reserved for men with severe osteoporosis or men with osteoporosis and a new fracture or men who did not respond to previous treatment. It is crucial that treatment with these agents is always followed by an antiresorptive agent.

Romosozumab, an agent with mixed anabolic and antiresorptive action, has shown an improvement in spinal and total hip BMD in men (62). A

REFERENCES

1. Wade, S.W., Strader, C., Fitzpatrick, L.A. et al. Estimating prevalence of osteoporosis: examples from industrialized countries. Arch Osteoporos 9, 182 (2014).
2. Osteoporosis or Low Bone Mass in Older Adults: United States, 2017–2018; NCHS Data Brief, March 2021. Available at: www.cdc.gov/nchs/products/databriefs/db405.htm (Accessed on October 18, 2022).
3. Trajanoska K, Schoufour JD, de Jonge EAL, Kieboom BCT, Mulder M, Stricker BH, Voortman T, Uitterlinden AG, Oei EHG, Ikram MA, Zillikens MC, Rivadeneira F, Oei L. Fracture incidence and secular trends between 1989 and 2013 in a population based cohort: The Rotterdam Study. Bone. 2018 Sep;114:116-124.
4. Ji MX, Yu Q. Primary osteoporosis in postmenopausal women. Chronic Dis Transl Med. 2015 Mar 21;1(1):9-13.
5. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res. 2014
6. Robling AG, Bonewald LF. The Osteocyte: New Insights. Annu Rev Physiol. 2020 Feb 10;82:485-506.
7. Bonjour JP, Theintz G, Buchs B, Slosman D, Rizzoli R. Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. J Clin Endocrinol Metab. 1991 Sep;73(3):555-63.
8. Finkelstein JS, Neer RM, Biller BM, Crawford JD, Klibanski A. Osteopenia in men with a history of delayed puberty. N Engl J Med. 1992 Feb 27;326(9):600-4.
9. Finkelstein JS, Klibanski A, Neer RM. A longitudinal evaluation of bone mineral density in adult men with histories of delayed puberty. J Clin Endocrinol Metab. 1996 Mar;81(3):1152-5.
10. Finkelstein JS, Klibanski A, Neer RM, Greenspan SL, Rosenthal DI, Crowley WF Jr. Osteoporosis in men with idiopathic hypogonadotropic hypogonadism. Ann Intern Med. 1987 Mar;106(3):354-61.
11. Guo CY, Jones TH, Eastell R. Treatment of isolated hypogonadotropic hypogonadism effect on bone mineral density and bone turnover. J Clin Endocrinol Metab. 1997 Feb;82(2):658-65.
12. Riggs BL, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, McDaniel L, Amin S, Rouleau PA, Khosla S. A population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. J Bone Miner Res. 2008 Feb;23(2):205-14.
13. Gennari L, Bilezikian JP. New and developing pharmacotherapy for osteoporosis in men. Expert Opin Pharmacother. 2018 Feb;19(3):253-264.
14. Orwoll ES, Klein RF. Osteoporosis in men. Endocr Rev. 1995 Feb;16(1):87-116.
15. Riggs BL, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, McDaniel L, Amin S, Rouleau PA, Khosla S. A population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. J Bone Miner Res. 2008 Feb;23(2):205-14.
16. Scane AC, Francis RM, Sutcliffe AM, Francis MJ, Rawlings DJ, Chapple CL. Case-control study of the pathogenesis and sequelae of symptomatic vertebral fractures in men. Osteoporos Int. 1999;9(1):91-7.
17. Kanis JA, Oden A, Johansson H, Borgström F, Ström O, McCloskey E. FRAX and its applications to clini-

cal practice. Bone. 2009 May;44(5):734-43.
18. Lewis CE, Ewing SK, Taylor BC, Shikany JM, Fink HA, Ensrud KE, Barrett-Connor E, Cummings SR, Orwoll E; Osteoporotic Fractures in Men (MrOS) Study Research Group. Predictors of non-spine fracture in elderly men: the MrOS study. J Bone Miner Res. 2007 Feb;22(2):211-9.
19. Finkelstein JS, Lee H, Leder BZ, Burnett-Bowie SA, Goldstein DW, Hahn CW, Hirsch SC, Linker A, Perros N, Servais AB, Taylor AP, Webb ML, Youngner JM, Yu EW. Gonadal steroid-dependent effects on bone turnover and bone mineral density in men. J Clin Invest. 2016 Mar 1;126(3):1114-25.
20. Szulc P, Munoz F, Claustrat B, Garnero P, Marchand F, Duboeuf F, Delmas PD. Bioavailable estradiol may be an important determinant of osteoporosis in men: the MINOS study. J Clin Endocrinol Metab. 2001 Jan;86(1):192-9.
21. Barrett-Connor E, Mueller JE, von Mühlen DG, Laughlin GA, Schneider DL, Sartoris DJ. Low levels of estradiol are associated with vertebral fractures in older men, but not women: the Rancho Bernardo Study. J Clin Endocrinol Metab. 2000 Jan;85(1):219-23.
22. Diamond T, Smerdely P, Kormas N, Sekel R, Vu T, Day P. Hip fracture in elderly men: the importance of subclinical vitamin D deficiency and hypogonadism. Med J Aust. 1998 Aug 3;169(3):138-41.
23. Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, Knol DL, Lips P. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab. 2007 Jun;92(6):2058-65.
24. Looker AC, Mussolino ME. Serum 25-hydroxyvitamin D and hip fracture risk in older U.S. white adults. J Bone Miner Res. 2008 Jan;23(1):143-50.
25. Daly RM, Brown M, Bass S, Kukuljan S, Nowson C. Calcium- and vitamin D3-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. J Bone Miner Res. 2006 Mar;21(3):397-405.
26. Meier C, Woitge HW, Witte K, Lemmer B, Seibel MJ. Supplementation with oral vitamin D3 and calcium during winter prevents seasonal bone loss: a randomized controlled open-label prospective trial. J Bone Miner Res. 2004 Aug;19(8):1221-30.
27. Cranney A, Weiler HA, O'Donnell S, Puil L. Summary of evidence-based review on vitamin D efficacy and safety in relation to bone health. Am J Clin Nutr. 2008 Aug;88(2):513S-519S.
28. Moinuddin MM, Jameson KA, Syddall HE, Sayer AA, Martin HJ, Robinson S, Cooper C, Dennison EM. Cigarette smoking, birthweight and osteoporosis in adulthood: results from the hertfordshire cohort study. Open Rheumatol J. 2008;2:33-7.
29. Jutberger H, Lorentzon M, Barrett-Connor E, Johansson H, Kanis JA, Ljunggren O, Karlsson MK, Rosengren BE, Redlund-Johnell I, Orwoll E, Ohlsson C, Mellström D. Smoking predicts incident fractures in elderly men: Mr OS Sweden. J Bone Miner Res. 2010 May;25(5):1010-6.
30. Drake MT, Murad MH, Mauck KF, Lane MA, Undavalli C, Elraiyah T, Stuart LM, Prasad C, Shahrour A, Mullan RJ, Hazem A, Erwin PJ, Montori VM. Clinical review. Risk factors for low bone mass-related fractures in men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2012 Jun;97(6):1861-70.
31. Haentjens P, Magaziner J, Colón-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, Boonen S. Meta-analysis: excess mortality after hip fracture among older women and men. Ann Intern Med. 2010 Mar 16;152(6):380-90.
32. Cummings SR, Cawthon PM, Ensrud KE, Cauley JA, Fink HA, Orwoll ES; Osteoporotic Fractures in Men (MrOS) Research Groups; Study of Osteoporotic Fractures Research Groups. BMD and risk of hip and nonvertebral fractures in older men: a prospective study and comparison with older women. J Bone Miner Res. 2006 Oct;21(10):1550-6.
33. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ 3rd, Khaltaev N. A reference standard for the description of osteoporosis. Bone. 2008 Mar;42(3):467-75.
34. Adult Official Positions of the ISCD as updated in 2019 (available on iscd.org)
35. Guidelines for the diagnosis and management of osteoporosis, Hellenic Society for the Study of Bone Metabolism, updated 2018 (available at eemmo.gr)

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36. World Health Organization. WHO Fracture Risk Assesment Tool. Available from: http://www.shef.ac.uk/FRAX.
37. Kukuljan S, Nowson CA, Sanders KM, Nicholson GC, Seibel MJ, Salmon J, Daly RM. Independent and combined effects of calcium-vitamin D3 and exercise on bone structure and strength in older men: an 18-month factorial design randomized controlled trial. J Clin Endocrinol Metab. 2011 Apr;96(4):955-63.
38. Fortinsky RH, Iannuzzi-Sucich M, Baker DI, Gottschalk M, King MB, Brown CJ, Tinetti ME. Fall-risk assessment and management in clinical practice: views from healthcare providers. J Am Geriatr Soc. 2004 Sep;52(9):1522-6.
39. Body JJ, Bergmann P, Boonen S, Boutsen Y, Bruyere O, Devogelaer JP, Goemaere S, Hollevoet N, Kaufman JM, Milisen K, Rozenberg S, Reginster JY. Non-pharmacological management of osteoporosis: a consensus of the Belgian Bone Club. Osteoporos Int. 2011 Nov;22(11):2769-88.
40. Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal DI, Anderson EJ, Klibanski A. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. J Clin Endocrinol Metab. 1996 Dec;81(12):4358-65.
41. Benito M, Vasilic B, Wehrli FW, Bunker B, Wald M, Gomberg B, Wright AC, Zemel B, Cucchiara A, Snyder PJ. Effect of testosterone replacement on trabecular architecture in hypogonadal men. J Bone Miner Res. 2005 Oct;20(10):1785-91.
42. Finkelstein JS, Klibanski A, Neer RM, Doppelt SH, Rosenthal DI, Segre GV, Crowley WF Jr. Increases in bone density during treatment of men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 1989 Oct;69(4):776-83. 43. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Berman N, Hull L, Swerdloff RS. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab. 2004 May;89(5):2085-98.
43. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab. 2004 Feb;89(2):503-10.
44. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad JG Jr, Strom BL. Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab. 1999 Jun;84(6):1966-72.
45. Basurto L, Zarate A, Gomez R, Vargas C, Saucedo R, Galván R. Effect of testosterone therapy on lumbar spine and hip mineral density in elderly men. Aging Male. 2008 Sep;11(3):140-5.
46. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, Ellenberg SS, Cauley JA, Ensrud KE, Lewis CE, Barrett-Connor E, Schwartz AV, Lee DC, Bhasin S, Cunningham GR, Gill TM, Matsumoto AM, Swerdloff RS, Basaria S, Diem SJ, Wang C, Hou X, Cifelli D, Dougar D, Zeldow B, Bauer DC, Keaveny TM. Effect of Testosterone Treatment on Volumetric Bone Density and Strength in Older Men With Low Testosterone: A Controlled Clinical Trial. JAMA Intern Med. 2017 Apr 1;177(4):471-479.
47. Watts NB, Adler RA, Bilezikian JP, Drake MT, Eastell R, Orwoll ES, Finkelstein JS; Endocrine Society. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012 Jun;97(6):1802-22.
48. LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, Siris ES. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022 Oct;33(10):2049-2102.
49. Qaseem A, Forciea MA, McLean RM, Denberg TD; Clinical Guidelines Committee of the American College of Physicians; Barry MJ, Cooke M, Fitterman N, Harris RP, Humphrey LL, Kansagara D, McLean RM, Mir TP, Schünemann HJ. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med. 2017 Jun 6;166(11):818-839.
50. Papaioannou A, Morin S, Cheung AM, Atkinson

S, Brown JP, Feldman S, Hanley DA, Hodsman A, Jamal SA, Kaiser SM, Kvern B, Siminoski K, Leslie WD; Scientific Advisory Council of Osteoporosis Canada. 2010 clinica practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ. 2010 Nov 23;182(17):1864-73.

51. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, Adami S, Weber K, Lorenc R, Pietschmann P, Vandormael K, Lombardi A. Alendronate for the treatment of osteoporosis in men. N Engl J Med. 2000 Aug 31;343(9):604-10.
52. Ringe JD, Faber H, Dorst A. Alendronate treatment of established primary osteoporosis in men: results of a 2-year prospective study. J Clin Endocrinol Metab. 2001 Nov;86(11):5252-5.
53. Ringe JD, Faber H, Farahmand P, Dorst A. Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. Rheumatol Int. 2006 Mar;26(5):427-31.
54. Ringe JD, Farahmand P, Faber H, Dorst A. Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. Rheumatol Int. 2009 Jan;29(3):311-5.
55. Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD. Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. J Bone Miner Res. 2009 Apr;24(4):719-25.
56. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S; HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007 Nov 1;357(18):1799-809.
57. Boonen S, Reginster JY, Kaufman JM, Lippuner K, Zanchetta J, Langdahl B, Rizzoli R, Lipschitz S, Dimai HP, Witvrouw R, Eriksen E, Brixen K, Russo L, Claessens F, Papanastasiou P, Antunez O, Su G, Bucci-Rechtweg C, Hruska J, Incera E, Vanderschueren D, Orwoll E. Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med. 2012 Nov 1;367(18):1714-23.
58. Orwoll E, Teglbjærg CS, Langdahl BL, Chapurlat R, Czerwinski E, Kendler DL, Reginster JY, Kivitz A, Lewiecki EM, Miller PD, Bolognese MA, McClung MR, Bone HG, Ljunggren Ö, Abrahamsen B, Gruntmanis U, Yang YC, Wagman RB, Siddhanti S, Grauer A, Hall JW, Boonen S. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. J Clin Endocrinol Metab. 2012 Sep;97(9):3161-9.
59. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, Kaufman JM, Clancy AD, Gaich GA. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res. 2003 Jan;18(1):9-17.
60. Czerwinski E, Cardona J, Plebanski R, Recknor C, Vokes T, Saag KG, Binkley N, Lewiecki EM, Adachi J, Knychas D, Kendler D, Orwoll E, Chen Y, Pearman L, Li YH, Mitlak B. The Efficacy and Safety of Abaloparatide-SC in Men With Osteoporosis: A Randomized Clinical Trial. J Bone Miner Res. 2022 Dec;37(12):2435-2442.
61. Lewiecki EM, Blicharski T, Goemaere S, Lippuner K, Meisner PD, Miller PD, Miyauchi A, Maddox J, Chen L, Horlait S. A Phase III Randomized Placebo-Controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men With Osteoporosis. J Clin Endocrinol Metab. 2018 Sep 1;103(9):3183-3193.

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REVIEW

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Obesity and osteoporosis

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ABSTRACT

Osteoporosis is the most common skeletal disease and a major public health problem. It affects around 1/3 of postmenopausal women, an incidence that is expected to double in the next thirty years due to the increase in life expectancy. Besides a significant increase in morbidity and mortality, osteoporosis and its complication i.e. the low energy fracture, also result in a considerable and continuously growing economic burden for healthcare systems. Understanding the factors involved in the manifestation of the disease and its complications is crucial for the development of disease prevention and treatment programs. On the other hand, obesity has become a global epidemic and obesity related medical conditions also infer a tremendous economic cost. The relationship between obesity and bone metabolism is complex and not fully understood. Several mechanical, biochemical and hormonal mechanisms have been suggested to explain the association between the adipose tissue and bone diseases. Most studies indicate a positive correlation between Body Mass Index (BMI) and bone density. However, the effect of obesity on the bone is probably not favourable in terms of skeletal micro-architecture, whereas low-grade systemic inflammation and specific peptides and adipokines seem to play a crucial role. The study of these factors and the interpretation of the events arising from the interaction between adipose tissue and bone metabolism seem to constitute an emerging field of research in the area of bone metabolism.

KEYWORDS: Adipose Tissue, Bone Mineral Density, Obesity, Overweight, Skeletal Microarchitecture

Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and progressive deterioration of the bone microarchitecture. Its main consequence is fragility of the bones and increased risk of low energy fractures [1,2]. Osteoporosis affects at least 200 million people globally, with high health cost involved [3]. In the US alone, osteoporosis is responsible for 1.3 million fractures, with 500,000 vertebral, 250,000 hip and 240,000 wrist fractures, costing $10 billion per annum with increasing prevalence and cost [4]. Its prevalence is expected to increase and by 2040 the relevant cost is expected to rise by 100–200% [5].

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Obesity represents the most common metabolic disease. It is characterised by increased body weight and especially an excess of adipose tissue. BMI is an imperfect, but a widely used measure of obesity as it provides a crude but easily estimated evaluation of the severity of this condition. It is defined as a person's height in kilograms divided by the square of his/her height in meters (kg/m^2). The World Health Organisation (WHO) defines obesity as a BMI of 30 kg/m^2 or higher, while a person with a BMI of 25-30 kg/m^2 is considered as overweight. Obesity has become a major health issue and a global epidemic. Its worldwide prevalence has been doubled in the last three decades [6]. It represents a serious public health issue alongside a major health risk factor for the individual. It is estimated that around 13% of adults are obese [7], whereas the combined overweight and obese individuals account for the majority of the adult population in some Western countries. Furthermore, alarming rates of obesity and overweight are observed in children [8]. Presence of obesity is strongly associated with several metabolic diseases including diabetes mellitus type 2 (T2DM), hyperlipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD), and furthermore with cardiovascular events and certain types of cancer.

The skeleton is tasked with ensuring two main functions. Firstly, to support, protect and facilitate soft tissue function (structural role) and secondly, to be a reservoir of calcium salts, from which the body draws calcium when it is in poverty due to reduced intake or increased losses (metabolic role). From the structural point of view, the size and strength of the skeleton must be proportional to the mass of soft tissues to serve its purpose. Regarding its function as a reservoir, there is a mechanism that releases calcium during periods of reduced intake or losses and moves calcium to the skeleton during periods of abundance. In order to exert both these functions, the skeleton utilizes a number of hormones and peptides. Both roles of the skeleton, i.e. supporting and storage, are based on the control of skeletal homeostasis, while it appears that body weight, and in particular adipose tissue, plays a leading role.

Adipose tissue is nowadays considered an endocrine gland, secreting numerous peptides collectively characterized as lipokines, rather than a simple fat store. Lipokines are currently a field of intensive research. The common evolutionary path of adipocytes and osteoblasts themselves, which originate from the same parenchymal stem cell, is of great interest because many of the mechanisms that determine the evolution of these cells in one direction or the other are common and could be common therapeutic goals for the treatment not only of metabolic bone diseases but also of the other obesity-related metabolic diseases that were mentioned above.

The interrelation between the skeletal and adipose tissues is complex, dynamic and not fully clarified yet. Various molecular pathways have been explored by which adipose tissue communicates and interacts with the skeleton. These pathways include several factors such as leptin, adiponectin, resistin, myokines, pro-inflammatory cytokines, and vitamin D. Additionally, the bone tissue affects metabolic parameters, including body weight control, through bone-derived factors, such as osteocalcin and osteopontin. In any case, the interplay between the adipose tissue and the skeleton is both mechanical and metabolic.

A. METABOLIC ASSOCIATION

Vitamin D

The impact of suboptimal vitamin D concentrations on the musculoskeletal system is well-documented and vitamin D deficiency is associated with osteoporosis. Vitamin D deficiency is quite common among obese adults. In particular, serum 25-hydroxy-vitamin D (25OHD) concentrations are about 20% lower in obese people compared with individuals of normal weight. Furthermore, serum 25OHD is inversely associated with body weight, BMI and fat mass [9, 10, 11, 12].

An important parameter with clinical implications is that restoration of vitamin D levels is much more difficult in obese compared to normal weight individuals [13, 14]. This is likely due to i) sequestration of vitamin D in the fat stores and ii) co-existent secondary hyperparathyroidism in obese adults. The clinical implication of this issue is that often considerably higher cumulative doses of vitamin D are required to achieve optimal levels in these indi-

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viduals.

Interestingly, although vitamin D levels have been shown to be persistently lower in obese adults, which theoretically would lead to lower BMD predominantly through reduced calcium absorption, studies have demonstrated that adults with obesity seem to have lower bone turnover compared with normal weight, and higher BMD with thicker and denser cortices [15]. This paradoxical phenomenon is not fully understood yet. Some theories support that obese individuals develop compensatory mechanisms whereas other studies hypothesize that fat may serve as reservoir for vitamin D, however, none of these theories has not been proven.

Oestrogens

Oestrogens are steroid hormones that have a key role in the maintenance of skeletal homeostasis exerting a protective effect by promoting bone formation and reducing bone resorption. Adipose tissue is one of the major sources of aromatase, an enzyme which synthesises oestrogens from androgen precursors. Obese post-menopausal women have been shown to have higher serum concentrations of oestrogens compared with non-obese controls [16]. Even though oestrogens are not the sole regulator of skeletal homeostasis, this difference can possibly explain, at least in part, the increased BMD observed in obese women (alongside the increased mechanical loading, which is discussed below).

High fat diet

One persistent finding in animal models of obesity is the reduced quality (increased porosity – poor microarchitecture) despite the increased bone mass. Especially high fat diet induced obesity is associated with increased bone quantity (larger bone size and mineral content) but decreased bone quality (lower size-independent mechanical properties) [17] as well as increased bone marrow adiposity [18]. It seems likely that bone microarchitecture is adversely affected leading to reduced bone quality.

Bone marrow adiposity and osteoporosis

A common progenitor, a pluripotential, bone marrow-derived mesenchymal stem cell (BMSC) gives rise to both adipocytes and osteocytes [19]. In fact, this stem cell has an equal propensity for differentiation into osteocytes or adipocytes or a number of other cell types (including endothelial, fibroblasts, chondrocytes). This differentiation is a complex process controlled by several transcription factors. The process, although characterised by plasticity, is irreversible once it has been completed [20]. A plausible mechanism that could lead to osteoporosis is that of switching of the differentiating process to adipocytes rather than osteocytes. This phenomenon is naturally observed with advancing age, but it has been described in generalised obesity and post-menopausal osteoporosis [21].

The factors involved in this process are not yet fully understood, with oestrogens [22] and peroxisome proliferator activated receptor-γ (PPARγ) [23] described in some studies as the possible parameters affecting the differentiation process.

In conclusion, emerging data over the last years have given rise to the hypothesis that fat infiltration of the bone marrow has been associated with osteoporosis [24].

Leptin

Leptin is a cytokine-like hormone, produced primarily by the adipocytes. It plays a key role in maintaining long-term energy and appetite control. Its effects on energy and appetite are exerted primarily on hypothalamus. Leptin concentrations are typically elevated in obesity, which represents a leptin-resistant condition. The impact of leptin on bone metabolism is complex, likely both direct and indirect and yet poorly understood with conflicting results. Studies in human have reported both positive roles of leptin [25, 26, 27, 28] and profoundly negative ones [29, 30] on bone health. The heterogeneity of the results of leptin on the skeleton likely reflect the different designs of the various studies and is an area where further, well-designed studies are required.

Inflammatory cytokines (TNF-a and IL-6)

Emerging evidence suggests that inflammation significantly affects bone homeostasis, inducing

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osteoporosis. Numerous pro-inflammatory cytokines have been implicated in the regulation of osteoblasts and osteoclasts. It is clearly documented that obesity represents a chronic low-grade inflammation state with elevated concentrations of cytokines, in particular TNF-α and IL-6.

TNF-α, which is raised in obesity, induces bone loss through stimulation of osteoclastogenesis via a number of different mechanisms [24]: 1) activates NFκB leading to increased expression of activator of nuclear factor kappa-B ligand (RANK) and RANK ligand (RANKL), which promote bone resorption [31]. 2) reduces the production of osteoprotogerin (OPG), which is the natural inhibitor of RANKL, leading to higher RANKL concentrations and further osteoclastic activity [32]. 3) directly modulates the RANKL-induced signalling pathways, leading to a synergistic activity with RANKL, which promotes further osteoclastic resorption [33].

The strong inflammatory response in obese individuals, as demonstrated by the high levels of mainly TNF-α and to a degree of IL-6, may be, at least partly, responsible for the complicated relationship between obesity and osteoporosis.

Adiponectin

Low adiponectin concentrations are a feature of obesity [34]. Studies, both *in vitro* and *in vivo*, indicate that adiponectin has a positive role on bone mass by stimulating osteoblastogenesis and suppressing osteoclastogenesis [35].

Indirect effects through other metabolic diseases associated with obesity

Metabolic diseases, especially T2DM [36] but also NAFLD [37] and others have adverse effects on bone metabolism, and their increased prevalence in obese individuals may indirectly affect the skeleton. Furthermore, medications used to treat these conditions may positively or negatively affect the bone [38].

B. MECHANICAL ASSOCIATION

The mechanical interplay between the bone and adipose tissues includes two important aspects; the effect of the mechanical loading and the risk of falls.

Mechanical loading

The mechanostat theory, developed by Harold M. Frost [39], describes the mechanisms by which mechanical loading influences bone structure by changing the mass and architecture to provide a the necessary adaption. It is universally demonstrated, in practically all the relevant studies, that obese individuals have higher BMD than lean subjects. Furthermore, biochemical markers of bone turnover are lower in obese compared with normal weight individuals [40]. Excessive adipose accumulation imposes a greater static mechanical stress on bone, and it provides an important positive loading effect [41]. It is plausible that is not solely the effect of the passive loading, but also the fact that, in general, obese individuals have increased lean mass (along with fat mass) leading to the favourable effects on the bone of the increased muscle strain [42]. An important exception here is osteosarcopenia, i.e. coexistence of obesity with sarcopenia.

Bony tissue can detect the mechanical forces induced by external loading and produces a compensatory response resulting to formation of new bone. An important parameter, and area of research over the last few years, is the role of sclerostin in bone's adaptive response to mechanical loading. In non-loading states osteocytes secrete inhibitors of the Wnt pathway, predominantly sclerostin, thus favoring osteoclastogenesis [43]. Under loading, instead, the expression of sclerostin by the osteocytes is inhibited. As a result, the Wnt ligands are able to activate this pathway, which, leads to a direct stimulation of osteoblastogenesis and osteoblast migration [44, 45].

However, the overall relationship seems to be complex and possibly site-specific. For example, a study showed that bone size at the radius and the tibia estimated by high-resolution peripheral quantitative computed tomography (hr-pCT) does not differ between obese and normal-weight controls [15].

In summary, the loading factor is an important aspect of the bone-fat interplay exerting a favourable impact. However, it is not sufficient to fully explain the interaction.

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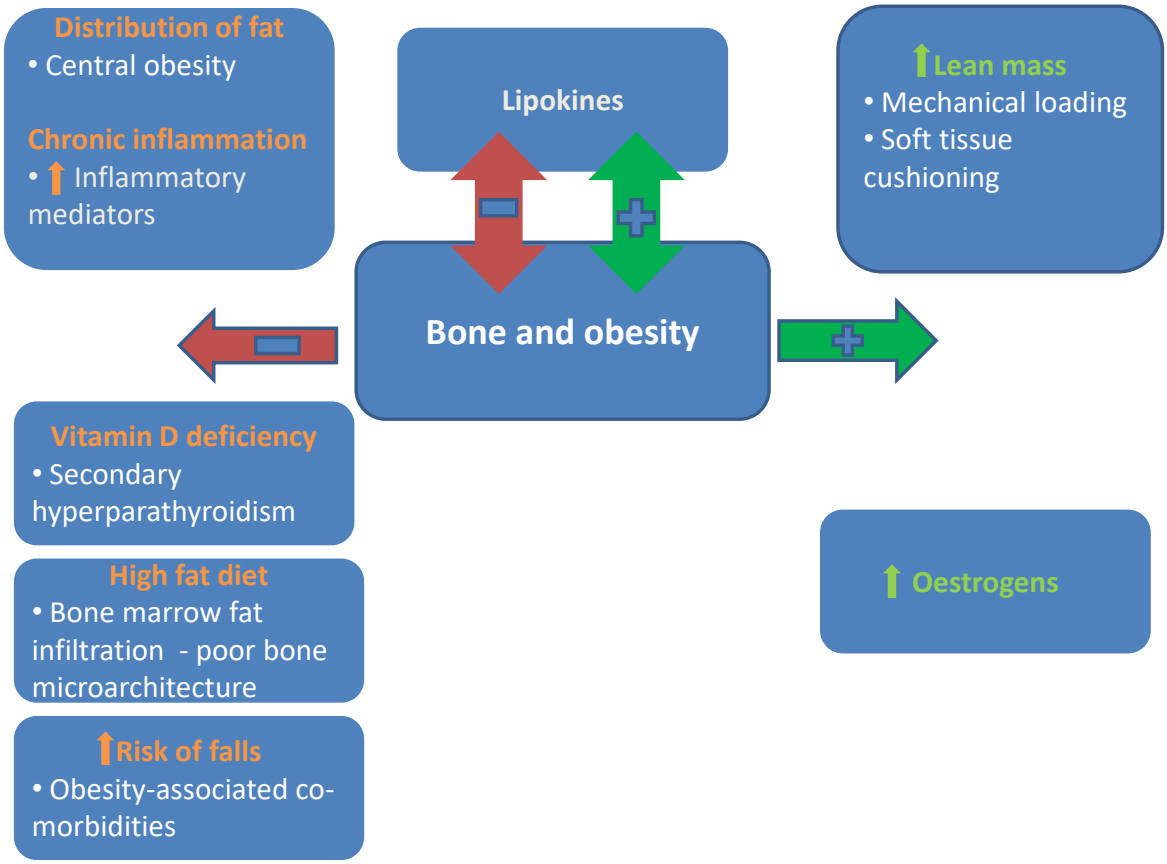

Obesity and risk of falls

Falls represent an important and independent risk factor for fractures. High incidence of falls has significant medical implications and results in high economic costs [46]. Several studies have showed that obese and overweight adults carry a higher risk of falls, the aetiology of which is multifactorial [24]:

i) Obesity causes or exacerbates important chronic conditions such as T2DM, cardiovascular disease, arthritis, autonomic dysfunction, orthostatic hypotension, sleep apnoea and hypertension. These metabolic conditions are independent risk factors for falls [47].

ii) Central adiposity compromises core stability and plays an independent role as a fall-related predictor in older women [48].

iii) Obesity is associated with loss of functional independence and reduced ability in performing daily tasks, such as standing up, walking unaided or climbing up stairs, which in turn increases the risks of falls [49].

iv) Finally, obesity adds pressure on the heels, which compromises postural stability and balance ability [50].

In the elderly population, obese individuals are more likely so sustain one or multiple falls compared to normal weight ones [51] leading to higher rates of hospitalisation [52] and reduced quality of life [53]. It is interesting, however, that the same meta-analysis [51] of 31 observational studies showed no evidence of an association between obesity and fall-related injuries in total. The most likely explanation is that the effect of falls in obese in fracture risk is site-dependent: Obesity seems to be protective against hip fracture in women but carries a high risk of fractures at other sites. Obese women sustain more fractures in the ankle [54], leg [55], humerus [56], and vertebral column [57] and fewer in the wrist [58], hip [56] and pelvis [56].

There have been two mechanisms proposed to ex-

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plain this site-specific discrepancy. First, the fact that the extra fat acts as a cushion protecting from hip and pelvic fractures [59]. Secondly, the pattern of falling appears to be different in obese individuals: they are more prone to sideward and backward falling, whereas normal weight individuals tend to fall forwards [60].

Conclusions

Bone and adipose tissues are both highly active metabolically and probably interact and affect each other but their association is highly complex and still not fully elucidated. They interplay through adipokines, oestrogens, inflammatory markers and bone derived metabolic factors.

Increased mechanical loading observed in obese individuals compared to their normal weight counterparts exerts a positive effect on bone. However, this probably is not the only effect. Increasing amount of evidence suggests that obesity may have a negative effect on fracture risk and that this effect is likely to be skeletal site-specific and age-dependent. Potential mechanisms contributing to that is the increased risk of falling among obese adults, the low-grade inflammation that accompanies obesity and the fat infiltration of bone marrow observed in such individuals.

A better understanding of the complex interplay between bone and fat may lead to the development of more specific molecular treatment targets and fracture prevention strategies.

REFERENCES

1. National Institutes of Health. Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy Osteoporosis prevention, diagnosis, and therapy. *JAMA* **2001**, *285*, 785–795
2. Kanis JA, Melton III LJ, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. *Journal of bone and mineral research.* 1994;9(8):1137–41
3. World Health Organization. Assessment of osteoporosis at the primary health care level:summary report of a WHO Scientific Group. *World Health Organization.* 2007
4. Osteoporosis or Low Bone Mass in Older Adults: United States, 2017–2018 Neda Sarafrazi, Ph.D., Edwina A. Wambogo, Ph.D., M.S., M.P.H., R.D., and John A. Shepherd, Ph.D., NCHS Data Brief ,No. 405, March 2021
5. US Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General*; US Department of Health and Human Services: Rockville, MD, USA, 2004.
6. World Health Organization Global. *Health Observatory, Obesity:situation and trends.* 2017
7. Obesity and Overweight. Available online: **https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight**
8. European Association for the Study of Obesity. *Facts &Statistics:Definitions of overweight and obese.* 2017
9. Samuel L, Borrell LN. The effect of body mass index on optimal vitamin D status in U.S. adults: the National Health and Nutrition Examination Survey 2001-2006. Ann Epidemiol 2013;23:409-414
10. Walsh JS, Evans AL, Bowles S et al. Free 25-hydroxyvitamin D is low in obesity, but there are no adverse associations with bone health. Am J Clin Nutr 2016;103:1465-1471.
11. Macdonald HM, Mavroeidi A, Barr RJ, Black AJ, Fraser WD, Reid DM. Vitamin D status in postmenopausal women living at higher latitudes in the UK in relation to bone health, overweight, sunlight exposure and dietary vitamin D. Bone 2008;42(5):996-1003.
12. Ardawi MS, Qari MH, Rouzi AA, Maimani

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AA, Raddadi RM. Vitamin D status in relation to obesity, bone mineral density, bone turnover markers and vitamin D receptor genotypes in healthy Saudi pre-and postmenopausal women. Osteoporosis international 2011;22(2):463-75

13. Rajakumar K, Fernstrom JD, Holick MF, Janosky JE, Greenspan SL. Vitamin D status and response to vitamin D3 in obese vs. non-obese African American Children. Obesity 2008;16(1):90-5.
14. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. The American journal of clinical nutrition 2000;72(3):690-3.
15. Evans AL, Paggiosi MA, Eastell R, Walsh JS. Bone density, microstructure and strength in obese and normal weight men and women in younger and older adulthood. Journal of Bone and Mineral Research 2015;30(5):920-8
16. Leeners B, Geary N, Tobler P, Asarian L. Ovarian hormones and obesity. Human Reproduction Update 2017;23(3):300-321.
17. Ionova-Martin SS, Do SH, Barth HD, Szadkowska M, Porter AE, Ager III JW, Ager Jr JW, Alliston T, Vaisse C, Ritchie RO. Reduced size-independent mechanical properties of cortical bone in high-fat diet-induced obesity. Bone 2010;46(1):217-25
18. Halade GV, El Jamali A, Williams PJ, Fajardo RJ, Fernandes G. Obesity-mediated inflammatory microenvironment stimulates osteoclastogenesis and bone loss in mice. Experimental gerontology. 2011 Jan 1;46(1):43-52.
19. Sekiya I, Larson BL, Vuoristo JT, Cui JG, Prockop DJ. Adipogenic differentiation of human adult stem cells from bone marrow stroma (MSCs). J Bone Miner Res 2004;19:256-64.
20. Schilling T, Kuffner R, Klein-Hitpass L, Zimmer R, Jakob F, Schutze N. Microarray analyses of transdifferentiated mesenchymal stem cells. J Cell Biochem 2008; 103:413-33
21. Menagh PJ, Turner RT, Jump DB, Wong CP, Lowry MB, Yakar S, Rosen CJ, Iwaniec UT. Growth hormone regulates the balance between bone formation and bone marrow adiposity. J Bone Miner Res 2010;25:757-68
22. Mani A, Radhakrishnan J, Wang H, Mani A, Mani MA, Nelson-William C, Carew KS, Mane S, Najmabadi H, Wu D, Lifton RP. LRP6 mutation in a family with early coronary disease and metabolic risk factors. Science. 2007; 315:1278-82.
23. Sekiya I, Larson BL, Vuoristo JT, Cui JG, Prockop DJ. Adipogenic differentiation of human adult stem cells from bone marrow stroma (MSCs). J Bone Miner Res 2004;19:256-64
24. Gkastaris K, Goulis DG, Potoupnis M, Anastasilakis AD, Kapetanos G. Obesity, osteoporosis and bone metabolism. J Musculoskelet Neuronal Interact. 2020 Sep 1;20(3):372-381. PMID: 32877973; PMCID: PMC7493444.
25. Pasco JA, Henry MJ, Kotowicz MA, Collier GR, Ball MJ, Ugoni AM, Nicholson GC. Serum leptin levels are associated with bone mass in nonobese women. The Journal of Clinical Endocrinology & Metabolism 2001; 86(5):1884-7.
26. Yamauchi M, Sugimoto T, Yamaguchi T, Nakaoka D, Kanzawa M, Yano S, Ozuru R, Sugishita T, Chihara K. Plasma leptin concentrations are associated with bone mineral density and the presence of vertebral fractures in postmenopausal women. Clinical endocrinology 2001;55(3):341-7.
27. Foo JP, Polyzos SA, Anastasilakis AD, Chou S, Mantzoros CS. The effect of leptin replacement on parathyroid hormone, RANKL-osteoprotegerin axis, and Wnt inhibitors in young women with hypothalamic amenorrhea. J Clin Endocrinol Metab. 2014 Nov;99(11):E2252-8. doi: 10.1210/jc.2014-2491. Epub 2014 Aug 22. PMID: 25148234
28. Mpalaris V, Anagnostis P, Anastasilakis AD, Goulis DG, Doumas A, Iakovou I. Serum leptin, adiponectin and ghrelin concentrations in post-menopausal women: Is there an as-

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sociation with bone mineral density? Maturitas. 2016 Jun;88:32-6. doi: 10.1016/j.maturitas.2016.03.004. Epub 2016 Mar 9. PMID: 27105694.
29. Ruhl CE, Everhart JE. Relationship of serum leptin concentration with bone mineral density in the United States population. Journal of Bone and Mineral Research 2002;17(10):1896-903.
30. Odabasi E, Ozata M, Turan M et al. Plasma leptin concentrations in postmenopausal women with osteoporosis. Eur J Endocrinol England 2000; 142:170-173.
31. Ootsuka T, Nakanishi A, Tsukamoto I. Increase in osteoclastogenesis in an obese Otsuka Long-Evans Tokushima fatty rat model. Molecular medicine reports 2015;12(3):3874-80.
32. Wei S, Kitaura H, Zhou P, Ross P, Teitelbaum SL. IL-1 mediates TNF-α-induce osteoclastogenesis. J Clin Invest 2005;115(2):282-90.
33. Cenci S, Weitzmann MN, Roggia C, Namba N, Novack D, Woodring J, Pacifici R. Estrogen deficiency induces bone loss by enhancing T-cell production of TNF-α. J Clin Invest 2000;106(10):1229-37
34. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudio K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T. The fat-derived hormone adiponectin reverses insulin resistance associated with body lipoatrophy and obesity. Nat Med 2001;7:941-6.
35. Jurimae J, Rembel K, Jurimae T, Rehand M. Adiponectin is associated with bone mineral density in perimenopausal women. Horm Metab Res 2005; 37:297-302.
36. Hofbauer LC, Busse B, Eastell R, Ferrari S, Frost M, Müller R, Burden AM, Rivadeneira F, Napoli N, Rauner M. Bone fragility in diabetes: novel concepts and clinical implications. Lancet Diabetes Endocrinol. 2022 Mar;10(3):207-220.
37. Vachliotis ID, Anastasilakis AD, Goulas A, Goulis DG, Polyzos SA. Nonalcoholic fatty liver disease and osteoporosis: A potential association with therapeutic implications. Diabetes Obes Metab. 2022 Sep;24(9):1702-1720.
38. Anastasilakis AD, Tsourdi E, Tabacco G, Naciu AM, Napoli N, Vescini F, Palermo A. The Impact of Antiosteoporotic Drugs on Glucose Metabolism and Fracture Risk in Diabetes: Good or Bad News? J Clin Med. 2021 Mar 2;10(5):996.
39. Frost HM. Bone's mechanostat: a 2003 update. Anat Rec A Discov Mol Cell Evol Biol. 2003 Dec;275(2):1081-101.
40. Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD. Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. Journal of Bone and Mineral Research 2000;15(8):1526-36
41. Tang H, He JH, Gu HB, Zhu K, Lu CJ, Sun LL, Gui GP, Deng FY, Lei SF. The different correlations between obesity and osteoporosis after adjustment of static mechanical loading from weight and fat free mass. J Musculoskelet Neuronal Interact. 2021 Sep 1;21(3):351-357. PMID: 34465673; PMCID: PMC8426647.
42. Addison O, Marcus RL, LaStayo PC, Ryan AS. Intermuscular fat: a review of the consequences and causes. International journal of endocrinology. 2014. Article ID 309570.
43. Gerosa L, Lombardi G. Bone-to-Brain: A Round Trip in the Adaptation to Mechanical Stimuli. Front Physiol. 2021 Apr 28;12:623893.
44. Delgado-Calle J, Sato AY, Bellido T. Role and mechanism of action of sclerostin in bone. Bone. 2017 Mar;96:29-37.
45. Galea GL, Lanyon LE, Price JS. Sclerostin's role in bone's adaptive response to mechanical loading. Bone. 2017 Mar;96:38-44.
46. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases

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and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380:2197-2223.
47. Mitchell RJ, Lord SR, Harvey LA, Close JC. Obesity and falls in older people: mediating effects of disease, sedentary behavior, mood, pain and medication use. Archives of gerontology and geriatrics 2015;60(1):52-8.
48. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1998;319:1701-1707
49. Vincent, HK, Mathews, A. Obesity and mobility in advancing age: mechanisms and interventions to preserve independent mobility. Curr Obes Rep 2013; 2:275-283.
50. Clark, BC, Manini TM. Functional consequences of sarcopenia and dynapenia in the elderly. Curr Opin Clin Nutr Metab Care 2010;13:271-276.
51. GR Neri S, S Oliveira J, B Dario A, M Lima R, Tiedemann A. Does obesity increase the risk and severity of falls in people aged 60 years and older? A systematic review and meta-analysis of observational studies. The Journals of Gerontology: Series A. 2019.
52. Himes CL, Reynolds SL. Effect of obesity on falls, injury, and disability. J Am Geriatr Soc 2012;60:124-129.
53. Fjeldstad C, Fjeldstad AS, Acree LS, Nickel KJ, Gardner AW. The influence of obesity on falls and quality of life. Dynamic Medicine 2008;7(1):4
54. King CM, Hamilton, GA, Cobb M, Carpenter D, Ford LA. Association between ankle fractures and obesity. J Foot Ankle Surg 2012;51:543-547.
55. Beck TJ, Petit MA, Wu G, LeBoff MS, Cauley JA, Chen Z. Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the Women's Health Initiative-observational study. J Bone Miner Res 2009; 24:1369-1379.
56. Prieto-Alhambra D, Premaor MO, Fina Aviles F, Hermosilla E, Martinez-Laguna D, Carbonell-Abella C, et al. The association between fracture and obesity is site dependent: a population-based study in postmenopausal women. J Bone Miner Res 2012;27:294-300.
57. Pirro M, Fabbriciani G, Leli C, Callarelli L, Manfredelli MR, Fioroni C, et al. High weight or body mass index increase the risk of vertebral fractures in postmenopausal osteoporotic women. J Bone Miner Metab 2010; 28:88-93.
58. Premaor MO, Ensrud K, Lui L, Parker RA, Cauley J, Hillier TA, et al. Risk factors for nonvertebral fracture in obese older women. J Clin Endocrinol Metab 2011; 96:2414-2421.
59. Bouxsein ML, Szulc P, Munoz F, Thrall E, Sornay Rendu E, Delmas PD. Contribution of trochanteric soft tissues to fall force estimates, the factor of risk, and prediction of hip fracture risk. J Bone Miner Res 2007;22:825-831.
60. Mignardot JB, Olivier I, Promayon E, Nougier V. Obesity impact on the attentional cost for controlling posture. PloS One 2010;5:e14387

READY - MADE CITATION

Gkastaris K, Anastasilakis AD. Obesity and osteoporosis. *Acta Orthop Trauma Hell* 2023; 74(3): 44-52.

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Spinal Cord Ischemia: A review of clinical and imaging features, risk factors and long-term prognosis

Vasiliki Batsou, Ioannis S Benetos, Ioannis Vlamis, Spiridon Pneumaticos

ABSTRACT

Spinal cord ischemia is a rare disorder carrying a high rate of morbidity. However, only a few case series concerning it have been published in the literature. The aim of this study was to determine the causes, the clinical characteristics, the functional outcomes and the prognostic indicators of spinal cord ischemia. For this reason, a review of the current literature was performed by following the PRISMA guidelines and by using the online PubMed database and the keywords "Spinal cord ischemia" and "Spinal cord infarction". Fourteen studies with a substantial total number of patients (526 patients) were finally included in this review, providing accurate and conductive results regarding spinal cord ischemia. The clinical presentation is nonspecific and characterized by rapid decline of function with a severe neurologic deficit. The cause remains unknown for half of the patients although multiple traditional cardiovascular risk factors are recognized. MRI is the imaging modality of choice for suspected spinal cord ischemia and a variety of characteristic MRI signs have been described such as the "pencil-like" zone and "owl's eye" sign. In contrast to cerebral ischemic infarction, in which guidelines for management are well-established, no consensus guidelines exist for the management of acute spinal cord ischemia.

Keywords: Spinal Cord Ischemia, Spinal Cord Vascular Diseases, Anterior Spinal Artery Syndrome, Posterior Spinal Artery Syndrome

Introduction

Spinal cord infarction (SCI) is an uncommon disorder that is considered a diagnostic challenge due to the variety of its clinical presentation. Its clinical signs are nonspecific, thus providing a challenging differential diagnoses and there is no consensus upon its management.

Before delving into the characteristics of spinal cord infarction, it is important to acknowledge the spinal cord's blood supply. The spinal cord is supplied by 3 longitudinal arteries: a single anterior spinal artery, which supplies the anterior two-thirds of the spinal cord and two, paired posterior spinal arteries, which are the primary blood supply to the posterior columns, dorsal grey matter and dorsal sensory columns. The entire blood supply to the cord is reinforced by numerous radiculomedullary or segmental medullary arteries. Segmental medullary arteries are the remnants of the multiple fetal segmental arteries and originate from the spinal branches of the ascending cervical,

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deep cervical, posterior intercostal and lumbosacral arteries. They penetrate the spinal canal through the intervertebral foramina and accompany the roots. The dominant and clinically most important segmental medullary/radiculomedullary artery is the artery of Adamkiewicz, also known as the great anterior radiculomedullary artery. [1] The artery of Adamkiewicz typically arises from the left posterior intercostal artery and is the only significant arterial supply feeding the anterior spinal artery along the lower thoracic, lumbar and sacral spinal cord (from T8 to the conus medullaris). [2] Injury to this artery can cause neurologic damage manifesting as fecal and urinary incontinence, impaired motor function and preserved sensory function. [3]

Considering this blood supply, spinal cord infarcts can occur in the territories of the anterior spinal artery (ASA) or posterior spinal artery (PSA), or both. [4] The most common clinical presentation of a spinal cord infarction is anterior spinal artery syndrome. The clinical manifestation includes bilateral loss of motor function and pain/temperature sensation, with relative sparing of proprioception and vibratory sense below the level of the lesion. The neurological deficits will manifest below the level of infarction due to the anatomical distribution of the spinal cord tracts affected. If the injury is at a high cervical level, dysfunction of the phrenic nerve may lead to respiratory failure. Clinical findings are usually bilateral due to the spinal cord supply by the anterior spinal artery. [5] In the case of incomplete spinal artery syndrome, when ischemia is localized at the level of the anterior horns, there is acute paraplegia without sensory abnormalities and without sphincter dysfunction. The ischemia of the spinal cord coming from infarction of the posterior spinal artery invokes loss of proprioception and vibratory senses below the level of the injury and total anesthesia at the level of the injury.

Spinal cord ischemia could be the result of low flow due to arterial hypotension, surgical injury to spinal arteries or embolic events. Thus it is useful to classify etiologies as spontaneous or periprocedural. However, in a significant share of patients the causative source cannot be identified.

Spontaneous causes of spinal cord ischemia include aortic pathology, atherosclerotic disease and degenerative spine disease[6] Other less common causes include embolic strokes from aortic atheroma, myxoma or infectious valvular vegetation. An abrupt motion when paired with large osteophytes and spinal stenosis can lead to acute cord ischemia. [7]

Iatrogenic causes of spinal cord ischemia account for at least 45% of all reported cord infarctions. [8] Aortic surgery is recognized as the highest risk factor, where spinal cord ischemia can occur during both cross-clamping and de-clamping. [9] The duration of cross-clamp time, pre-existing vascular risk factors and length of the repaired aortic segment contribute to the risk. Other less common causes of perioprocedural spinal cord infarction include orthopedic lumbar surgery, epidural steroid injection, intra-aortic balloon pump and lumbar epidural catheter placement.

Materials and Methods

The aim of this study was to determine the causes, the clinical characteristics, the functional outcomes and the prognostic indicators of spinal cord ischemia. For this reason, a review of the current literature was performed by following the PRISMA guidelines and by using the online PubMed database and the keywords "Spinal cord ischemia" and "Spinal cord infarction". Studies that were written in English related to SCI with the full text available were screened. Furthermore, the search was narrowed to studies published after 2000 to provide the most recent data and to case series studies. Case reports were excluded from the study. Finally, 14 papers were selected and included in the current study.

Inclusion criteria to the review were case studies written in English language. The primary search included 6474 articles. By excluding the articles prior to 2000, 5826 articles were found to contain the key words "spinal cord ischemia" and "spinal cord infarction". Furthermore, 5781 records were excluded for not being relevant with the topic of spinal cord ischemia or not having spinal cord ischemia as their main research theme. Subsequently, a scan of the articles' reference list was performed to check for more eligible articles to be included in the review. Case reports, reviews and animal studies were excluded. Following the above procedure, 14 articles were finally included in this review. (Table 1).

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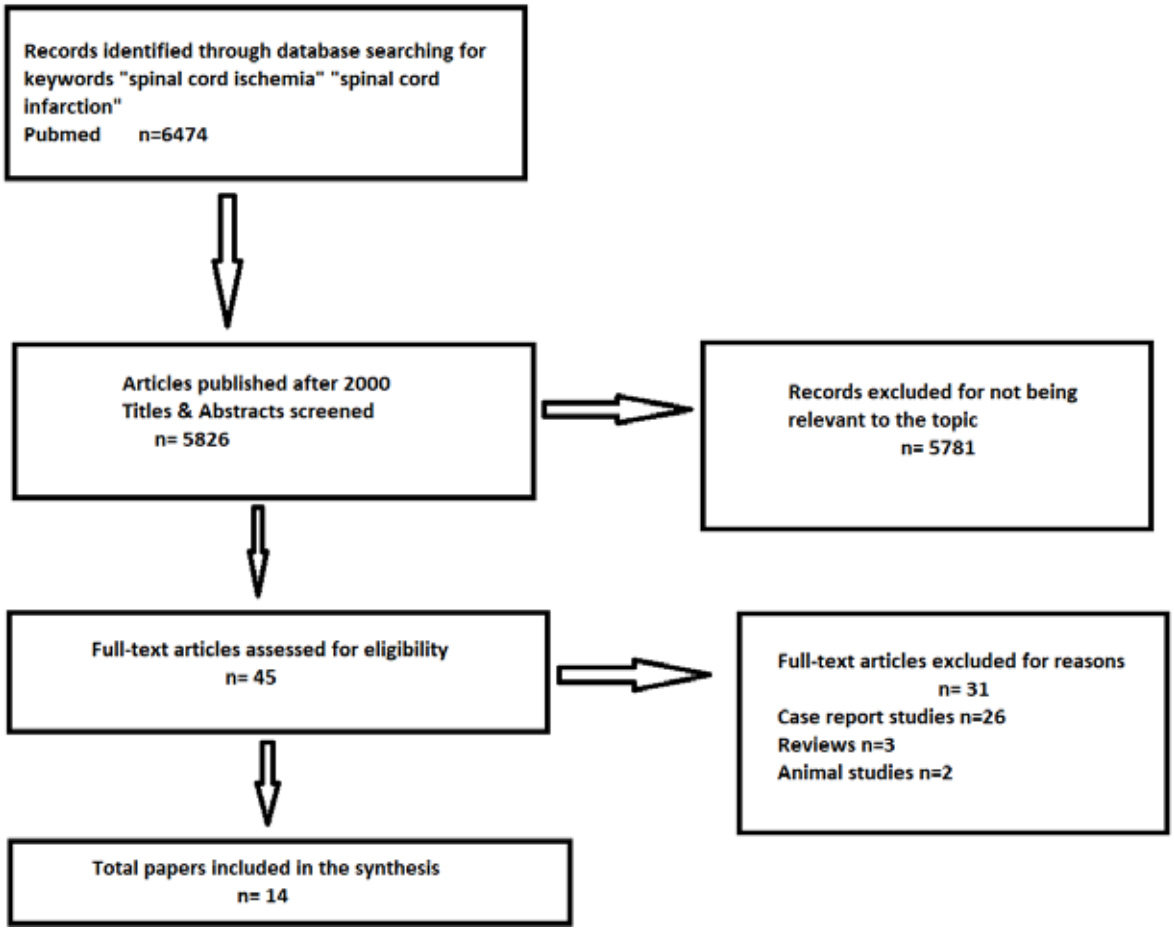

Table 1. Flowchart of the review

Results

Patient characteristics

Demographic data from the 14 studies included in this review were collected and averaged. There were a total of 526 patients suffering from SCI with an average age of 53.1 years (range 9-89 years). One study didn't specify the ratio between male and female patients. As a result, in a total of 444 patients (283 male and 161 female) the male to female ratio was 1.7.

Clinical Presentation

The clinical features of spinal cord ischemia include muscle weakness, sensory loss, pain, absent reflexes and hypotonia. Based on the results of 3 studies ([8], [10], [11]) including the larger number of patients and the most detailed clinical evaluation, it appears that at the initial examination muscle weakness was present at 87-99% of patients, sensory loss at 86-93% of patients and pain at 15-62% of patients. In the study of Cheng et al, [12] it was noted that pain was adjacent to the SCI level, ranging from back pain to neck pain. In a study by Zalewski et al [10], including 133 patients, the maximum neurologic deficit was observed in less than 4 hours at 55% of the patients, while 81% of them required a wheelchair for mobility and 86% had to be catheterized. Motor deficits were the most serious and prominent characteristics of spinal cord ischemia, affecting almost 100% of patients. Paraparesis was the most frequent presentation, followed by paraplegia and quadriplegia. Absent reflexes and hypotonia in the lower extremities occurred in 31-64% of patients.

Etiology

It is quite obvious that spinal cord ischemia re-

mains without identifiable cause in almost half the cases. In 24-74% of patients included in the studies of this review the cause of infarction remained unknown. Studies that were conducted in centers where spinal and aortic surgeries were performed included more postprocedural SCI cases. Data collected mainly in neurological departments depicted factors such as aortic dissection, hypertension and diabetes mellitus as contributing risk factors. In a recent study by Zalewski et al [10], including 133 patients, a history of one or more vascular risk factors was present in 101 patients (76%). The results of the study by Cheng et al [12], further reinforced this finding by identifying at least 1 vascular risk factor in 81% of patients and at least 3 vascular risk factors in 45,5% of patients. The risk factors for spinal cord ischemia as gathered from the 14 studies included in this review include hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, peripheral artery disease, previous stroke, and previous myocardial infarction.

Interestingly enough, the study of Novy et al, [13] showed that ischemic symptoms appeared immediately after a movement in 48% of patients (13 patients out of 27). In 7 patients this was a movement of the back, in 3 it was an arm movement and in the remaining 3 patients it was a Valsalva movement or a gait initiation. In all cases, the level of the spinal cord lesion corresponded to the level of mechanical stress in the spine.

MRI Findings

MRI is the examination of choice for the diagnosis of spinal cord ischemia [14]. In the acute phase, the use of intravenous contrast media can aid in the differential diagnosis between ischemia and inflammatory, tumoral or infectious diseases because usually enhancement is absent at this stage of ischemia. Nevertheless, in a study by Zalewski et al, 43% of spinal MRIs showed enhancement within the spinal cord parenchyma, after the administration of gadolinium[15] .

Another point to be noticed regarding MRI and spinal cord ischemia, is that 10% of patients with SCI may have a normal initial MRI despite a severe deficit.[15] Patients with severe impairments (ASIA A or B) are more likely to have a positive MRI for infarction than patients with less severe deficits. Indeed, 78% of the negative MRIs performed in the initial phase corresponded to patients whose deficits were mild to moderate (ASIA C and D). The ideal time for performing an MRI seems to be 3 to 4 hours after the onset of symptoms.

In the acute phase, ischemia presents as a restriction in diffusion-weighted imaging of the spinal cord. Classic findings of owl eyes (T2-hyperintensity restricted to anterior horns on axial views) or anterior pencil-like hyperintensity were found in 40,5-100% of cases. The cause for these findings is that the grey matter of the anterior horns exhibits the highest vulnerability to ischemia due to its high metabolic demands.

The posterior one-third of the spinal cord is more rarely involved. In the study of Novy et al, [13] including 27 patients, 37% of patients had anterior spinal artery patterns, 15% had anterior and 15% posterior unilateral patterns, 11% had central patterns and 7% had posterior spinal artery patterns. The most frequent location of infarction is the thoracic region. However, this is highly affected by the cause of spinal cord ischemia. If the infarction is postprocedural (after aortic or spinal surgery) the highest MRI abnormality will be most definitely located in the thoracic region followed by cervical and lumbar/conus regions.

Cerebrospinal fluid examination

The articles of Cheng et al, Zalewski et al, Novy et al, and Robertson et al, provided data regarding the evaluation of cerebrospinal fluid (CSF). In the study of Cheng et al, [12] including 22 patients, 7 patients were tested and 5 of them were found having elevated CSF protein concentrations without pleocytosis. Similarly, in the study of Novy et al, [13] 12 patients had an increased CSF protein concentration but no pleocytosis. In two studies by Zalewski et al, [10,15] 74% of the patients underwent a CSF examination and all demonstrated elevated protein levels. Only 8% had elevated nucleated cell count and 2% had supernumerary oligonuclonal bands. Finally, in the study of Robertson et al [8], including 27 patients, 44% of patients demonstrated elevated protein levels but normal cell count and only 7% demonstrated both elevated protein levels and cell counts.

Treatment

No treatment has been proven to reverse or treat ischemic spinal cord injury outside the surgical realm. Accordingly, there are no guidelines regarding spe-

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cific therapeutic regimens in patients who have suffered spinal cord ischemia. Preventive measures, such as avoiding prolonged and profound hypotension during aortic surgery or the use of spinal somatosensory evoked potentials during aneurysm surgery have shown to be effective in preventing cord ischemia. Correction of underlying risk factors such as hypertension, smoking, heart disease and diabetes mellitus is very important. Regarding the studies included in this review, only 5 out of 14 provided data upon treatment of spinal cord infarction. In the largest study included in this review, conducted by Zalewski et al [10], immunotherapy for a suspected immune-mediated condition was given to 56% of patients, blood pressure augmentation to 6% and lumbar drain to 6%. Anticoagulation was initiated in 8% of 135 patients and at least one antiplatelet agent was used in 68% of patients. Antiplatelet and anticoagulation therapies have proven to be the most used treatments, for cerebral infarction. The perioperative role of CSF drainage is recognized in thoracic and abdominal aortic surgery; however, its role in the treatment of spinal cord infarction has not been studied.

Outcomes

Based on the case series included in this review, the percentage of favorable functional outcome is around 40-50%. As stated, predictors of poor outcome include severe neurological impairment (ASIA A or B) on initial examination, absence of Babinski sign, presence of sensory level and longitudinally extensive MRI lesions [8]. In general, motor deficits showed a higher frequency of recovery than sensory or sphincter deficits. In the study of Qureshi et al [11], through studying the long-term follow-up data of 89 survivors, it was shown that 42% of patients were using a wheelchair, 26% were using a gait aid, 33% walked unaided, 54% needed a bladder catheter and 29% still had significant pain. The long-term mortality after spinal cord infarction can range from 9% to 23%, as shown in different studies and it varies depending on etiology. Mortality is higher for patients with spinal cord infarction related to surgery or aortic aneurysm and dissection with poor prognosis. [16]

Discussion

Spinal cord ischemia can cause a great diagnostic confusion, making this entity underrecognized and frequently misdiagnosed as transverse myelitis. Zalewski et al, after studying most of SCI cases included in the published literature, proposed some diagnostic criteria. Based on these, spinal cord infarction has 3 major criteria. [10] The first criterion is a clinical one, and is no other than the rapid development of severe neurologic deficits within the first 12 hours after the onset of symptoms. The second criterion is the MRI findings supporting the infarction and excluding the spinal cord compression and the third criterion is the non-inflammatory cerebrospinal fluid profile that differentiates SCI from infectious and inflammatory disorders. Based on these three parameters, patients were classified as having definite, probable, or possible spinal cord ischemia. To further validate these criteria, the authors applied them in a cohort of 280 patients with non-ischemic diagnoses. Only 3.2% of patients met the criteria for possible spinal cord ischemia and none for definite ischemia, suggesting that the presented criteria are highly specific. [10]

The symptoms of spinal cord infarction develop quickly and usually reach a maximum within 12 hours in 50% of patients and within 72 hours in almost all patients. The clinical presentation depends on the vascular territory involved and the severity of the impairment varies widely from paraplegia to minor weakness.[4] Different clinical subtypes have been recognized: anterior and posterior spinal artery syndrome due to radicular territory infarction, and central and transverse infarctions due to general spinal cord hypoperfusion. Consistent with its functional neuroanatomy, ASA syndrome typically presents with abrupt onset of bilateral weakness, sudden back pain, flaccid paraplegia, loss of pain and temperature sensation below the level of the lesion, and autonomic dysfunction involving the bowel and the bladder. In ASA syndrome there is a sparing of proprioception and vibration sense. The posterior spinal artery syndrome leads to ipsilateral loss of light touch, vibration and proprioception while mostly sparing motor function. The PSA syndrome is usually unilateral and less severe, due to the presence of two posterior spinal arteries. Moreover, the central spinal infarction includes bilateral spinothalamic sensory deficit with sparing of the posterior columns. Motor deficits and sphincter

dysfunction are usually absent. The transverse medullary infarction provides a rare presentation of sudden paraplegia/paraparesis, with complete sensory loss and autonomic dysfunction.

Diffusion-weighted magnetic resonance imaging seems to be the most reliable diagnostic tool for spinal cord ischemia. [17]However, it is technically challenging due to important limitations. The bone enclosing the spine causes magnetic field distortions and also the motion distortion caused by respiration, CSF, and arterial pulsation, as well as swallowing can result in distorted images.[18] The classical MRI findings in spinal cord ischemia are pencil-like hyperintensities from the involvement of anterior horn cells and on axial imaging this appears as two bright dots, the so-called owl eyes' sign. However, these changes are not specific and it is often difficult to distinguish SCI from other causes of acute non-compressive myelopathies based on MRI alone.

In their study, including 24 patients, Mawad et a,l [19] suggested that MRI lesions start in the anterior horns of the gray matter and progress to the posterior horns. They made a correlation between the presence of owl's eyes signs and motor deficit outcome. Patients with owl's eye signs usually retained partial motor function and had better outcomes than those with diffuse lesions involving the adjacent white matter. However, in the early stages the extent of the infarct can be difficult to be defined and this correlation hasn't been proven by other studies in this review.

Nonetheless, the absence of proprioceptive impairment at onset was associated with a better outcome. In anterior spinal artery syndrome, when there is proprioceptive impairment, it is suggestive of a more extensive infarct which involves the inner part of the dorsal columns and the posterolateral part of the lateral columns. The long-term outcome can remain poor in patients with complete or nearly complete syndromes, but the optimistic finding is that delayed functional recovery is possible and not infrequent. Half of surviving patients unable to walk after the onset of spinal infarction were able to walk on follow-up and even in patients with severe deficits, substantial functional recovery may occur over time. [20]

Regarding the treatment of spinal stroke, there are no clear guidelines. Immunotherapy, anticoagulant and antiplatelet therapy, and lumbar drain have been used. However, Seze et al, [21] in their retrospective study, found no difference in the clinical course of patients who all received antiplatelet therapy and some were additionally treated with corticosteroids or anticoagulation therapy. The use of agents such as prostaglandins, nimodipine, naloxone hydrochloride, adenosine, thiopental sodium, and magnesium has yielded some promising results in animal investigations; however, their effect in SCI needs further investigation. [22] The value of the modification of the risk factors of spinal cord ischemia, which are similar to many common vascular disorders such as stroke, myocardial infarction and renal failure, cannot be overestimated. Moreover, because this serious condition can occur in a wide variety of iatrogenic settings, special attention should be given during aortic and spinal surgery[23].

The current review has several limitations mostly inherent to the retrospective design of the studies included. In addition, the search was conducted by using one search engine (PubMed). Moreover, regarding the case series, not all of them shared the same characteristics or number of details. The timing of MRI scanning was variable and diffusion-weighted sequences were not routinely obtained. The value of therapeutic interventions could not be evaluated because of the lack of treatment standardization and the timing and duration of follow-up were not uniform.

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REFERENCES

1. Kalogeropoulos, P. *et al.* The Artery of Adamkiewicz: Anatomy and Considerations in Spine Surgery - A Review of the Literature. *J. Long. Term Eff. Med. Implants* **32**, 81–86 (2022).
2. Bosmia, A. N., Hogan, E., Loukas, M., Tubbs, R. S. & Cohen-Gadol, A. A. Blood supply to the human spinal cord: part I. Anatomy and hemodynamics. *Clin. Anat. N. Y. N* **28**, 52–64 (2015).
3. Lindeire, S. & Hauser, J. M. Anatomy, Back, Artery Of Adamkiewicz. in *StatPearls* (StatPearls Publishing, 2022).
4. Yadav, N., Pendharkar, H. & Kulkarni, G. B. Spinal Cord Infarction: Clinical and Radiological Features. *J. Stroke Cerebrovasc. Dis. Off. J. Natl. Stroke Assoc.* **27**, 2810–2821 (2018).
5. Sandoval, J. I. & De Jesus, O. Anterior Spinal Artery Syndrome. in *StatPearls* (StatPearls Publishing, 2022).
6. Nedeltchev, K. *et al.* Long-term outcome of acute spinal cord ischemia syndrome. *Stroke* **35**, 560–565 (2004).
7. Cheshire, W. P., Santos, C. C., Massey, E. W. & Howard, J. F. Spinal cord infarction: etiology and outcome. *Neurology* **47**, 321–330 (1996).
8. Robertson, C. E., Brown, R. D., Wijdicks, E. F. M. & Rabinstein, A. A. Recovery after spinal cord infarcts: long-term outcome in 115 patients. *Neurology* **78**, 114–121 (2012).
9. Weidauer, S., Nichtweiß, M., Hattingen, E. & Berkefeld, J. Spinal cord ischemia: aetiology, clinical syndromes and imaging features. *Neuroradiology* **57**, 241–257 (2015).
10. Zalewski, N. L. *et al.* Characteristics of Spontaneous Spinal Cord Infarction and Proposed Diagnostic Criteria. *JAMA Neurol.* **76**, 56–63 (2019).
11. Qureshi, A. I., Afzal, M. R. & Suri, M. F. K. A Population-Based Study of the Incidence of Acute Spinal Cord Infarction. *J. Vasc. Interv. Neurol.* **9**, 44–48 (2017).
12. Cheng, M.-Y. *et al.* Spinal cord infarction in Chinese patients. Clinical features, risk factors, imaging and prognosis. *Cerebrovasc. Dis. Basel Switz.* **26**, 502–508 (2008).
13. Novy, J., Carruzzo, A., Maeder, P. & Bogousslavsky, J. Spinal cord ischemia: clinical and imaging patterns, pathogenesis, and outcomes in 27 patients. *Arch. Neurol.* **63**, 1113–1120 (2006).
14. Vargas, M. I. *et al.* Spinal cord ischemia: practical imaging tips, pearls, and pitfalls. *AJNR Am. J. Neuroradiol.* **36**, 825–830 (2015).
15. Zalewski, N. L. *et al.* Spinal cord infarction: Clinical and imaging insights from the periprocedural setting. *J. Neurol. Sci.* **388**, 162–167 (2018).
16. Hanson, S. R., Romi, F., Rekand, T. & Naess, H. Long-term outcome after spinal cord infarctions. *Acta Neurol. Scand.* **131**, 253–257 (2015).
17. Nogueira, R. G. *et al.* Restricted diffusion in spinal cord infarction demonstrated by magnetic resonance line scan diffusion imaging. *Stroke* **43**, 532–535 (2012).
18. Costamagna, G. *et al.* Hyperacute extensive spinal cord infarction and negative spine magnetic resonance imaging: a case report and review of the literature. *Medicine (Baltimore)* **99**, e22900 (2020).
19. Mawad, M. E., Rivera, V., Crawford, S., Ramirez, A. & Breitbach, W. Spinal cord ischemia after resection of thoracoabdominal aortic aneurysms: MR findings in 24 patients. *AJNR Am. J. Neuroradiol.* **11**, 987–991 (1990).
20. Salvador de la Barrera, S. *et al.* Spinal cord infarction: prognosis and recovery in a series of 36 patients. *Spinal Cord* **39**, 520–525 (2001).
21. Seze, S., Joseph. Pronostic fonctionnel des paraplégies par ischémie médullaire : étude rétrospective de 23 cas. *EM-Consulte* https://www.em-consulte.com/article/104479/pronostic-fonctionnel-des-paraplegies-par-ischemie.
22. de Haan, P., Kalkman, C. J. & Jacobs, M. J. Pharmacologic neuroprotection in experimental spinal cord ischemia: a systematic review. *J. Neurosurg. Anesthesiol.* **13**, 3–12 (2001).
23. Rahman, M. *et al.* A Review on the Pathophysiology and Management of Anterior Spinal Artery Syndrome. *J. Spine Res. Surg.* **2**, 85–96 (2020).

READY - MADE CITATION

Batsou V, Benetos IS, Vlamis I, Pneumaticos S. Spinal Cord Ischemia: A review of clinical and imaging features, risk factors and long-term prognosis. *Acta Orthop Trauma Hell* 2023; 74(3): 54-60.

The Role of Physiotherapy in the Management of Whiplash Injury: A Narrative Review

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ABSTRACT

Many people in the developed countries have experienced a whiplash injury, in which their cervical spine followed a rapid force of acceleration-deceleration in their neck, in a small or a greater scale, mostly as a result of a vehicle injury. Whiplash associated disorders (WAD) is the term that is used to describe injuries which sustained as a result of these sudden acceleration-deceleration movements. This term also refers to the presence of a total of symptoms that a patient can experience after a whiplash injury such as pain, headache, stiffness and dizziness. As a result, these injuries have many effects and costs in a patient's daily and work life, work ability and psychology, making it necessary to find treatments that can relieve them. The published reviews have shown the importance of including the therapeutic exercises in a rehabilitation programme aiming to the reduction of those symptoms. Many reviews and researches have been published referring to different therapeutic methods in a whiplash injury, so it is important to discover the appropriate physiotherapy methods for the management of the whiplash injury's symptomatology. This review is about investigate the role of physiotherapy methods to treat the short-term and long-term symptoms of the whiplash injury.

Key words: whiplash, whiplash injury, whiplash-associated disorders (WAD), physiotherapy, management.

Introduction

A very common traumatic injury that is estimated to affect between 70 and 420 people in every 100.000 and is produced most likely by a road traffic crash is a whiplash injury [1] . It is caused by a sudden passive extension of the neck, followed by a sudden flexion, in a whip-like fashion [2-3].

Campbell et al indicate that one in two individuals who experience a whiplash injury will never fully recover and up to 30% will remain moderately to severely disabled by this condition [4].

After the whiplash injury, characteristic morphological changes occurred. Some of these changes are fatty infiltration in the multifidus muscle and ligaments injury, sprain in the nuchal ligament and in the anterior longitudinal ligament, who naturally offer

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stability in the cervical spine and also altered superfacial and deep cervical muscle behaviour is observed. Deconditioned neck muscles may affect the physical support of the cervical spine [5]. Pain, stiffness, neck and/or shoulder pain with or without radicular symptoms, kinesiophobia, headache, loss of cervical mobility, reduced range of motion in the cervical spine and neurological deficits, not only in the early stages of the accident, but also years later, are the most commonly symptoms that a patient has. Patients with neurological signs report arm pain, paraesthesia or hyperalgesia without other known causes that occurred in the same dermatome/myotome.

The anatomy of the upper cervical region in combination to the direct connection and access to the vestibular nuclear complex are very important for the postural control, and for this reason, if a disorder occurs, it directly affects the vestibular system and the neck movement which might be a possible cause of symptoms such as dizziness among patients with whiplash-associated disorders (WAD)[6-7].

After a whiplash injury, there are a lot of people with neurological symptoms that don't recover fully and these signs may be caused by brachial plexus traction and/or disc protrusions, which rather seem to progress over time in WAD [8].This study supports that the somatosensory system of the patients is also affected and Castaldo et al [9] reinforced this view by adding that the patients exhibit changes in their central sensitisation. For instance, myofascial trigger points are affected and lead to the presence of persistent pain and sensitization in chronic pain patients.

The presence of these total symptoms impose a significant effect in a patient's life and it is a characteristic of a term called whiplash associated disorders (WAD) which is used to describe injuries sustained as a result of sudden acceleration-deceleration movements, affecting a high percentage of the individuals involved in road traffic incidents [9] .

Physiotherapy interventions have shown amazing results in the management of WAD. The majority of the published studies and reviews have demonstrated the effects of therapeutic exercise, before and after the injury and have emphasized the importance of the therapeutic methods in the reduction of those symptoms. It is therefore, necessary to investigate and to treat the short-term and long-term symptoms of the whiplash injury. The current narrative review is about understanding the role of physiotherapy interventions in the management of the whiplash injury. Finding the appropriate and the most effective therapeutic method, among many different ones, is an increasingly important issue.

This review aims to evaluate and appraise the current evidence of the effects of physiotherapy interventions on the management of the whiplash injury. For this cause, a literature review was conducted based on the PubMed internet database. Inclusion criteria comprised randomized controlled trials and randomized comparative clinical studies, where the participants could be of any gender and age. Studies describing any physiotherapy intervention that had to do with pain, dizziness, stiffness, stress and low quality of life, were also included. Studies comparing no intervention to standard care group or contrasting the differences between two or three therapeutic methods were included. Furthermore, keywords that were used in the PubMed database, were "whiplash", "whiplash injury", "cervical acceleration-deceleration", "whiplash injury syndrome", "whiplash neck injury '. The studies that were selected were published in the last decade, from 01/01/2012 to 02/2022. Furthermore, the narrative review does not include those studies that were referring to interventions such as drugs and / or surgeries, those studies that were reviews, and those studies that dealt with the cost of the treatment for whiplash injury.

Discussion

The study selection had initially found 143 citations in the international databases (n=143), of which 59 were rejected, because they were reviews. Following the removal of duplicates and verification of titles, 106 remained, of which 47 studies were remained after checking on the abstract. Finally, after screening abstracts and manuscripts, 29 studies finally included (Figure 1).

Dealing with a whiplash injury

***Basic Body Awareness Therapy (BAT)*:** Basic body awareness therapy (BAT) is a method used by physiotherapists, for the treatment of chronic musculoskeletal pain disorders, that includes the postural assessment,

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patient's awareness of its body and its posture. It is a method that has shown great improvements in cognitive function, cervical range of motion and quality of life. The researchers Seferiadis et al [10] demonstrate that patients who followed the basic body awareness therapy, have shown greater improvements compared with the patients in the exercise therapy group, such as the increase of their physical functioning, a greater body pain reduction and a better social. Basic body awareness therapy (BAT), not only produced a greater impact in patients with WAD, but it had been suggested by the researchers to be a part of the rehabilitation programme [10].

Acupuncture versus Relaxation therapy: A high percentage of therapists uses acupuncture as a main treatment for managing chronic pain by activating analgesia and reducing patient's pain and disability level. Other therapists suggest another effective method that is relaxation therapy in patients with chronic WAD. On the other hand, Tobbackx, et al. [11] discovered that acupuncture is a more effective method in decreasing local and referred pain but also in offering stronger improvements in local pressure pain sensitivity painful region, than relaxation therapy.

Dry-needling: Sterling M et al [12] suggested that dry-needling may have effects on central nociceptive processes in individuals with WAD. They examine the effectiveness and cost effectiveness of dry needling and exercise in patients with chronic WAD grade II. The dry-needling had greater results compared to sham-needling, concerning the pain-related disability, pain catastrophizing, cold hyperalgesia and post-traumatic stress symptoms [12].

Vestibular Rehabilitation: The anatomy of the upper cervical spine is very special and has an important role in the vestibular functions. When a pathology of the cervical spine has been occurred, the postural control will be affected and therefore the vestibular system will react with a total of symptoms, such as dizziness.

The majority of patients with WAD have shown dizziness, as the second most common symptom after neck pain. Likewise, Hansson et al [6] had examined the neck pain intensity, the cervical range of motion (CROM) and the balance in their patients, using a vestibular rehabilitation programme. In the vestibular rehabilitation group, participants have shown a significant greater improvement in their balance and in their self-perceived dizziness handicap, and they reported lower pain intensity. In the same study [6] it was suggested that even though the vestibular rehabilitation is an important tool in the physiotherapist's hand, as long as it can improve the patient's body posture and the mobility in flexion and in the orientation of the patient, further investigation is needed.

Psychological Factors & Stress: Psychological (i.e stress, depression, fear of re-injury) and psychosocial factors have an important role in the prediction of whiplash injury, as well as high pain intensity and pain related disability and they can make the transition from the sub-acute to chronic phase. The psychological condition of the patient, can reduce or otherwise increase the pain intensity and dysfunction in a daily routine and the most critical phase is two or three months after the injury. Patients who believed that they can make a full recovery, had lower disability six months after the incident, compared to those who did not. With this in mind, researchers Åsenlöf et al [13] found that individuals with mild symptomatology, did not have a good physical activity previously to the accident, although they had a better health condition. On the other hand, patients with severer clinical signs, who had already experienced a road traffic accident before, it was found that they have higher levels of pain intensity, fear of movement and re-injury, post-traumatic stress symptoms and lower level of functional self-efficacy. For this reason, Campbell et al [4] combined evidenced-based physiotherapy sessions with trauma-focused cognitive behavioural approach and their main goal was to decrease the levels of pain and disability in individuals with chronic whiplash and post-traumatic stress disorder. On the other hand, another multiply approach [7], including specific individualized physiotherapy, psychology for post-stress syndrome and pharmaceutical care in patients with a acute whiplash injury, failed to achieve the reduction of the rate of chronicity by 50% , the reduction of the proportion of the patients with persistent pain by 30% and the raise by 70% of those who recovered.

In patients with acute WAD grade II or III and are at risk of poor recovery, another study[14] have demonstrated a combined intervention, consisted of physiotherapy exercise with a physiotherapist-deliv-

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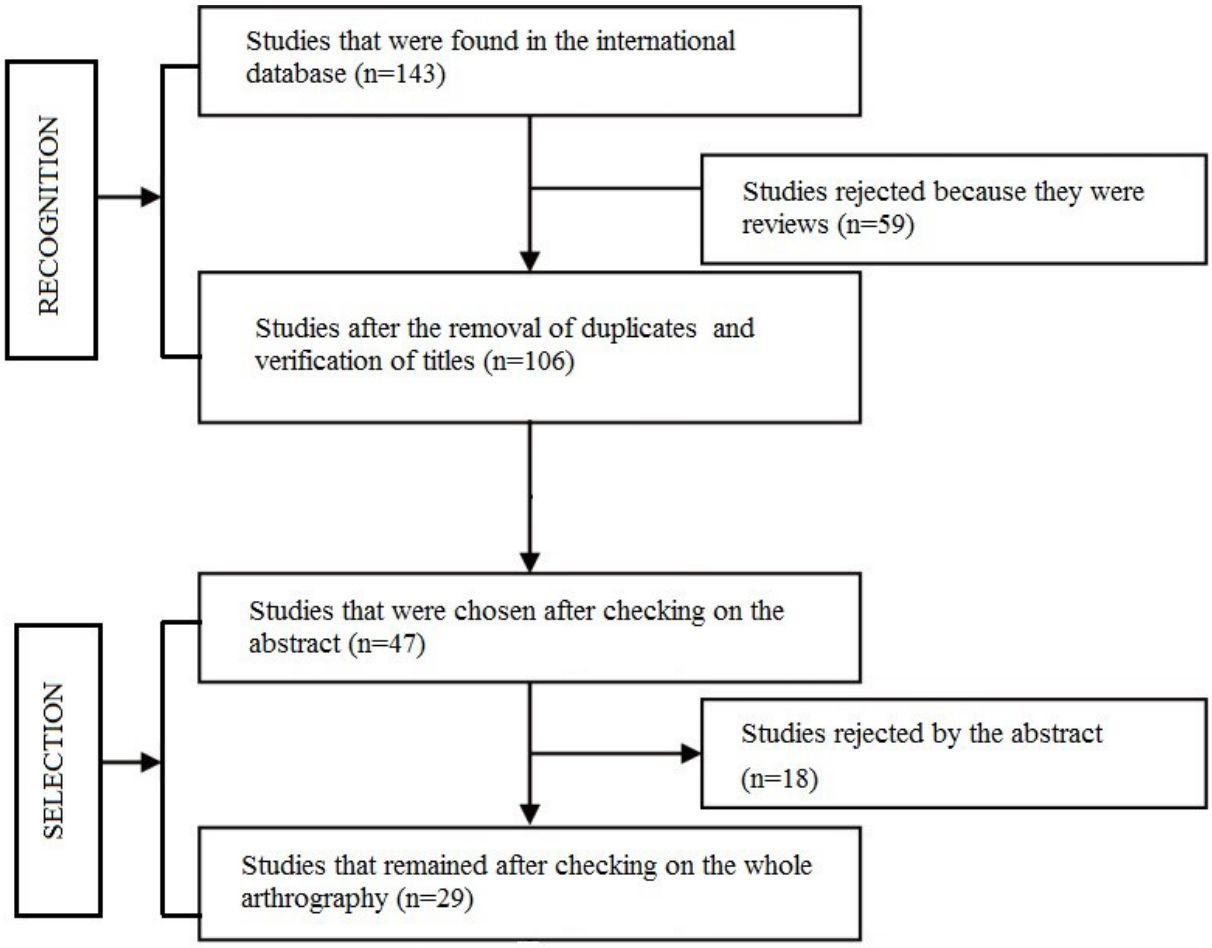

Figure 1: *The flowchart of trial identification and selection for inclusion in the narrative review*

ered stress inoculation training (Stress Model) compared with guideline-based exercise alone. This combined intervention has better primary and secondary outcomes regarding pain and general health and physiotherapists with the appropriate training can provide early psychological care and can effectively deliver a psychological type of intervention, helping with the management of the stress - related symptoms and providing greater effect on later disability, pain and mental health outcomes. Having said that, Ludvigsson et al [15] proved that the psychological condition of a patient did not change the initial outcome following intervention in chronic WAD.

Percutaneous Needle Electrolysis (PNE: The whiplash-associated disorders (WAD) occurred, more often, in a low energy traffic accidents but can also happen in sport activities, causing symptoms from mild to strong severity, such as brachialgia or vertiginous syndrome. Garcia Naranjo et al [2] found that PNE intervention is a therapeutic method that is cheaper than the basic physiotherapy protocol and can be considered to be a very effective option for the treatment of acute whiplash injury, alone or additionally to the standardized physiotherapy programmes. The participants receiving this therapy report decrease of their pain and pressure-pain threshold

Spinal Manual Therapy: Spinal manual therapy is commonly used for the treatment of neck-associated disorders. It is an important tool in the hands of physiotherapists and can also be used with combination with exercises. Castaldo et al [9] demonstrate that following a multimodal physical therapy intervention, patients with mechanical neck pain and WAD exhibit similar clinical and neurophysiological responses de-

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spite having higher neck-related disability and widespread pressure pain sensitivity.

Active Behavioural Physiotherapy Intervention (ABPI): The Active Behavioural Physiotherapy Intervention (ABPI) combines the active physiotherapy approach such as education, manual therapy, exercise therapy and home exercises, and the behavioural approach of a patient aiming to prevent the transition of acute WAD to chronicity. Researchers Wiangkham et al [16] have conclusively shown that ABPI is an important tool for the rehabilitation, causing a reduction in the neck disability and pain intensity.

Training the Emergency staff

The researchers Lamb et al [17] suggested that one year of training the staff in the emergency department to provide active consultation in the initial meeting with patients with acute whiplash injury of grade I-III, is more effective than usual consultation. This approach is more effective, if a physiotherapy package is following the initial approach, to strengthen the advice they took from the emergency department. This physiotherapy package has a meaningful role in the reduction of the work day loss caused by the whiplash injury by 40% and also can improve the self-rated efficacy of each individual. Additionally, Lo et al [18] referred to the important effects in the patient's work life, caused by this injury.

Neck Specific Exercises with or without a Behavioural approach and Prescription of Physical Activity (PPA): Neck specific exercises (NSE) aim to deep cervical muscles with a focus of maintaining a good body posture, while the patients are supervised by a physical therapist, while doing those exercises and they follow a similar exercise programme at home. The most recent studies [3-19] suggested another intervention combining NSE, with behavioural approaches, called neck-specific exercise with a behavioural approach (NSEB). Patients are learning the way for managing their pain through activities, such as breathing and relaxation exercises. Hence, a prescription of physical activity (PPA) was used, including activities that can be performed outside of the health care system [5-20].

Health in general is multidimensional, and socioeconomic factors, age and low social status can have an impact in health-related quality of life (HRQoL). HRQoL in patients with WAD is lower than in another neck-pain related disorders and is related with non-pain factors, such as pain catastrophizing and depression. Moreover, the HRQoL, may be affected positively by NSE and NSEB, more than PPA. Ludvigsson et al [19] found that there were no differences between the NSE/NSEB groups, which they examined, in any of the HRQoL outcomes at any time point and they may improve the HRQoL, more than PPA in chronic WAD grade II or III, claiming that the reduction of the depression had a positive impact in the HRQoL while the improvement of work ability can reduce the pain. The researchers [19], had also found that NSE and NSEB can cause a rapid reduction of preliminary headache symptoms and maximum headache by 50%, in contrast with PPA intervention. Similarly, adding a behavioural component to neck specific exercises(NSE), which are better than general physical activity, had limited advantages over NSE alone,even though NSEB moderates the psychological and the pain factors that impact the health related quality of life in patients with acute and subacute WAD [5,15,20].

Taking into account that balance, dizziness, proprioception and unsteadiness occur early after the initial injury and are connected to poorer outcome following a whiplash trauma, Treleaven et al [21] claimed that an intervention concluded a behavioural approach (NSEB) can be beneficial for the recovery of a patient with WAD, who has low self-efficacy, psychological distress, fear of re-injury and dizziness during activity. In addition, Peterson et al [22] found that both the NSE and NSEB groups improved in dorsal neck muscle endurance (NME) and they had presented greater reduction of pain compared with the PPA group. However, an added behavioral approach cannot improve the results of an exercise intervention.

Up to 90% of people who suffer from a chronic whiplash injury, they often complain about having radiating signs and symptoms in the arm that are relevant to neurological deficits after one year. Not all people with cervical radiculopathy present muscle weakness, pain nor decreased tendon reflexes but on their study, Ludvigsson et al [23] including participants with cervical radiculopathy from C4 to C7, stated that neck-specific exercise may alleviate neurological signs and symptoms as well as radiating arm discomfort. However,

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adding a behavioural approach to those exercises does not appear to be of further benefit, and thus the prescription of PPA is not supported. Similarly, Peterson et al [24] indicated that if exercise interventions (NSE, NSEB) are used with a focus on the neck muscles, persistent disability following whiplash injury can be reduced and reduced active cervical range of motion and grip strength may improve. Peterson et al [25] found that individuals in the NSE approach had greater improvements in pain intensity and muscle interactions than those in the waiting list and that ultrasound is a useful diagnostic tool for muscle impairment and can also evaluate exercises for the neck, thus being a holistic management for chronic WAD.

Comprehensive Physiotherapy Exercise Programme: Considering a comprehensive exercise programme delivered by physiotherapists in patients with chronic whiplash-associated disorder grade I or II, Michaleff et al [26] argued that it is not more effective for pain reduction than simple advice alone (one session and telephone support). Other studies support the importance of exercises in a whiplash injury rehabilitation programme [27-28].

Therapeutic Ultrasound: The therapeutic ultrasound is a useful tool in the hands of physiotherapists as long as it can affect the pain not directly but secondarily in the treatment process, taking into account its pro-inflammatory effect [29]. Active ultrasound can reduce the pain and accelerate the healing process 20 days after completing the implementation of ultrasound, more than placebo, but it cannot increase the joint mobility, in acute traumatic cervical sprain grades I and II.

Conclusion

Whiplash injury is a common health problem associated with a mechanism of injury in the cervical spine. The whiplash-associated disorders occurred, more often, in low energy traffic accidents but also may occur in sport activities and can cause symptoms from mild to strong severity. The range of symptoms concerns not only the musculoskeletal system of the patient, but has also an important role to the patient's psychological condition, as long as they affect their daily and work life. Health-care professionals' assessment is crucial for the prognosis of the rehabilitation, likewise many physiotherapy methods have been used in the deal with chronic pathologies. The role of the physiotherapy science in the management of whiplash injury and whiplash-associated disorders (WAD) is necessary and there are many physiotherapy methods to use, individually or in combination. Taking into account that the ligaments in the cervical region are only responsible for the 25% of the stability in this area, the superficial and especially the deep cervical muscles is the crucial key point for the rehabilitation. Focusing on strengthening these muscles and improving body posture, can reduce symptoms' intensity. Good posture can reduce forces exerted on the cervical spine, and together with the right ergonomic, can provide a better daily life. Physiotherapist should provide a multidimensional approach to the patient, emphasizing also on patient's psychological condition, as it may affect treatment's results and retard rehabilitation.

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REFERENCES

1. Ardern CL, Peterson G, Ludvigsson ML, et al. Satisfaction with the Outcome of Physical Therapist-Prescribed Exercise in Chronic Whiplash-Associated Disorders: Secondary Analysis of a Randomized Clinical Trial. J Orthop Sports Phys Ther. 2016;46(8):640-9
2. Garcva NJ, Barroso RS, Loro Ferrer JF, et al. A novel approach in the treatment of acute whiplash syndrome:Ultrasound-guided needle percutaneous electrolysis. A randomized controlled trial. Orthop Traumatol Surg Res. 2017;103(8):1229-34.
3. Ludvigsson ML, Peterson G, Widh S, et al. Exercise, headache, and factors associated with headache in chronic whiplash: Analysis of a randomized clinical trial. Medicine (Baltimore). 2019;98(48):e18130.
4. Campbell L, Kenardy J, Andersen T, et al. Trauma-focused cognitive behaviour therapy and exercise for chronic whiplash: protocol of a randomised, controlled trial. J Physiother. 2015 ;61(4):218
5. Ludvigsson ML, Peterson G, O'Leary S, et al. The effect of neck-specific exercise with, or without a behavioral approach, on pain, disability and self-efficacy in chronic whiplash-associated disorders: a randomized clinical trial. Clin J Pain. 2015;31(4):294-303
6. Hansson EE, Persson L, Malmstrom EM.J. Influence of vestibular rehabilitation on neck pain and cervical range of motion among patients with whiplash-associated disorder: a randomized controlled trial. J Rehabil Med. 2013;45(9):906-10.
7. Jull G, Kenardy J, Hendrikz J et al. Management of acute whiplash: a randomized controlled trial of multidisciplinary stratified treatments. Pain. 2013;154(9):1798-806
8. Ludvigsson M.L, Peterson G, Peolsson A. Neck-specific exercise may reduce radiating pain and signs of neurological deficits in chronic whiplash - Analyses of a randomized clinical trial. Sci Rep. 2018;8(1):12409.
9. Castaldo M, Catena A, Chiarotto A, et al. Do Subjects with Whiplash-Associated Disorders Respond Differently in the Short-Term to Manual Therapy and Exercise than Those with Mechanical Neck Pain?. Pain Med. 2017;18(4):791-803
10. Seferiadis A, Ohlin P, Billhult A, et al. Basic body awareness therapy or exercise therapy for the treatment of chronic whiplash associated disorders: a randomized comparative clinical trial. Disabil Rehabil. 2016;38(5):442-51
11. Tobbackx Y, Meeus M, Wauters L, et al. Does acupuncture activate endogenous analgesia in chronic whiplash-associated disorders? A randomized crossover trial. Eur J Pain. 2013;17(2):279-89.
12. Sterling M, Vicenzino B, Souvlis T, et al. Dry-needling and exercise for chronic whiplash-associated disorders: a randomized single-blind placebo-controlled trial. Pain. 2015;156(4):635-43.
13. Åsenlöf P, Bring A, Söderlund A. The clinical course over the first year of whiplash associated disorders (WAD): pain-related disability predicts outcome in a mildly affected sample. BMC Musculoskelet Disord. 2013;14:361.
14. Sterling M, Smeets R, Keijzers G, et al. Physiotherapist delivered stress inoculation training integrated with exercise versus physiotherapy exercise alone for acute whiplash-associated disorder (StressModex): a randomised controlled trial of a combined psychological/physical intervention. Br J Sports Med. 2019;53(19):1240-47.
15. Ludvigsson ML, Peterson G, Dedering E, et al. Factors associated with pain and disability reduction following exercise interventions in chronic whiplash. Eur J Pain. 2016;20(2):307-15
16. Wiangkham T, Duda J, Haque MS, et al. A cluster randomised, double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute whiplash-associated disorder (WAD)II. PLoS One. 2019;14(5):e0215803.
17. Lamb SE, Gates S, Williams MA. Emergency department treatments and physiotherapy for acute whiplash: a pragmatic, two-step, randomised controlled trial; Managing Injuries of the Neck Trial (MINT). Lancet. 2013;381(9866):546-56.
18. Lo HK, Johnston V, Landın Ludvigsson M, et al. Factors associated with work ability following exercise interventions for people with chronic whiplash-associated disorders: Secondary analysis of a randomized controlled trial. J Rehabil Med. 2018;50(9):828-36.
19. Ludvigsson ML, Peterson G, Peolsson A. The effect

of three exercise approaches on health-related quality of life, and factors associated with its improvement in chronic whiplash-associated disorders: analysis of a randomized controlled trial. Qual Life Res. 2019;28(2):357-368.

20. Peolsson A, Landın Ludvigsson M, Tigerfors AM, et al. Effects of Neck-Specific Exercises Compared to Waiting List for Individuals with Chronic Whiplash-Associated Disorders: A Prospective, Randomized Controlled Study. Arch Phys Med Rehabil. 2016;97(2):189-95
21. Treleaven J, Peterson G, Ludvigsson ML, et al. Balance, dizziness and proprioception in patients with chronic whiplash associated disorders complaining of dizziness: A prospective randomized study comparing three exercise programs. Man Ther. 2016;22:122-30
22. Peterson GE, Landın Ludvigsson MH, O'Leary SP, et al. The effect of 3 different exercise approaches on neck muscle endurance, kinesiophobia, exercise compliance, and patient satisfaction in chronic whiplash. J Manipulative Physiol Ther. 2015;38(7):465-476.e4.
23. Ludvigsson ML, Peterson G, Peolsson A. Neck-specific exercise for radiating pain and neurological deficits in chronic whiplash, a 1-year follow-up of a randomised clinical trial. Sci Rep. 2020;10(1):6758.
24. Peterson G, Landın Ludvigsson M, Peolsson AE. Neck-related function and its connection with disability in chronic whiplash-associated disorders: secondary analysis of a randomized controlled study. Eur J Phys Rehabil Med. 2021;57(4):607-19.
25. Peterson G, Nilsson D, Trygg J, et al. Neck-specific exercise improves impaired interactions between ventral neck muscles in chronic whiplash: A randomized controlled ultrasound study. Sci Rep. 2018;8(1):9649
26. Michaleff ZA, Maher CG, Lin CW, et al. Comprehensive physiotherapy exercise programme or advice for chronic whiplash (PROMISE): a pragmatic randomised controlled trial. Lancet. 2014 Jul 12;384(9938):133-41.
27. Ritchie C, Kenardy J, Smeets R, et al. StressModEx—Physiotherapist-led Stress Inoculation Training integrated with exercise for acute whiplash injury: study protocol for a randomised controlled trial. J Physiother. 2015;61(3):157
28. Ludvigsson ML, Peterson G, Dedering E, et al. One- and two-year followup of a randomized trial of neck-specific exercise with or without a behavioural approach compared with prescription of physical activity in chronic whiplash disorder. J Rehabil Med. 2016;48(1):56-64.
29. Ruiz-Molinero C, Jimenez-Rejano JJ, Chillon-Martinez R, et al. Efficacy of therapeutic ultrasound in pain and joint mobility in whiplash traumatic acute and subacute phases. Ultrasound Med Biol. 2014;40(9):2089-95

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Contribution of Botulinum Toxin for the Treatment of Neuropathic Pain.

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ABSTRACT

Neuropathic pain is caused by an injury or a disease of the somatosensory system, including peripheral nerve fibres and central neurons. Botulinum toxin (BTX) is a neurotoxic protein produced by the bacterium Clostridium botulinum. BTX interferes with the release of the neurotransmitter acetylcholine from neuroaxon terminals at the neuromuscular synapse and thus causes flaccid paralysis. This literature review investigates the recent data regarding the efficacy of BTX in the treatment of various forms of neuropathic pain. A total of 18 original clinical trials published after 2010 were selected, 12 of which were randomized controlled studies, one was a non-randomized controlled study and the remaining 5 were case series. A total of 1,131 patients were enrolled. BTX represents an effective treatment for neuropathic pain. Further randomised controlled trials are needed to demonstrate treatment efficacy, provide guidelines in relation to its application protocols and establish possible treatment variations at different sub-groups of patients.

Key words: Neuralgia, Botulinum toxins, Therapeutics

Introduction

Neuropathic pain is mediated through the somatosensory system, including peripheral nerve fibers (Aβ, Aδ, and C) and central neurons, and affects 7–10% of the general population (1). Its frequency is more likely to increase due to population' aging, increased number of diabetes mellitus and post-chemotherapy cancer patients. There are several pathophysiologic mechanisms that are involved in the development of neuropathic pain, including imbalance between excitatory and inhibitory somatosensory signalling, changes in ion channels and variability pain signals' modulation in the central nervous system.

Patient burden due to chronic neuropathic pain appears to be related to the: (a) complexity of neuropathic symptoms, (b) poor outcome of applied therapeutic interventions, and (c) difficulty in choosing the optimal therapeutic method. Progress of understanding

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the pathophysiology of neuropathic pain prompts the development of new diagnostic methods and personalized therapeutic interventions, which highlight the need for a multi-level and multidisciplinary approach to the management of neuropathic pain (1).

Botulinum toxin (BTX) is a neurotoxic protein produced by the bacterium Clostridium botulinum. It prevents the release of the neurotransmitter acetylcholine from the axonal endings at the neuromuscular synapse and thus causes flaccid paralysis. BTX is one of the most poisonous biological agents known. Eight antigenically distinct exotoxins (A, B, C1, C2, D, E, F and G) are produced by C. botulinum. All serotypes interfere with nerve transmission by blocking the release of acetylcholine causing muscle paralysis. The muscle weakness caused by the BTX-A injection usually lasts for three months. BTX play an important role in the management of a wide variety of pathological conditions, such as strabismus and focal dystonias, hemifacial spasm and various spastic movement disorders, headaches, hyperalgesia, hyperhidrosis, and some chronic conditions that are only partially responsive in conventional medical treatment in fact, the list of potential new indications is expanding rapidly (2).

The aim of this review was to investigate the data of the recent literature in relation to the effectiveness of BTX in the treatment of the various forms of neuropathic pain. To achieve the above-mentioned aim of the present diploma thesis, the tool of the systematic literature review was chosen (3). The databases searched for relevant published clinical studies were PubMed/NCBI, Google Scholar and Cochrane Library of Systematic Reviews. The key words (mesh terms) entered into the search engines of the specific databases were Botulinum, Toxin, Neuropathic, Pain, Treatment, in various combinations and with the use of AND and OR disjunctive terms. For the study entry we used the following criteria: (i) randomized and non-randomized clinical studies with a control group as well as series studies, (ii) date of publication later than year 2010, (iii) publication language English and possibility to study the full text, or at least an extended summary of the study, (iv) clinical studies conducted on humans. On the other hand, the review did not include single case reports as well as reviews / systematic reviews / meta-analyses of the literature, animal studies as well as experimental – in vitro studies. Figure 3 shows the flow diagram of the review, according to the PRISMA principles (4).

Discussion

According to the above-mentioned method of collecting the scientific data, 18 original clinical studies were isolated and studied, of which 12 were randomized controlled studies, one was a non-randomized controlled study, and the remaining 5 were series studies. A total of 1,131 patients participated. Table 1 summarizes the findings of the specific studies. Their findings will then be presented in more detail, grouped according to the specific pathological condition to which the studies referred.

Treatment of trigeminal neuralgia

Trigeminal neuralgia is a chronic painful pathological condition with repeated episodes of neuropathic pain in the distribution of the fifth cerebral conjugation (trigeminal nerve), which innervates the area of the forehead, cheek, and lower jaw. In most cases the condition occurs contralaterally and affects one or more of the three main branches of the trigeminal nerve (ophthalmic - V1, maxillary - V2 and mandibular - V3 nerve). Several pharmaceutical agents have been used in the attempt to treat trigeminal neuralgia, such as carbamazepine, oxcarbazepine, baclofen, gabapentin and valproic acid (5). The use of BTX has been proposed as a therapeutic intervention in specific groups of patients (especially middle-aged and older) who have failed drug therapy, or do not tolerate its adverse effects (6).

In 2013 Zuniga et al. (7), published the results of a double-blind randomized controlled trial to investigate the efficacy of BTX - A injection in 36 patients with trigeminal neuralgia. In a study group 20 patients 50 IU were administered subcutaneously in the affected area. The primary outcome measure was VAS pain scale. The results of the study showed the statistically significant superiority of the BTX group compared to the control group (infusion of 0.95 saline), at a period of 2 months (VAS 4.9 vs. 6.63, $p = 0.07$), and 3 months follow-up (VAS 4.75 vs. 6.94, $p = 0.01$). According to the authors, botulinum toxin is an effective, very well tolerated and without clinically significant side effects,

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treatment for trigeminal neuralgia.

One year later, the results of a new randomized double-blind controlled study (8) in 84 patients with trigeminal neuralgia were published. Two topical BTX-A regimens, 25 IU and 75 IU, were studied with control patients receiving placebo (saline). The results of the study showed, a statistically significant superiority of both treatment regimens compared to the control group8 weeks after the injections. On the other hand, no statistically significant difference was found between the two dosages of BTX-A, while at the same time, all side effects of the drug were rated by patients as "mild" or "moderate". In 2016, Xia et al.(9), published the results of a prospective study of 87 patients with bilateral trigeminal neuralgia who received topical BTX-A. With a follow-up time of 8 weeks, a gradual improvement in pain was recorded (from 48.28% in the first week to 80.46% in the eighth week), while at the same time a reduction in anxiety and depression levels was found (90.32% and 96.77% respectively). At the same time, a series of parameters of patients' quality of life improved significantly ($p < 0.01$) after the therapeutic intervention, while patients' physical activity showed no impronement ($p = 0.317$). In 2017, Zhang et al. (10), in a pilot randomized controlled trial, investigated the efficacy of two different regimens in 87 patients with trigeminal neuralgia. Patients in the first group received one injection of BTX-A 70-100 IU in the affected area, while those in group B received two doses, 50-70 IU, over a period of two weeks. The results of the study showed a no significant remission of patients' symptoms, between the two study groups, in terms of their effectiveness and safety, at the 6th month's follow-up. Wu et al., (2019) (6), in a retrospective study investigated the efficacy of local infusion of 100 U BTX-A in 104 elderly patients (mean age 59.2 years) with persistent trigeminal neuralgia. The results of the study, with a total patient follow-up time of 12 months, showed that 1) 83.7% successful treatment. The age group > 50 years had the best results ($p = 0.033$) at the 12 mont's follow-up. Crespi et al. (11) investigated the efficacy of 25 IU BTX-A injection into the sphenoid ganglion in 10 patients with persistent trigeminal neuralgia. Although the treatment proved to be safe and well tolerated by the patients, the main outcome criterion of the study (reduction of the frequency of seizures by at least 50% during the 5-8 week period after the intervention) did not prove the effectiveness. Conclusively, botulinum toxin for trigeminal neuralgia was found to be a safe and well-tolerated treatment with non-significant clinical side effects. The local injection of BTX-A in the affected area was particularly effective in reducing the frequency of seizures as well as the intensity of pain. The single-dose regimen appears to be non-inferior to re-dosing after two weeks. Patients of an older age group (> 50 years old) seem to have a better response to the therapeutic intervention.

Treatment of postherpetic neuralgia and atypical dental pain

Post-herpetic neuralgia (PHN) is the common complication, causing long-term and excruciating neuropathic pain. In addition, over 50% of patients with PHN report significant profound sleep disturbances, limitations in their daily activity and significant burden of their social life (12). Apalla et al. (2013) (13), in a randomized, double-blind, controlled study, investigated the efficacy of a 100 IU dose of BTX-A subcutaneously, in the affected area, in 30 patients suffering from PHN. The study outcome criteria were patients' pain level (VAS scale), sleep quality and clinical improvement > 50%. The results showed that 13 patients in the intervention group experienced at least a 50% reduction in the VAS scale, compared to none in the control group ($p < 0.001$), an improvement that was maintained for a mean time of 16 weeks. According to the authors, this is a particularly effective therapeutic option in the treatment of PHN. Hu et al., (2020) (14), published the results of a randomized control trial in 33 patients with persistent PHN. The 13 patients received a subcutaneous injection of BTX-A (50-100 IU) in the affected area while the remaining 20 were treated with 0.3 g gabapentin orally, three times a day. The primary outcome measure was pain (VAS scale) at 1, 2, 4-, 8-, 12- and 16-weeks post-intervention. The main findings of the study were that patients in the intervention group had a statistically significant improvement in pain level as early as week 2, both compared to their status before BTX-A infusion and compared to patients in gabapentin group. In one of the most recently published randomized controlled trials, Chen et al. (2022)

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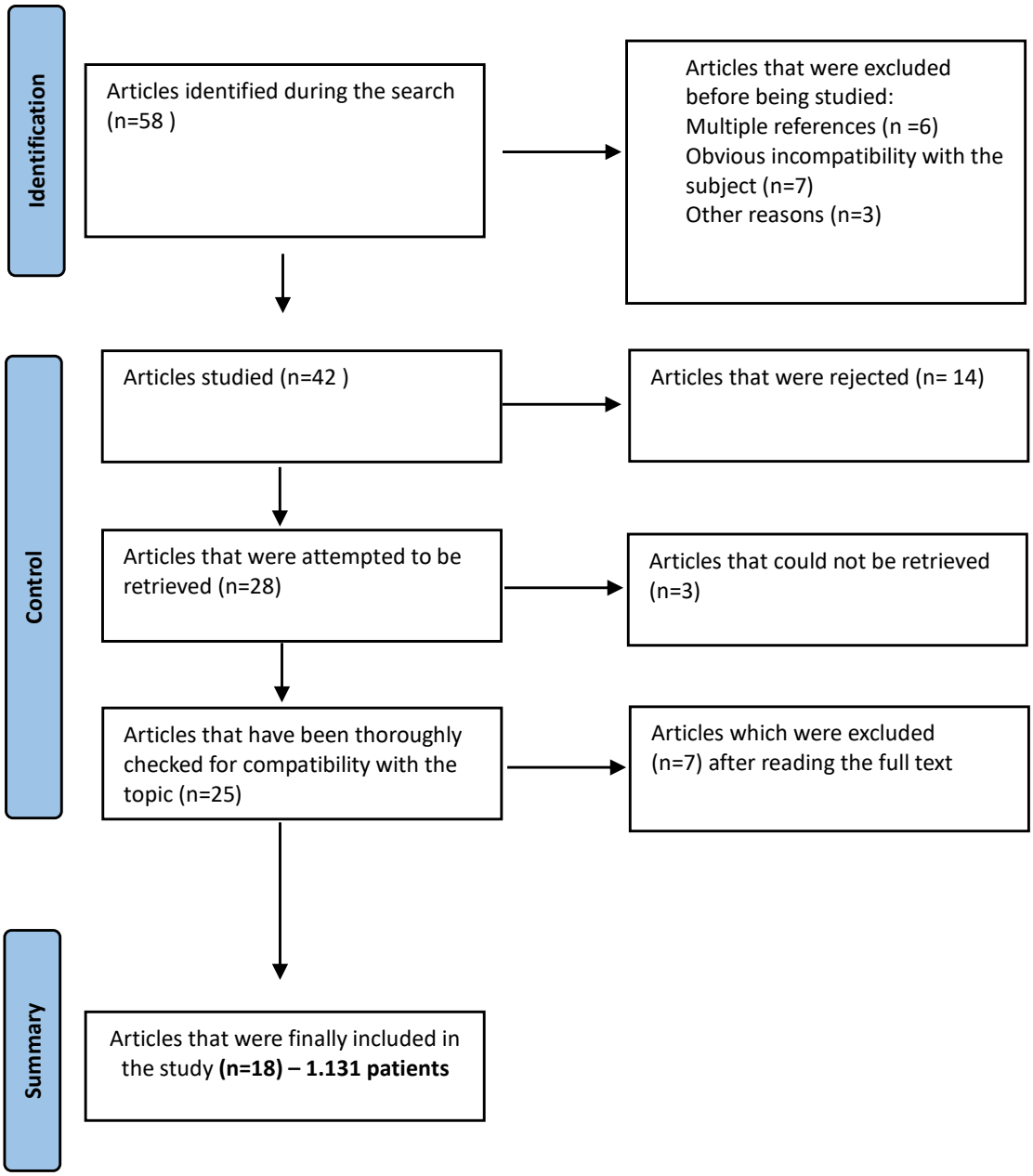

table 1: The flow chart of the systematic literature review.

(15) compared the efficacy of a 100 IU m BTX-A infusion and a pulsed radiofrequency treatment session in 100 patients with postherpetic neuralgia. With the primary outcome measure of pain and a follow-up duration of 24 weeks, it was found that patients in both study groups had a statistically significant reduction of pain ($p < 0.05$) compared to the state before the intervention. In addition, botulinum toxin injection was an easy and a less expensive treatment, compared to pulsed radiofrequency therapy.

Atypical ododalgia (AO) is a subcategory of persistent idiopathic facial pain, defined as persistent dental pain for which thorough examination does not reveal any dental pathology. It is a pain of neuropathic eti-

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Table 2: The IASP guidelines for the pharmacological management of neuropathic pain. Source: Finnerup et al., (2015) (10).

Drug guideline	Medical drugs
First-line SNRI*	duloxetine, venlafaxine Tricyclic antidepressants Gabapentin, pregabalin
Second Line	Capsaicin Patches 8% Lidocaine (lignocaine) patches Tramadol
Third-line	Strong opioid pain relievers

*SNRI: Serotonin noradrenaline reuptake inhibitors.

ology, for the treatment of which a series of local and systemic pharmaceutical treatments have been used, with unsatisfactory results in most cases (16). Cuadrado et al. (2016) (17) showed that local injections of Onabotulinum toxin A (5-30 IU, from two to five infusion cycles), resulted in almost complete elimination of the pain, with the analgesic effect of the method appearing as early as the 3rd-14th day of the intervention and lasting for a period of 2-6 months.

Treatment of neuropathic pain after spinal cord injury

Pain is one of the most common complications following spinal cord injury (SCI), it has the characteristics of classic neuropathic pain and causes a significant burden on patient's quality of life, affecting his physical, cognitive, and emotional functions (18). Its incidence in patients with SCI is estimated to be 75%-81% of the cases (19). Han et al. (2016) (20) investigated the efficacy of subcutaneously injecting 200 IU of BTX-A into the affected area. The results showed a statistically significant reduction in pain at both 4th and 8th week post-injection, with simultaneous maintenance of patient's motor and sensory function peripheral to the level of neurological damage.

One year later, Li et al., (2017) (21) showed that local subcutaneous injection of 200 IU BTX-A resulted in statistically significant improvement in patients' pain, at both 4 and 8 weeks post-intervention. At the same time, statistically significant improvements were also recorded in patients 'quality of life, according WHO Quality of Life questionnaire (WHOQOL-BREF). Finally, Chun et al., (2019) (22) showed that local subcutaneous injection of 400 IU BTX-A had no significant improvement in the level of pain, compared to patients in the control group. According to the authors, this method may prove to be effective in the control of neuropathic pain following SCI and should be further studied with high-quality clinical studies that include many participating patients.

Treatment of various forms of neuropathic pain

Diabetic polyneuropathy is a serious complication that affects more than 25% of patients with type II diabetes, relapsing their sleep and quality of life (23). Chen et al., (2013) (24) showed that treatment with a local injection of BTX-A 50 IU in each leg (two injections with an interval 12 weeks), led to a statistically significant reduction in both tactile and mechanical pain of patients in the intervention group, up to the 24th week of follow-up.

The sciatic muscle syndrome is a neuromuscular disorder caused by the pressure of the sciatic nerve by the sciatic muscle as it exits the sciatic foramen. Its etiology is not yet fully understood, its diagnosis is difficult and even more difficult may prove to

TABLE 3:

The Summary Findings Of The Clinical Studies Which Were Isolated.

Authors, Country	Type of study	Participants	Method	Outcome criteria	Results
Zuniga et al., (2013), Argentina (24)	Randomized, double-blind, control-group study	36 patients with trigeminal neuralgia	Control group: saline infusion. Intervention group: 50 IU BTX infusion	VAS pain scale. 3 months follow up.	Statistically significant superiority in favor of the BTX group
Zhang et al., (2014), China (25)	Randomized, double-blind, control-group study	84 patients with trigeminal neuralgia	Group A: placebo Group B: BTX-A 25 IU Group C: BTX-A 75 IU	VAS pain scale. 2 months follow up.	Statistically significant superiority in favor of the BTX group – no difference was found between the two dosage regimens.
Xia et al., (2016), China (26)	Prospective series study	87 patients with trigeminal neuralgia	Local injection BTX-A	VAS pain scale, Hamilton Anxiety Scale, Hamilton Depression Scale. 2 months follow up.	Significant improvement of all studied outcome criteria, without substantial adverse effects
Zhang et al., (2017), China (27)	Randomized, pilot study with a control group	81 patients with trigeminal neuralgia	Group A: 1 infusion BTX-A 70 – 100 IU Group B: Initial dose of BTX 50 – 70 IU and repeated 2 weeks later.	VAS scale, incidence of symptoms, side effects. 6 months follow up.	Both regimens were effective in treating symptoms, with no statistically significant difference between them.
Wu et al., (2019), Κίνα (23)	Retrospective series study	104 elderly patients (mean age 59.2 years) with persistent trigeminal neuralgia	Local injection 100 IU BTX-A	VAS scale, frequency of symptoms, side effects.	87 patients (rate 83.7%) reported success of the intervention. Statistically significant difference in favor of the age group of > 50 years.
Crespi et al., (2019), Norway (28)	Prospective pilot series study	10 patients with persistent trigeminal neuralgia	Infusion 25 IU BTX-A into the sphenoid ganglion	Side effects, seizure frequency, patient functional level. 3 months follow up. 6 months follow up.	The efficacy of the method was not confirmed in the primary outcome criterion (reduction in seizure frequency during the 5-8 week period)
Apalla et al., (2013), Greece (30)	Randomized, double-blind, control-group study	30 patients with chronic postherpetic neuralgia	Infusion 100 IU BTX-A into the affected area	Pain (VAS scale), sleep quality. 24-week follow-up	Statistically significant reduction in pain and improvement in sleep quality, lasting at least 16 weeks

Hu et al., (2020), China (31)	Randomized control group study	33 patients with chronic postherpetic neuralgia	Group A: Infusion 50 – 100 IU BTX-A Group B: 0,3 g gabapentin, 3 times daily	Pain (VAS scale). 16-week follow-up	Statistically significant reduction in the pain level of patients in the intervention group both in relation to their previous condition and in relation to patients in the control group (gabapentin)
Chen et al., (2022), China (32)	Randomized control group study	100 patients with chronic postherpetic neuralgia	Group A: Infusion 100 IU BTX-A Group B: One session of pulsed radio frequencies	Pain (VAS scale). 24-week follow-up.	Statistically significant improvement of patients in both study groups – No difference was found between the two groups. Injecting BTX-A is easier and less expensive.
Cuadrado et al., (2016), Spain (34)	Prospective series study	4 patients with atypical ododalgia	Local injection BTX-A 15 – 30 IU, 2 -5 therapy sessions	Pain levels. Follow-up range 6 -20 months.	Almost complete or even complete remission of symptoms in all patients.
Han et al., (2016), N. Korea (37)	Randomized, double-blind, control-group study	40 patients with SCI	One injection of 200 IU BTX-A s.c	VAS scale, 8-week follow-up	Statistically significant reduction in pain at 4^{th} and 8^{th} weeks.
Li et al., (2017), China (38)	Randomized control group study	44 patients with SCI	One injection of 200 IU BTX-A s.c	VAS, SF-MPQ and WHOQOL-BREF scales, 8-week follow-up	Statistically significant improvement in all outcome criteria at 4^{th} and 8^{th} weeks post-intervention.
Chan et al., (2019) US (39)	Randomized, double-blind, control-group study	8 patients with complete SCI	One injection of 400 IU BTX-A s.c	VAS scale, 12-week follow-up	Reduction in pain level in the intervention group, with values that were not statistically significant.
Chen et al., (2013), Taiwan (41)	Randomized control group study	18 patients with painful diabetic polyneuropathy	Two infusions of BTX-A 50 IU in each leg, 12 weeks apart	Level of pain (mechanical and tactile). 24-week follow-up	Statistically significant improvement in pain levels during follow-up

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Mitchel et al., (2013), Γαλλία (43)	Non-randomized study with control group	280 patients with piriformis syndrome	Infusions (1-5) of BTX-A 50-100 IU into the apioid muscle	VAS scale	77% of patients reported very good remission of symptoms
Attal et al., (2016), France (44)	Randomized, double-blind, control-group study	66 patients with peripheral neuropathic pain from nerve injury	2 infusions of BTX-A up to 300 IU 12 weeks apart	Brief Pain Inventory (BPI), 24-week follow-up	Statistically significant improvement in the symptomatology of patients in the intervention group
Eitner et al., (2017) (45), Germany	Randomized control group study	46 patients with peripheral neuropathic pain from nerve injury	Subcutaneous injection of BTX-A (100 - 300 IU).	NRS scale, QST scale, 24-week follow-up	Statistically significant reduction in patient symptoms
Meyer-Friebem et al., (2019), Germany (46)	Prospective series study	60 patients with peripheral neuropathic pain from nerve injury	Perineural infusion, under ultrasound guidance of 25 – 100 IU BTX-A	Quantitative sensory testing and NRS scale	Reduction of pain levels by 24.8%, without disturbing the sensibility of the area. Further clinical studies need at least 84 participants in order to have statistical power.

be its definitive treatment (25). Mitchel et al., (2013) (26) in a non-randomized study with a local injections of 50-100 IU BTX-A in the opioid muscle, found that 77% of patients reported very good symptom relief, 7.4% moderate and the remaining 15.6% poor. In 2016 Attal et al., (27) in a double-blind randomized controlled trial in 66 patients with peripheral neuropathic pain due to a peripheral nerve injury, showed that local injection of BTX-A resulted in a statistically significant reduction of pain in the intervention group. The dose of BTX-A was not higher than 300 IU, and the beneficial effect lasted for at least for 24 weeks. Eitner et al., (28) in a randomized controlled trial, showed a statistically significant improvement in neuropathic pain symptomatology in 46 patients with peripheral nerve injury following subcutaneous injection of BTX-A. This improvement was maintained for period of at least 24 weeks. Finally, in 2019 Meyer-Friebem et al., (29) published the results of a prospective series study in 60 patients with painful peripheral nerve injury, who were treated with perineural injection, under ultrasound guidance, with 25-100 IU BTX-A, to treat single peripheral nerve damage. The results of the study showed that the rate of pain reduction was 24.8% ($p<0.0001$). As the specific findings are promising, the authors of the study suggested that in the future, randomized controlled trials with at least 84 patients will be conducted to draw clearer conclusions regarding the effectiveness of the method.

With the present systematic review of the literature, recent research data were investigated in relation to the effectiveness of the action of botulinum toxin in the treatment of neuropathic pain. The main conclusions drawn from this review can be summarized as follows:

Statistically significant efficacy versus placebo was found in the treatment of neuropathic pain for trigeminal neuralgia (6), postherpetic neuralgia (13)), atypical ododalgia (17), neuropathic pain after spinal cord injury (20), diabetic neuropathy (24), piriformis syndrome (26) and peripheral nerve injury (27-29).

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Even though there is no specific protocol for the administration of the botulinum toxin (both in administration dose and repetitions) in the various cases of the above-mentioned pathological conditions, all researchers agree that t side / adverse effects are minimal and clinically insignificant.

Further research is needed with high-quality randomized control group studies as well as their meta-analyses, to accurately establish the effectiveness, indications, and protocols of use of the method.

Conclusion

This literature review reached the conclusion that the use of botulinum toxin is an effective treatment for neuropathic pain arising from a range of pathological conditions. Complications and side effects of the method are not clinically significant. Additional randomized controlled clinical studies with many patients are needed to further demonstrate the effectiveness of the method, to provide guidelines regarding its application protocols, and to identify possible differences in the effectiveness of the method in the various subgroups of patients.

Conflict of interest:

The authors declared no conflicts of interest.

REFERENCES

1. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nat Rev Dis Primer. 2017 Feb 16;3(1):17002.
2. Nigam P, Nigam A. Botulinum toxin. Indian J Dermatol. 2010;55(1):8.
3. Gastel B, Day RA. How to write and publish a scientific paper. Ninth edition. Santa Barbara, California: Greenwood; 2022. 348 p.
4. Sarkis-Onofre R, Catalá-López F, Aromataris E, Lockwood C. How to properly use the PRISMA Statement. Syst Rev. 2021 Dec;10(1):117, s13643-021-01671-z.
5. Shankar Kikkeri N, Nagalli S. Trigeminal Neuralgia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Apr 23]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554486/
6. Wu S, Lian Y, Zhang H, Chen Y, Wu C, Li S, et al. Botulinum Toxin Type A for refractory trigeminal neuralgia in older patients: a better therapeutic effect. J Pain Res. 2019 Jul;Volume 12:2177–86.
7. Zúñiga C, Piedimonte F, Díaz S, Micheli F. Acute Treatment of Trigeminal Neuralgia with Onabotulinum Toxin A. Clin Neuropharmacol. 2013 Sep;36(5):146–50.
8. Zhang H, Lian Y, Ma Y, Chen Y, He C, Xie N, et al. Two doses of botulinum toxin type A for the treatment of trigeminal neuralgia: observation of therapeutic effect from a randomized, double-blind, placebo-controlled trial. J Headache Pain. 2014 Dec;15(1):65.
9. Xia JH, He CH, Zhang HF, Lian YJ, Chen Y, Wu CJ, et al. Botulinum toxin A in the treatment of trigeminal neuralgia. Int J Neurosci. 2016 Apr 2;126(4):348–53.
10. Zhang H, Lian Y, Xie N, Chen C, Zheng Y. Single-dose botulinum toxin type a compared with repeated-dose for treatment of trigeminal neuralgia: a pilot study. J Headache Pain. 2017 Dec;18(1):81.
11. Crespi J, Bratbak D, Dodick DW, Matharu M, Jamtøy KA, Tronvik E. Pilot Study of Injection of OnabotulinumtoxinA Toward the Sphenopalatine Ganglion for the Treatment of Classical Trigeminal Neuralgia. Headache J Head Face Pain. 2019 Sep;59(8):1229–39.
12. Johnson RW, Rice ASC. Postherpetic Neuralgia. Solomon CG, editor. N Engl J Med. 2014 Oct 16;371(16):1526–33.
13. Apalla Z, Sotiriou E, Lallas A, Lazaridou E, Ioannides D. Botulinum Toxin A in Postherpetic Neuralgia: A Parallel, Randomized, Double-Blind, Single-Dose, Placebo-controlled Trial. Clin J Pain. 2013 Oct;29(10):857–64.
14. Hu Y, Zou L, Qi X, Lu Y, Zhou X, Mao Z, et al. Subcutaneous botulinum toxin-A injection for treating postherpetic neuralgia. Dermatol Ther [Internet]. 2020 Jan [cited 2023 Apr 23];33(1).

VOLUME 74 | ISSUE 3 | JULY - SEPTEMBER 2023

Available from: https://onlinelibrary.wiley.com/doi/10.1111/dth.13181
15. Chen L, Zhang Y, Chen Y, Wang T, Sun K, Tang H, et al. Efficacy and Safety of Botulinum Toxin A and Pulsed Radiofrequency on Postherpetic Neuralgia: A Randomized Clinical Trial. Teekaraman Y, editor. Contrast Media Mol Imaging. 2022 May 30;2022:1–9.
16. Melis M, Secci S. Diagnosis and treatment of atypical odontalgia: a review of the literature and two case reports. J Contemp Dent Pract. 2007 Mar 1;8(3):81–9.
17. Cuadrado ML, García-Moreno H, Arias JA, Pareja JA. Botulinum Neurotoxin Type-A for the Treatment of Atypical Odontalgia. Pain Med. 2016 Sep;17(9):1717–21.
18. Murray RF, Asghari A, Egorov DD, Rutkowski SB, Siddall PJ, Soden RJ, et al. Impact of spinal cord injury on self-perceived pre- and postmorbid cognitive, emotional and physical functioning. Spinal Cord. 2007 Jun;45(6):429–36.
19. Rintala DH, Holmes SA, Courtade RNFD, Courtade D, Loubser PG. Prevalence and characteristics of chronic pain in veterans with spinal cord injury. J Rehabil Res Dev. 2005;42(5):573.
20. Han ZA, Song DH, Oh HM, Chung ME. Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. Ann Neurol. 2016 Apr;79(4):569–78.
21. Li G, Lv CA, Tian L, Jin LJ, Sun P, Zhao W. A randomized controlled trial of botulinum toxin A for treating neuropathic pain in patients with spinal cord injury. Medicine (Baltimore). 2017 Dec;96(20):e6919.
22. Chun A, Levy I, Yang A, Delgado A, Tsai CY, Leung E, et al. Treatment of at-level spinal cord injury pain with botulinum toxin A. Spinal Cord Ser Cases. 2019;5:77.
23. Davies M, Brophy S, Williams R, Taylor A. The Prevalence, Severity, and Impact of Painful Diabetic Peripheral Neuropathy in Type 2 Diabetes. Diabetes Care. 2006 Jul 1;29(7):1518–22.
24. Chen WT, Yuan RY, Chiang SC, Sheu JJ, Yu JM, Tseng IJ, et al. OnabotulinumtoxinA Improves Tactile and Mechanical Pain Perception in Painful Diabetic Polyneuropathy. Clin J Pain. 2013 Apr;29(4):305–10.
25. Jankovic D, Peng P, van Zundert A. Brief review: Piriformis syndrome: etiology, diagnosis, and management. Can J Anesth Can Anesth. 2013 Oct;60(10):1003–12.
26. Michel F, Decavel P, Toussirot E, Tatu L, Aleton E, Monnier G, et al. Piriformis muscle syndrome: Diagnostic criteria and treatment of a monocentric series of 250 patients. Ann Phys Rehabil Med. 2013 Jul;56(5):371–83.
27. Attal N, de Andrade DC, Adam F, Ranoux D, Teixeira MJ, Galhardoni R, et al. Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2016 Dec;15(6):555–65.
28. Eitner L, Vollert J, Maier C, Attal N. Botulinumtoxin-A-Injektionen bei neuropathischem Schmerz: Eine Post-hoc-Subgruppenanalyse bei Patienten mit peripherer Nervenverletzung. Schmerz. 2017 Oct;31(5):524–6.
29. Meyer-Frießem CH, Eitner LB, Kaisler M, Maier C, Vollert J, Westermann A, et al. Perineural injection of botulinum toxin-A in painful peripheral nerve injury - a case series: pain relief, safety, sensory profile and sample size recommendation. Curr Med Res Opin. 2019 Oct;35(10):1793–803.

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Applications, effectiveness and limitations of robotic physiotherapy in patients with spinal cord injury

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ABSTRACT

Spinal cord injury (SCI) is a particularly serious pathological condition which puts a great strain on the health and functional status of the affected patient, while at the same time is accompanied by a very high morbidity and mortality rate. Among the various rehabilitation methods that have been used for the treatment of SCIs, since the 1990's, robotic physiotherapy has been an innovative alternative option. Robotic physiotherapy involves the application of a series of robotic devices the use of which is intended to assist and enhance the level of a number of the patient's functions that have been severely affected form the SCI, including their motor and sensory performance. This paper will attempt a brief narrative review of the literature in relation to the most recent research data regarding the applications, the effectiveness and the limitations of the use of robotic physiotherapy in patients suffering from spinal cord injury.

A total of 73 published papers since 2010 were isolated and studied, including 49 original research studies and 24 reviews / systematic reviews / meta-analyses. The main conclusion of the review is that with the use of these devices, patients with SCI have the possibility of a satisfactory level of safe walking, combined with the improvement of their activities of daily living and their quality of living. Ongoing research in this field will most probably enable the further improvement of the applications of the method in the coming years.

Key words: Spinal cord injury, Robotic, Rehabilitationw

Introduction

Spinal cord injury (SCI) is a particularly serious pathological condition which puts a great strain on the health and functional status of the affected patient, while at the same time it is accompanied by a very high morbidity and mortality rate. According to the recent epidemiologic data, it is estimated that for the year 2019, an incidence of 900.000 new cases were recorded globally, while at the same time, the total number of patients suffering from this injury during this period of time (prevalence) was estimated at 20.6 million [1]. At the same time, the highly significant epidemiological indicator of years in which patients lived with severe functional impairment (years lived with disability - YLD) was estimated at 6.2 million years; during the same period of time, the incidence of the injury was increasing, while the age of the affected

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patients was decreasing. It has now become apparent that both the incidence and severity of injury have been steadily increasing over the last 30 years, with the most severe effect being recorded in men and patients in older age groups [2].

The most commonly accepted and currently used classification of SCIs is the I.S.N.C.S.C.I. system (International Standards for Neurological Classification of Spinal Cord Injury system), which is more commonly known as the ASIA system (American Spinal Injury Association classification system) [3]; ASIA system classifies SCIs into five separate categories (A, B, C, D, E), according to the sensory and the motor impairments that have resulted from the injury. Grade A designates complete injury, whereas grade E patients present with no impairment at all [4]. In addition, incomplete SCIs can be classified into six syndromes with different clinical features one from the others: those are the anterior cord, the posterior cord, the central cord, the Brown-Sequard, the connus medullaris and the cauda equine syndromes, with varying clinical features and prognosis [5].

The effects of a severe SCI are not only limited to the impaired mobility and independence of the patient, but also include a large number of complications of the injury, including bowel and bladder disturbances (including recurrent and severe urinary tract infections), cardiovascular and pulmonary pathologies (orthostatic hypotension, deep vein thromboses, respiratory system infections), autonomic system complications (spasticity, autonomic dysreflexia) and even musculoskeletal system complications (fractures and pressure ulcers) [6]. Taking all the above into account, it is obvious the great importance of a comprehensive and well-designed rehabilitation programme, which will seek to improve the patient's mobility, while minimising, as far as possible, the complications of the SCI; this involves, in the vast majority of the cases, a long, expensive and even exhausting for the patient – and the therapists – rehabilitation program [7].

Among the various rehabilitation methods and systems that have been used for the treatment of SCIs, since the 1990's, robotic physiotherapy has been an innovative alternative option. Robotic physiotherapy involves the application of a series of robotic devices the use of which is intended to assist and enhance the level of a number of the patient's functions that have been severely affected form the SCI, including their motor and sensory performance [8]. A number of studies have shown that compared to conventional rehabilitation techniques, robotic applications have the potential to offer a fully controlled and intensive rehabilitation regimen, providing accurate information on the patient's progress, while at the same time greatly reducing the physical burden on therapists [9,10]. The use of robotic devices for the gait training commenced in 1994 with "Lokomat" [11], and in the following years, a wide range of rehabilitation robotic devices were developed and applied, which were classified into four main categories: 1) Grounded exoskeletons, 2) End – effector devices, 3) Wearable exoskeletons and the most recently developed 4) Soft exoskeletons or "exosuits" [12].

Despite, however, the significant recent technological development and the scientific research in this field, it is still not clear which type of robotic devices and rehabilitation protocols are the optimum for each therapeutic indication [13].

This paper will attempt a brief narrative review of the literature in relation to the most recent research data regarding the applications, the effectiveness and the limitations of the use of robotic physiotherapy in patients suffering from spinal cord injury. An extensive literature review was carried out on the following scientific databases: PubMed/NCBI, Scopus, Science Direct, Nature and PEDro, starting from the year 2010. The key-words (mesh terms) used in the search engines of the above data bases were: *spinal cord injury* AND *robotics* AND (*physiotherapy* OR *rehabilitation*). The inclusion criteria were original research studies, reviews and systematic reviews / meta-analyses concerning human participants. The flow-diagram of the literature review, according to the principles of PRISMA [14] is presented in Diagram 1.

Discussion

A total of 73 published papers were isolated and studied, including 49 original research studies and 24 reviews / systematic reviews / meta-analyses. The main findings of the present literature review are going to be presented in the following sections.

Applications of robotic physiotherapy

Following serious traumatic injury to the central nervous system, whether it involves the brain (head injuries) or the spinal cord, patient's balanced is significantly disturbed, due to spasticity, muscle weakness and muscle

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imbalance [15]; the end result is that motor commands given by the patient do not produce the expected motion, causing gross disturbances in his movement patterns. It is therefore obvious that the rehabilitation process following severe spinal cord injury is a very complex and demanding process.

As early as the beginning of this century, hospitals and rehabilitation centers gradually began to incorporate the use of robotic physiotherapy as a key part of the multi-level rehabilitation program for patients with severe traumatic spinal cord injuries. The main advantages offered by robotic physiotherapy can be summarized as follows [16]: (a) the robotic devices that are available today allow the patient to practice a wide range of motor activities, at various levels of intensity and with the possibility of unlimited repeatability, (b) during training with robotic devices, the patient is offered continuous feedback on the results of his/her movements, either in the form of visual or local-sensory stimuli, (c) robotic devices provide the advantage of training diversity, both in generic movements and activities, but also in their variations, along with special tasks and skills of the patient's activities of his daily life, (d) finally, robotic physiotherapy provides a safe environment for exploring their motion skills.

The first robotic physiotherapy device used was the "Locomat" (Hocoma AG, Volketswil, Switzerland) [17], whose function was based on the use of two robotic arms adapted to the patient's legs and assisted the movements of his knee and hip joints during the patient's practice of walking on an electric treadmill; at the same time, one part of the patient's body is supported by an overhead unloading device, thus allowing the patients, even in cases of great muscular weakness, to start exercising in the early stages after the injury.

Nowadays, a fairly large number of robotic devices are used in the rehabilitation of patients with severe spinal cord injuries, including the ARGO, the Brain-controlled robotic exoskeleton (EXO), the EKSO Bionics, the HAL (Hybric assisted limb), the INTEGO, LokoHelp robotic device, the Lokomat FreeD Module Pelvic, the Lokomat-Pro (without FreeD Module), the LOPES exoskeleton robotic device, the Mindwalker exoskeleton, the ReWalk exoskeleton, the WPAL (wearable power-assist locomotor) and the Welwalk WW-1000 robotic device [18]. Their purpose is to assist rehabilitation of the musculoskeletal, cardio-respiratory, urinary, neuronal and somatosensory system at all stages, while at the same time reducing to the best possible extent the physical fatigue and strain of their therapists [19].

Recent literature data

Since it is not possible, in the context of a short literature review, to present all the encountered original clinical studies, the results of the systematic reviews and meta-analyses will be presented. Table 1 summarizes the main findings of those systematic literature reviews.

Swinnnen et al. in 2010 [20] published a systematic literature review regarding the effectiveness of robot – assisted training of the gait of patients who sustained a serious spinal cord injury. The authors included four pre-experimental cohort clinical trials and two randomized-controlled trials, with 43, in total, participants. Lokomat was the robotic device used in five of the clinical trials and the LokoHelp robotic device was used in the last one. The main research questions of the review were to assume whether robot-assisted gait training (a) improved SCI patients' motor ability, while at the same time reduced spasticity, (b) improved performance and participation in daily-life activities, (c) improved social participation and overall quality of life and, (d) improved components of the International Classification of Functioning, Disability and Health (ICF 19) scale [21] better than other rehabilitation methods. The final conclusion was that they is insufficient evidence to reach to solid scientific findings in relation to the efficacy of the method since the participants' sample was very small, the rehabilitation and training procedures were heterogenous, the follow-up periods were not sufficient and higher quality clinical trials are needed in order to answer the above mentioned research questions.

Two years later, Mehrholz et al., [22] published in Cochrane Database of Systematic Reviews a systematic review and meta-analysis of 5 randomized-controlled studies (309 participants in total), regarding the efficacy of the various locomotor training methods, including robotic devices, after SCI. Lokomat was the robotic device used for the patients' rehabilitation, and the primary outcome measures of the review was speed of walking and walking capacity. The main finding of the study were that there was no clear evidence in relation to the superiority of any of the rehabilitation methods compared to the others; particularly for the robotic (Lokomat) assisted training, the effects regarding the outcome criteria of the

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TABLE 1:

The main findings of the systematic literature reviews

Author / country	Type of study	Participants	Method of robotic rehabilitation	Research questions	Results
Swinnen et al, (2010), Belgium [20]	Systematic literature review	6 clinical trials, 43 patients with SCI	Lokomat, LokoHelp	Improvements in motor ability, spasticity, daily life activities, social participation, quality of life and ICF 19 score	Cannot reach to a definite conclusion – small sample, methodological flaws, heterogenous rehabilitation procedures, small follow-up.
Mehrholz et al., (2012), Germany [22]	Systematic literature review and meta-analysis	5 randomized-controlled clinical trials, 309 patients with SCI	Lokomat	Speed of walking, walking capacity	No clear evidence regarding the superiority of any rehabilitation method, including the robotic-assisted.
Saartje Duerinck and Swinnen (2012), Belgium [24]	Systematic literature review	15 clinical trials	4 different types of robotic-assisted ankle-foot actuation orthotic devices	Neuromotor control of walking, restoration of normal gait pattern	Difficult to draw solid conclusions – robotic-assisted orthotic devices are a promising prospective for restoring normal gait pattern after SCI
Morawietz and Moffat, (2013), U.K. [23]	Systematic literature review	8 randomized-controlled clinical trials, 411 patients with incomplete SCI	Lokomat	Ambulatory function and gait characteristics	Inconclusive findings – no obvious superiority of one method (including the robotic-assisted) over the others.
Mehrholz et al., (2017), Germany [13]	Systematic literature review	13 randomized-controlled clinical trials, 586 patients with incomplete SCI	Lokomat	Walking distance and walking speed	There is strong evidence that robotic-assisted training is not superior in comparison to the conventional rehabilitation methods

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Cheung et al., (2017), Hong Kong [25]	Systematic literature review and meta-analysis	11 randomized-controlled clinical trials, 443 patients with SCI (both complete and incomplete)	Lokomat	Physical activity, mobility and functional ability	Walking impendence and endurance had better improvement in the robotic-assisted group; lower limb robotic-assisted training was as effective as the other forms of rehabilitation.
Nam et al., (2017), S. Korea [26]	Systematic literature review and meta-analysis	10 clinical trials, 502 patients with SCI	Lokomat	Gait distance, leg strength, functional level of mobility and independence	Lokomat-assisted gait training is superior to the conventional methods in improving mobility-related outcomes of patients with incomplete SCI.
Hollanda et al., (2017), Brazil [17]	Systematic literature review	39 clinical trials	12 different rehabilitation robotic devices	Multiple functional parameters	The rapid evolution of technology provides multiple opportunities to improve the results of SCIs patients' rehabilitation with the aid of various types of robotic devices.
Singh et al., 2018, Canada [27]	Systematic literature review	12 clinical trials, 72 patients with SCI	Upper extremity robotic rehabilitation devices: RiceWrist, Haptic Master, Armeo Spring, ReoGo, MAHI Exo-II and the InMotion 3.0 Wrist robot.	Body structure, function and activity level outcome measures	Substantial clinical improvement was observed in patients who had mild to moderate impairment of their neurological function (those who had mild spasticity while maintaining some level of motor function).

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Hayes et al., (2018), UK [28]	Systematic literature review	12 clinical trials, 521 patients with SCI	ReWalk, Lokomat	Walking distance and walking speed	The use of robotic - assisted therapy did not improve the patients' outcome criteria more than conventional methods of rehabilitation; this method provides the best results in the context of a multimodality rehabilitation intervention.
Sackleton et al., (2019), S. Africa [29]	Systematic literature review and meta analysis	27 clinical trials, 308 patients with SCI	ReWalk, Ekso, Indego, Rex	Walking perforamce, cardiovascular demand, VAS, Quality of life	The most favorable findings were found in relation to walking parameters; limited evidence regarding its training effects.
Alashram et al., (2021) [30]	Systematic literature review	16 clinical trials, 658 patients with SCI	Lokomat	Various functional parameters	The Lokomat robotic device has the potential to improve walking speed and distance, range of motion, strength and mobility of the patients - the so-far evidence does not support its effectiveness on balance, cardiorespiratory fitness, quality of life and depression.
Zhang et al., (2022), China [30]	Systematic literature review	12 clinical trials, 353 patients with SCI	Lokomat versus wearable exoskeleton	Walking paramaters.	Both robotic device systems had positive clinical effects on the rehabilitation of this group of patients, especially on walking distance and speed; wearable exoskeleton robotic devices have an advantage over the Lokomat robotic device in walking speed rehabilitation.

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study were not clear. The following year, the systematic review of Morawietz and Moffat [23], which investigated the same research question, came to roughly the same conclusions: the current evidence regarding the effectiveness of the various methods of locomotor rehabilitation (including the robotic – assisted physiotherapy methods) in patients with incomplete SCI is inconclusive, without demonstrating the clear superiority of one method over the others.

In a different context, Saartje Duerinck and Swinnen (2013) [24] published a systematic literature review regarding the efficacy and the added value of the robotic-assisted, actuated ankle-foot orthotic devices in restoring gait function in patients with SCI. Fifteen relevant clinical studies were analyzed, in which four different ankle-foot actuation orthotic devices were used according to their actuator and control mechanism. Once more, the small sample of the participants along with the wide variety of the studies' designs, made it impossible to reach into solid conclusions; nevertheless, it seems that artificial pneumatic muscles along with myoelectric control are a promising perspective in the effort to restore the normal gait pattern of patients with severe SCI.

Mehrholz et al., (2017) [13] conducted a systematic literature review comparing the effectiveness of robotic-assisted gait training or body-weight-supported treadmill training (BWSTT) to other rehabilitation methods in patients with SCI. They included 13 randomized-controlled studies with 586 patients, with the primary outcome criteria being walking distance and walking speed. The main conclusion of the review was that both robotic-assisted training and BWSTT did not show superior results in gait training compared to conventional rehabilitation methods. In fact, these results were so strong, based on very good quality studies, that according to the authors, no further research is needed in this specific area.

Another systematic literature review and meta-analysis was published in the same year [25] regarding the efficacy of robot-assisted training in patients with SCI; 11 randomized-controlled studies with 443 participants were included in the statistical analysis. The results of the study showed that walking impendence and endurance had better improvement in the robotic-assisted group, whereas lower limb robotic-assisted training was as effective as the other forms of rehabilitation. According to the authors, robot-assisted training seems to be a useful adjunct rehabilitation method for patients suffering from severe SCI. Similar positive results in relation to the use of the robotic device Lokomat for the improvement of walking function and activity of patients with SCI concluded the systematic review and meta-analysis of Nam et al., (2017) [26], which analyzed 10 trials (both randomized-controlled trials and parallel group or crossover design trial), with 502 participants. The main finding of this review was that robot-assisted gait training is superior to the conventional methods in improving mobility-related outcomes of patients with incomplete SCI, especially in the acute stages of the injury.

Holanda et al., (2017) [18], published a large systematic literature review (39 published papers) on the efficacy of robotic assisted gait rehabilitation for patient with SCI; they included a large number of different and novel robotic devices, which showed very promising results in many outcome criteria (pain perception, spasticity, proprioception, sensitivity to pressure, vibration and temperature, walking parameters, sitting posture and even psychological functions). The authors' final conclusion was that the rapid evolution of technology provides multiple opportunities to improve the results of SCIs patients' rehabilitation with the aid of various types of robotic devices.

Singh et al., [27], one year later, in a different context, published a systematic literature review regarding the efficacy of robot-assisted rehabilitation for the upper extremity in patients with SCI; they included 12 original papers, with 73 participants in total. The robotic devices used in the rehabilitation process were the RiceWrist, Haptic Master, Armeo Spring, ReoGo, MAHI Exo-II and the InMotion 3.0 Wrist robot. The results of the study showed that substantial clinical improvement was observed in patients who had mild to moderate impairment of their neurological function and more specifically in those who had mild spasticity while maintaining some level of motor function.

In another systematic literature review, Hayes et al., (2018) [28], studied the effect of robot assisted gait training on the temporo-spatial characteristic in patients with SCI; the study involved 12 clinical trials with 521 participants, whose neurological level of injury ranged from C1 – L3. The primary outcome measures of the study were the patients' walking distance and walking speed. The key finding of the study was that the use of robotic - as-

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sisted therapy did not improve the patients' outcome criteria more than conventional methods of rehabilitation. Some potential for improving patient's mobility was observed, but it is not clear exactly which robotic device and which group of patients offers the greatest benefit. It appears that this method provides the best results in the context of a multimodality rehabilitation intervention rather than monotherapy.

Sackleton et al., (2019) [29], in a systematic literature review and meta-analysis studied the effectiveness of robotic-assisted locomotor training on a number of parameters of patients with SCI, including gait performance, cardiovascular system functions, secondary complications of the injury and overall patient satisfaction with the rehabilitation method. The most favourable findings were found in relation to walking parameters (6 and 10 minutes walking test), whereas, no statistical significant changes were found in the cardiovascular indices. According to the authors, robotic-assisted physiotherapy is a useful tool in the rehabilitation process of patients with SCI, with limited evidence regarding its training effects.

Alashram et al., (2021) [30], investigated the effectiveness of the robotic device Lokomat for the gait training in patients suffering from SCI; after analyzing 16 clinical trials (658 patients), they concluded that 1) After an incomplete SCI, the Lokomat robotic device has the potential to improve walking speed and distance, range of motion, strength and mobility of the patients, but on the other hand, 2) The so-far evidence does not support its effectiveness on balance, cardiorespiratory fitness, quality of life and depression. The last study that will be discussed in the context of this literature review is the recently published systematic literature review of Zhang et al., (2022) [11], who compared the efficacy of Lokomat and wearable exoskeleton-assisted gait training in patients after SCI. The authors, after analyzing 12 clinical trials (353 patients in total), concluded that both robotic device systems had positive clinical effects on the rehabilitation of this group of patients, especially on walking distance and speed; it seems that wearable exoskeleton robotic devices have an advantage over the Lokomat robotic device in walking speed rehabilitation.

Over the last 20 years, the use of robotic devices in the rehabilitation process of patients with severe neurological impairments caused by either acute stroke or SCI has gained increasing acceptance in the scientific community. These are devices that have the ability to provide continuous, repetitive and systematic physiotherapy movements and interventions, greatly assisting the role of physiotherapists [31,32]. In addition, apart from the relief they offer to the difficult daily tasks of the physiotherapists, through the various sensors integrated in them, they give continuous feedback to the patients in relation to their performance of the exercises, while at the same time they evaluate the general progress of their rehabilitation process [16, 33]. In recent years, a large number of robotic devices have been manufactured and used in clinical practice, most of which are wearable and at the same time operate very close to the joints of patients, exerting a synergistic action with them [34]. Lokomat was the first robotic device used widely for this purpose, a fixed exoskeleton which was suspended over a treadmill [35]. Gradually, with the evolution of technology and the experience that was acquired, rehabilitation with the help of robotic devices gradually began to move away from this model and focus on the use of overground powered lower limb exoskeletons which allow the SCI patients with a significant degree of muscular weakness of the lower limbs to stand and walk with a type of gait that closely resembles the normal one [36, 37].

In the present literature review, recent scientific data regarding the applications, the effectiveness and the limitations of robotic physiotherapy were investigated, analysing the relevant systematic reviews and meta-analyses that have been published since 2010. The main findings of the review can be summarized in the following: (a) none of the earliest chronological reviews had reached a clear conclusion regarding the effectiveness of robotic physiotherapy [13,20,22-24]. For example Mehrhrolz et al., (2017) [13], reported that robotic-assisted physiotherapy had no advantage over conventional rehabilitation methods in improving patients' walking speed, (b) gradually, over time, as the experience of therapists in the use of these devices increased and their technical characteristics improved outcomes were more favorable. For example, Nam et al., (2017) [26], reported that Lokomat-assisted gait training is superior to the conventional methods in improving mobility-related outcomes of patients with incomplete SCI, whereas Singh et al., (2018) [28] observed the best results in those patients with SCI who had relatively mild degrees of spasticity, while retaining acceptable motor function and (c) nowadays research

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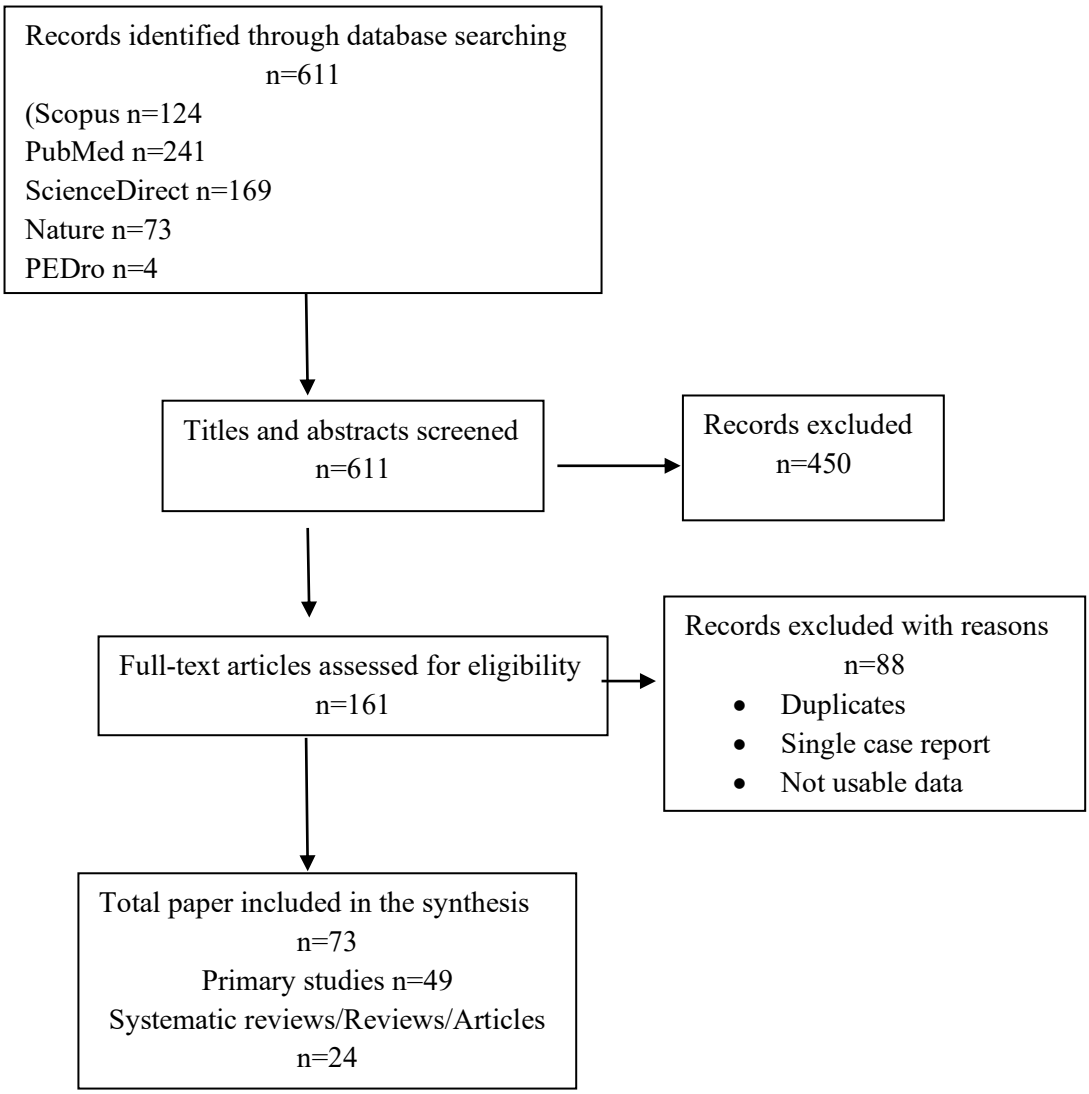

Diagram 1: The flow-diagram of the present literature review

data suggest that it is likely that the newest exoskeleton robotic devices, have some advantage over Lokomat – the first introduced one, for walking speed [30].

Conclusion

With the contribution of modern technology the applications of robotic-assisted physiotherapy are now an important tool in the multimodal rehabilitation effort of patients with severe SCIs. The recent research data show that with the use of these devices, patients with SCI have the possibility of a satisfactory level of safe walking, combined with the improvement of their activities of daily living and their quality of living. Ongoing research in this field will most probably enable the further improvement of the applications of the method in the coming years.

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REFERENCES

1. Ding W, Hu S, Wang P et al. Spinal Cord Injury: The Global Incidence, Prevalence, and Disability From the Global Burden of Disease Study 2019. Spine (Phila Pa 1976). 2022;47(21):1532–40.
2. Holmes D. Spinal-cord injury: spurring regrowth. Nature. 2017;552(7684):S49.
3. ASIA and ISCoS International Standards Committee. The 2019 revision of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)-What's new? Spinal Cord. 2019;57(10):815–7.
4. Osunronbi T, Sharma H. International Standards for Neurological Classification of Spinal Cord Injury: factors influencing the frequency, completion and accuracy of documentation of neurology for patients with traumatic spinal cord injuries. Eur J Orthop Surg Traumatol. 2019;29(8):1639–48.
5. Chay W, Kirshblum S. Predicting Outcomes After Spinal Cord Injury. Phys Med Rehabil Clin N Am. 2020;31(3):331–43.
6. Nas K, Yazmalar L, Şah V et al. Rehabilitation of spinal cord injuries. World J Orthop. 2015;6(1):8–16.
7. Munce SEP, Wodchis WP, Guilcher SJT et al. Direct costs of adult traumatic spinal cord injury in Ontario. Spinal Cord. 2013;51(1):64–9.
8. Balasubramanian S, Klein J, Burdet E. Robot-assisted rehabilitation of hand function. Curr Opin Neurol. 2010;23(6):661–70.
9. Rodríguez-Fernández A, Lobo-Prat J, Font-Llagunes JM. Systematic review on wearable lower-limb exoskeletons for gait training in neuromuscular impairments. J Neuroeng Rehabil. 2021;18(1):22.
10. Carpino G, Pezzola A, Urbano M et al. Response to: Comment on "Assessing Effectiveness and Costs in Robot-Mediated Lower Limbs Rehabilitation: A Meta-Analysis and State of the Art." J Healthc Eng. 2019;2019:9693801.
11. Zhang L, Lin F, Sun L et al. Comparison of Efficacy of Lokomat and Wearable Exoskeleton-Assisted Gait Training in People With Spinal Cord Injury: A Systematic Review and Network Meta-Analysis. Front Neurol. 2022;13:772660.
12. Schmidt K, Duarte JE, Grimmer M et al. The Myosuit: Bi-articular Anti-gravity Exosuit That Reduces Hip Extensor Activity in Sitting Transfers. Front Neurorobot. 2017;11:57.
13. Mehrholz J, Harvey LA, Thomas S et al. Is body-weight-supported treadmill training or robotic-assisted gait training superior to overground gait training and other forms of physiotherapy in people with spinal cord injury? A systematic review. Spinal Cord. 2017;55(8):722–9.
14. PRISMA [Internet]. [cited 2023 Jan 28]. Available from: https://www.prisma-statement.org/
15. Hidler J, Sainburg R. Role of Robotics in Neurorehabilitation. Top Spinal Cord Inj Rehabil. 2011;17(1):42–9.
16. Jayaraman A, Burt S, Rymer WZ. Use of Lower-Limb Robotics to Enhance Practice and Participation in Individuals With Neurological Conditions. Pediatr Phys Ther. 2017;29 Suppl 3:S48–56.
17. Hornby G, Campbell D, Zemon D, Kahn J. Clinical and quantitative evaluation of robotic-assisted treadmill walking to retrain ambulation after spinal cord injury. Topics in Spinal Cord Injury Rehabilitation. 2005;11(2):1–17.
18. Holanda LJ, Silva PMM, Amorim TC et al.. Robotic assisted gait as a tool for rehabilitation of individuals with spinal cord injury: a systematic review. J Neuroeng Rehabil. 2017;14(1):126.
19. Schwartz I, Sajina A, Neeb M et al. Locomotor training using a robotic device in patients with subacute spinal cord injury. Spinal Cord. 2011;49(10):1062–7.
20. Swinnen E, Duerinck S, Baeyens JP et al. Effectiveness of robot-assisted gait training in persons with spinal cord injury: a systematic review. J Rehabil Med. 2010;42(6):520–6.
21. Stucki G. International Classification of Functioning, Disability, and Health (ICF): a promising framework and classification for rehabilitation medicine. American journal of physical medicine & rehabilitation. 2005;84(10):733–40.
22. Mehrholz J, Kugler J, Pohl M. Locomotor training for walking after spinal cord injury. Cochrane Da-

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tabase Syst Rev. 2012;11:CD006676.
23. Morawietz C, Moffat F. Effects of locomotor training after incomplete spinal cord injury: a systematic review. Arch Phys Med Rehabil. 2013;94(11):2297–308.
24. Duerinck SM, Swinnen EM. The added value of an actuated ankle-foot orthosis to restore normal gait function in patients with spinal cord injury: a systematic review. J Rehabil Med. 2012;44:299–309.
25. Cheung EYY, Ng TKW, Yu KKK et al.. Robot-Assisted Training for People With Spinal Cord Injury: A Meta-Analysis. Arch Phys Med Rehabil. 2017;98(11):2320-31.e12.
26. Nam KY, Kim HJ, Kwon BS et al. Robot-assisted gait training (Lokomat) improves walking function and activity in people with spinal cord injury: a systematic review. J Neuroeng Rehabil. 2017;14(1):24.
27. Singh H, Unger J, Zariffa J et al. Robot-assisted upper extremity rehabilitation for cervical spinal cord injuries: a systematic scoping review. Disabil Rehabil Assist Technol. 2018;13(7):704–15.
28. Hayes SC, Wilcox JCR, White FHS, Vanicek N. The effects of robot assisted gait training on temporal-spatial characteristics of people with spinal cord injuries: A systematic review. J Spinal Cord Med. 2018;41(5):529–43.
29. Shackleton C, Evans R, Shamley D et al. Effectiveness of over-ground robotic locomotor training in improving walking performance, cardiovascular demands, secondary complications and user-satisfaction in individuals with spinal cord injuries: A systematic review. J Rehabil Med. 2019;51(10):723–33.
30. Alashram AR, Annino G, Padua E. Robot-assisted gait training in individuals with spinal cord injury: A systematic review for the clinical effectiveness of Lokomat. J Clin Neurosci. 2021;91:260–9.
31. Jamwal PK, Hussain S, Ghayesh MH. Robotic orthoses for gait rehabilitation: An overview of mechanical design and control strategies. Proc Inst Mech Eng H. 2020;234(5):444–57.
32. Dunkelberger N, Schearer EM, O'Malley MK. A review of methods for achieving upper limb movement following spinal cord injury through hybrid muscle stimulation and robotic assistance. Exp Neurol. 2020;328:113274.
33. Calabrò RS, Cacciola A, Bertè F et al. Robotic gait rehabilitation and substitution devices in neurological disorders: where are we now? Neurol Sci. 2016;37(4):503–14.
34. del-Ama AJ, Koutsou AD, Moreno JC, de-los-Reyes A, Gil-Agudo A, Pons JL. Review of hybrid exoskeletons to restore gait following spinal cord injury. J Rehabil Res Dev. 2012;49(4):497–514.
35. Kressler J, Thomas CK, Field-Fote EC et al. Understanding therapeutic benefits of overground bionic ambulation: exploratory case series in persons with chronic, complete spinal cord injury. Arch Phys Med Rehabil. 2014;95(10):1878-87.e4.
36. Kerdraon J, Previnaire JG, Tucker M et al. Evaluation of safety and performance of the self balancing walking system Atalante in patients with complete motor spinal cord injury. Spinal Cord Ser Cases. 2021;7(1):71.
37. Xiang XN, Zong HY, Ou Y et al. Exoskeleton-assisted walking improves pulmonary function and walking parameters among individuals with spinal cord injury: a randomized controlled pilot study. J Neuroeng Rehabil. 2021;18(1):86.

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Depression and Spinal Cord Injury

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ABSTRACT

Spinal Cord Injury refers to damage to the spinal cord. It may cause permanent disability or to some extent loss of sensation in parts of the body below the level of the damage. Literature data supports that Spinal Cord Injury (SCI) patients show symptoms of depression as a secondary complication. The purpose of this review is to demonstrate the association of major depressive disorder (MDD) with Spinal Cord Injury. A large proportion of patients will be diagnosed with depression 1 to 5 years after the injury. Tools for assessing such a mental disorder vary, the most common being the Patient Health Questionnaire (PHQ-9) which includes 9 relevant questions. Also, Major Depressive Disorder is related to the gender, age and ethnicity of the patient. The immediate need to deal with it is necessary as there is a high possibility that it will become chronic or recrudesce. In addition, it is necessary to evaluate the quality of life of people with spinal cord injury, which decreases after the injury and increases the likelihood of mental disorder.

Keywords: Spinal Cord Injury, Major Depressive Disorder, quality of life, assessment tools.

Introduction

Spinal Cord Injury represents a major traumatic event in a person's life and usually leads to pain and loss of motor and sensory function. People with Traumatic Spinal Cord Injury (SCI) may be vulnerable to complications such as pneumonia, urinary tract infections, cardiovascular disease, chronic pain and depression. This can reduce their quality of life and disturb their mental state. Depressive disorders are the most common form of psychological distress in SCI and appear to be more common than in the non-disabled population [5][14].

Research conducted at Dhulikhel Hospital and Spinal Injury Rehabilitation Center, showed that 68% of people with Spinal Cord Injury, who were on average at the age of 34,8 years, were in a depressed mood. Most of the participants were male (67.4) and had paraplegia (73.7). This state of depressed mood was significantly associated with gender, education, type of injury, and with the time of its occurrence since the injury [2]. Depressive symptoms are particularly prevalent after SCI and are related to aging, gender, or ethnicity, and there

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appear to be lower levels of subjective well-being SWB related to income, work, and educational opportunities among minority participants, with these differences possibly related to ethnic differences in socioeconomic status. (education and income) [5].

The aim of this study was to investigate the prevalence of depression after SCI and its association with pathophysiological, demographic, and socioeconomic factors, such as gender, age, level of injury, economic status, and suicidal ideation and highlight the importance of detecting and validly treating depression after a Spinal Cord Injury.

A review of the current literature was performed using the PUBMED online database and the following keywords: Spinal Cord Injury, Major Depressive Disorder, quality of life, assessment tools. Inclusion criteria for the review were: Primary studies of people with SCI, published after 2000 in the English language; the initial search came to 50 articles. After screening titles and abstracts, 26 articles were rejected because they did not meet the inclusion criteria. More specifically, studies were rejected because of their irrelevant title and because the population examined was animals or people without SCI. Eleven of the studies were rejected because they did not involve Spinal Cord Injury and 15 because they did not include the term depression.

Discussion

Finally, there were 24 studies included in the present review (Table 1). A cross-sectional study of 134 adults (≥18 years) with SCI was conducted by the Brain and Spinal Cord Injury Research Center (BASIR) clinic, Tehran University of Medical Sciences. The Beck Depression Inventory (BDI-II Persian), a multiple-choice inventory with 21 questions, was used to measure the presence and severity of depression. Data were collected through interview. The results were that (49.3%) of the participants had mild to severe depression. There was a greater likelihood of depression in people with SCI who were female and had quadriplegia, suicidal thoughts, a history of attempted suicide, a low educational level, or cared for a family member other than a spouse or parents. Conclusion: Depression was highly prevalent in individuals with SCI and was associated with certain demographic, pathophysiological and socioeconomic indicators. The main predictors and factors affecting depression should be determined to provide early detection and early treatment to prevent more complications and improve the quality of life of people with SCI [7,11].

Other research conducted with the Patient-Reported Outcomes Measurement System (PROMIS). Physical Function Bank data), depression (Patient Health Questionnaire-9 (PHQ-9)), pain severity (0–10 numerical rating scale (NRS)) and fatigue (0–10 NRS) showed that pain and fatigue were independently associated with depression.

In addition, depression was more severe in middle-aged participants than in younger or older participants. Physical function decreased with increasing age, as well as with higher level of injury [10].

Depression

The term 'depression' does not only refer to an emotional state. It is also associated with thought, behavior and certain physical changes. Patients with depression tend to have negative thoughts about themselves, their experiences and their future. Initial experiments validate the tests for depression, creating a powerful model system for further understanding of the relationships between molecular changes induced by SCI and the development of depression [13].

People living with a Spinal Cord Injury (SCI) run an increased risk of a number of chronic health conditions, including secondary comorbidities that may develop or be affected by the injury, the presence of the lesion, and/or the aging process [4,9].

Having Major Depressive Disorder (MDD) is associated with poorer subjective health, lower satisfaction in life, and greater difficulty in daily role functioning. Both physical and psychological symptoms predict potential MDD [3]. Individuals at highest risk are those with a history of depression prior injury [hazard ratio (HRR) 1.6; 95% CI: 1.1–2.3],history of substance abuse (HRR 1.6; 95% CI: 1.2–2.3) or permanent neurological deficit (HRR 1.6; 95% CI: 1.2–2.1). Depression occurs frequently and early on, in people suffering from SCI. Both the patient and the injury factors are related to the development of depression. These data should be used to target patients for mental health assessment and services during initial hospitalization and after

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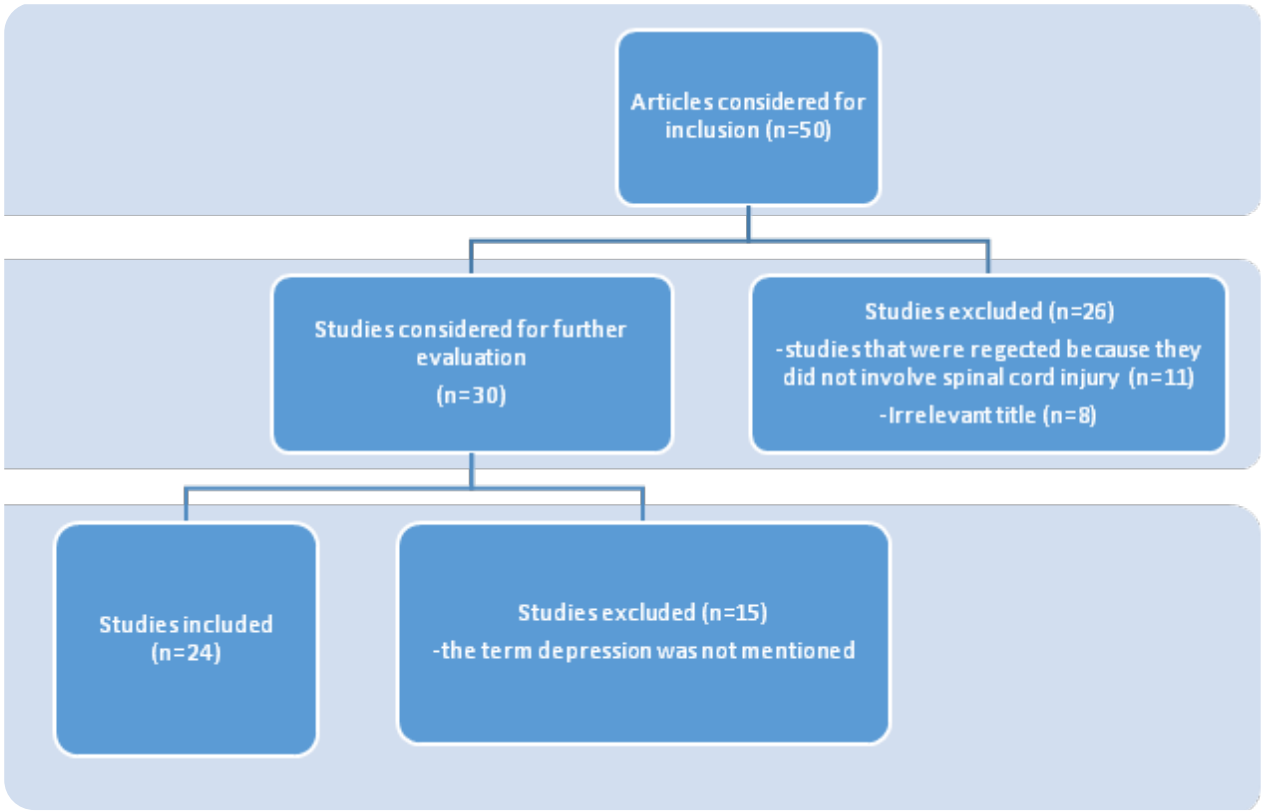

discharge from hospital and their intergration into the community [6,12,21].

The complexity of the mental health problems faced by many people with Spinal Cord Injury living in the community needs to be highlighted. Providing mental health services to this vulnerable population requires recognition of co-morbidity and issues of mobility [15]. However, recent studies indicate that depressive symptomatology increases immediately after hospital discharge but decreases significantly 36 months thereafter [18].

Depression, Quality of life and Anxiety

Quality of life is related to health (HRQOL) and well-being. With various instruments of measurement HRQOL (SF-36 and Illness Impact Profile) and well-being (Life Satisfaction Scale and Life Satisfaction Questionnaire) domains are identified where the quality of life of people with SCI is inferior, compared to that of the general population [22,24].

Depression and assessment

A variety of tools such as a depression scale can be used to assess depression so as to rate its symptoms, weekly score recording as well as questionnaires such as the PHQ-9. A reliable scientific tool used to determine the presence of depression with the help of only 9 questions. The authors investigated the PHQ-9 factor structure among individuals with SCI at various time points post-injury. Contingency factors were associated with life satisfaction. This resulted in a 2-factor solution for all groups, with 3 emotional-reported items (feeling depressed/hopeless, feeling bad about self/failure, and suicidal ideation) and 3 physical-reported items (sleep disturbance, low energy/fatigue, and appetite disturbance) loading consistently on Emotional and Physical factors, respectively, at all time points. Factor scores were negatively correlated with life satisfaction.

It remains unclear whether body object validation

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reflects depressive symptomatology per se. However, validation is still associated with life satisfaction [3,12,19,20,21,25,26].

Depression and treatment

The response to SCI was a stable low depression, whereas persistent moderate to severe depression, mainly, represented a continuation or recrudescence of prior to injury depression. This line of research has the potential to improve identification of subgroups destined for negative outcomes and inform early intervention studies [17]. Depression is almost always treatable. The strategies used are cognitive psychotherapy, medication, improving interpersonal relationships and behavioral activation. Cognitive behavioral therapy for depression helps patients learn new ways of thinking and behaving to ensure lasting results in improving their emotional state. It is essential, however, that α combination of these strategies must be applied in order to better deal with it. The low rate of mental health treatment for people with SCI and possible major depression has implications for improving the effectiveness of depression treatment in people with SCI [1,8,23].

To address this high prevalence, clinical doctors should use these risk factors and on-going systematic screening to identify those at risk of depression. Aggravating health problems and the lack of effective depression treatment in SCI patients may contribute to high rates of chronic or recurrent depression [9]. There is a necessity for group psychological intervention with the aim to improve psychological adjustment, self-concept and adaptive coping following Spinal Cord Injury. The theoretical foundations of the Coping Effectiveness Training Program (CET) are based on Lazarus and Folkman's (1984) cognitive theory of stress and coping and cognitive behavioral therapy techniques [16]. A significant ($p<0.001$) 57% reduction in depressive symptoms occurred in the group being treated, whereas there was no significant change in the untreated group. At the end of 6 months, 30% of participants were not depressed, 42% were mildly depressed, and 29% were still majorly depressed, but to a lesser extent. Activities in the community increased significantly during the treatment period, as did life satisfaction. In conclusion, while it is suggested that depression is treatable in this population, 6 months may not be a sufficient time frame to achieve maximum benefit [27].

REFERENCES

1. Elliott, T.R., Kennedy, P. Treatment of Depression Following Spinal Cord Injury: An Evidence-Based Review *Rehabilitation Psychology 2004;49*(2):134–39. https://psycnet.apa.org/doiLanding?doi=10.1037%2F0090-5550.49.2.134
2. Adhikari, S.P., Gurung, G., Khadka, B., 'et all'. Factors influencing depression in individuals with traumatic spinal cord injury and caregivers perceived burden in low-income country: a cross sectional study. *Family Med Prim Care 2002;*30(9):4890-96. https://pubmed.ncbi.nlm.nih.gov/32203068/
3. Bombardier, C.H., Richards, J.S., Krause, J.S., 'et all'. (2004). Symptoms of major depression in people with spinal cord injury: implications for screening. *Archives of Physical Medicine and Rehabilitation* 2004;85(11):1749-56. https://www.sciencedirect.com/science/article/abs/pii/S0003999304010846
4. Paterson, M.D, Kamdar, N., Whitney, D.G., 'et all'. (2019). Psychological morbidity and chronic disease among adults with non traumatic spinal cord injuries: a cohort study of privately insured beneficiaries. *Mayo Clinic Proceedings* 2019;19(10):1680-86. https://www.sciencedirect.com/science/article/abs/pii/S1529943019307880
5. Krause, J.S., Kemp, B., Coker, J. (2000). Depression after spinal cord injury: relation to gender, ethnicity, aging, and socioeconomic indicators. *Archives of Physical Medicine and Rehabilitation 2000;*81(8):1099-109. https://www.sciencedirect.com/science/article/abs/pii/S0003999300085555

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6. Dryden, D.M., Saunders, L.D., Rowe, B.H., 'et all'. Depression following Traumatic Spinal Cord Injury. *Neuroepidemiology* 2005;25(2):55-61.https://www.karger.com/Article/Abstract/86284
7. Khazaeipour, Z., Taheri-Otaghsara, S., Naghdi, M. Depression following spinal cord injury: it's relationship to demographic and socioeconomic indicators. *Spinal Cord Injury Rehabilitation*, 2015;21(2):149-55. https://meridian.allenpress.com/tscir/article/21/2/149/190757/Depression-Following-Spinal-Cord-Injury-Its
8. Fann, J.R., Bombardier, C.H., Richards, J.S., 'et all'. Depression after spinal injury: comorbidities, mental health service use, and adequacy of treatment. *Archives of Physical Medicine and Rehabilitation* 2011;92(3):352-60. https://pubmed.ncbi.nlm.nih.gov/21255766/
9. Hoffman, J.M., Bombardier, C.H., Graves D.E., 'et all'. A longitudinal study of depression from 1 to 5 years after spinal cord injury. *Archives of Physical of Physical Medicine and Rehabilitation,* 2011;12(3):411-8. https://pubmed.ncbi.nlm.nih.gov/21353823/
10. Alschuler, K.N., Jensen, M.P., Sullivan-Singh, S.J., 'et all'. The association of age, pain, and fatigue with physical functioning and depressive symptoms in persons with spinal cord injury. *The Journal of Spinal of Spinal Medicine* 2013;36(5):483-91. https://www.tandfonline.com/doi/abs/10.1179/2045772312Y.0000000072
11. Bonanno, G.A., Kenedy, P., Galatzer-Levy, I.R., 'et all'. Trajectories of resilience, depression, and anxiety following spinal cord injury. *Rehabilitation Psychology* 2012;57(3):236-47. https://psycnet.apa.org/doiLanding?doi=10.1037%2Fa0029256
12. Graves, D.E., Bombardier, C.H. Improving the efficiency of screening for major depression in people with spinal cord injury. *The Journal of Spinal Cord Medicine 2008;*31(2):177-84. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2565478/
13. Luedtke, K., Maldonado-Bouchard, S., Wolle, S.A., 'et all'. Assessment of depression in a rodent model of spinal cord injury. *Journal of Neurotrauma 2004;*31(2). https://www.liebertpub.com/doi/full/10.1089/neu.2013.3204
14. Shin, L.C., Goo, H.R., Yu, S.G., 'et all'. Depression and quality of life in patients within the first 6 months after the spinal cord injury. *Annals of Rehabilitation Medicine* 2012;36(1):119-25. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3309324/
15. Migliorini, C., Tonge, B., Taleporos, G. Spinal cord injury and mental health. *Australian and New Zealand Journal of Psychiatry*, 2008;42(4). https://journals.sagepub.com/doi/abs/10.1080/00048670801886080
16. Kennedy, P., Duff, J., Evans, M., 'et all'. Coping effectiveness training reduces depression and anxiety following traumatic spinal cord injuries. *British Journal Clinical Psychology, 2010;*42(1):41-52. https://bpspsychub.onlinelibrary.wiley.com/doi/abs/10.1348/014466503762842002
17. Bombardier, C.H., Adams, L.M., Fann, J.S., 'et all'. (2016). Depression trajectories during the first year after spinal cord injury. *Archives of Physical Medicine and Rehabilitation, 2016;*97(2):196-203. https://pubmed.ncbi.nlm.nih.gov/26525525/
18. Dorsett, P., Garagthy, T. Depression and adjustment after spinal cord injury: a three-year longitudinal study. *Spinal Cord Injury Rehabilitation* 2004;9(4):43-56. https://meridian.allenpress.com/tscir/article/9/4/43/66545/Depression-and Adjustment-After-Spinal-Cord-Injury
19. Richardson, E.S., Richards, S.S. (2008). Factor structure of the PHQ-9 screen for depression across time since injury among persons with spinal cord injury. *Rehabilitation Psychology* 2008;53(3):243-49. https://psycnet.apa.org/record/2008-06402-016?doi=1
20. Krause JS., Bombardier C, Carter RE. Assessment of depressive symptoms during inpatient rehabilitation for spinal cord injury: is there an underlying somatic factor when using the PHQ? *Rehabilitation Psychology* 2008;53(4):513-2 https://psycnet.apa.org/record/2008-17022-011?doi=1
21. Ulrich, P.M., Linconin, R.K., Tachett, M.S., 'et

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all'. Pain, depression, and health care utilization over time after spinal cord injury. *Rehabilitation Psychology* 201358(2):158-65. https://psycnet.apa.org/doiLanding?doi=10.1037%2Fa0032047

22. Post, M., Noreau, L. Quality of life after spinal cord injury. *Journal of Neurologic Physical Therapy* 2005;29(3):139-46. https://journals.lww.com/jnpt/FullText/2005/09000/Quality_of_Life_After_Spinal_Cord_Injury.5.aspx
23. Fann, J.R., Bombardier, C.H., Richards J.S., 'et all'. Depression after spinal cord injury: comorbidities, mental health service use, and adequacy of treatment. *Archives of Physical Medicine and Rehabilitation 2011;*92(3):352-60. https://www.sciencedirect.com/science/article/abs/pii/S0003999310003746
24. Bonanno, G.A., Kennedy, P., Galatzer-Levy, I.R., 'et all'. Trajectories of resilience, depression, and anxiety following spinal cord injury. *Rehabilitation Psychology 2012;*57(3):236-47. https://psycnet.apa.org/record/2012-23562-006?doi=1
25. Kalpakjian, C.Z., Bombardier, C.H., Schomer, K., 'et all'. Measuring depression in persons with spinal cord injury: a systematic review. *The Journal of Spinal Cord Medicine 2009;*32(1):6-24. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2647502/
26. Bombardier, C.H., Kalpakjian C.Z., Graves, D.E., 'et all' Validity of patient health questionnaire-9 in assessing major depressive disorder during inpatient spinal cord injury rehabilitation. *Archives of Physical Medicine and Rehabilitation* 2012;93(10):1838-45. https://www.sciencedirect.com/science/article/abs/pii/S0003999312003152
27. Kemp, B.J., Kahan, J.S., Krause, J.S., 'et all'. Treatment of major depression in individuals with spinal cord injury. *The Journal of Spinal Cord Medicine* 2008;27(1):22-8. https://www.tandfonline.com/doi/abs/10.1080/10790268.2004.11753726

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Spinal Cord Injury Associated with Spinal Stenosis: Outcomes and Prognostic Features.

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ABSTRACT

Spinal cord injury (SCI) is gradually considered to be a health priority worldwide, due to its ever-growing occurrence in the recent years. When associated with spinal stenosis, it results in substantial pain and disability and becomes the most prevalent reason for spinal surgery in individuals exceeding the 50 years of age. The aim of this review is to examine and compare functional outcomes and define the prognostic features for patients suffering from spinal cord injury (SCI) associated with spinal stenosis. A search in PubMed, ScienceDirect, EMBASE and AMED was conducted, using keywords such as, "Spinal Cord injury" and "Spinal Stenosis". Our literature research was completed in April 2022 and the review was carried out according to the guidelines of the PRISMA. 23 studies were included. Approximately 7,900 patients were observed in 20 studies and a considerable number of those were followed for time period ranging from 1 to 4 years. Study's outcomes indicate that best prognostic factors lie with patients suffering from incomplete CSCI without major fracture or pre-existing CSCS when undergoing early surgery. Age is a good prognostic factor. Studies are contradictory whether early surgical treatment determines positive outcomes.

Keywords: spinal cord injury (SCI); spinal canal stenosis; lumbar spinal stenosis, cervical spinal stenosis.

Introduction

Spinal Stenosis interprets the narrowing of the spinal canal or the intervertebral foramina at various anatomic levels, secondary to pathologic processes of the vertebral elements. Lumbar spinal stenosis (LSS), Cervical spinal stenosis (CSS) and Central canal stenosis are classified under the label of Spinal Stenosis.

Spinal Stenosis is a degenerative chronic condition in which the spaces around the neurovascular structures of the spine become narrower, usually in the cervical or lumbar spine, mostly due to aging process. It evokes pain in the lower parts of the body, instability, impaired ambulation, neurological deterioration in the case of LSS or pain in the neck and upper ligaments, cervical radiculopathy, cervical myelopathy in the case of CSS [1,2]. Spinal Stenosis may also be related to spi-

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nal cord injury (SCI). The yearly incidence of spinal cord injury (SCI) in the United States is estimated to amount to approximately 17.810 new cases [3]. Yet, it is growingly regarded as a health priority globally [4-6]. Motor and sensory impairment, pain, respiratory and cardiovascular alterations, loss of bladder and bowel function, tetraplegia are some of its direct complications [7,8]. Given the impact of Spinal Stenosis in the mobility, autonomy and quality of life of a considerable amount of people worldwide, it is the most common reason for spinal surgical treatment [5,6.9-11] . This study aims to review outcomes and prognostic factors for patients suffering from SCI associated with spinal stenosis.

PubMed databases, MEDLINE, Embase and AMED were searched for studies published between 1990 and 2022 employing keywords such as, "Spinal Cord injury" and "Spinal Stenosis". Our literature research was completed in March 2022 and the review was conducted in accordance with the guidelines of the PRISMA [12].

Eligibility criteria: Studies providing information on outcome measures and prognostic factors about recovery from Spinal Cord injury associated with Spinal Stenosis. The articles had to be either written or translated into English. Access to full text was essential.

Study exclusion criteria: Articles that were not written or translated in English or German were excluded. Articles that were impossible to be accessed in full text were excluded as well. Articles that failed to associate spinal cord injury with spinal stenosis or lacked prognostic factors were not included either. We decided to also exclude studies that examined a specific age group, omitting large ratios of the general population and studies that involved a single patient. Three studies were conducted on animals and therefore were excluded, too.

Each record that fulfilled the inclusion criteria was fully read. 27 reports were retrieved by the reviewer (Figure 1). No automation tools were used in the process.

Discussion

The initial electronic database search produced an overall of 52 articles of these, 23 were considered for inclusion in this review (Figure 1). Approximately 7,900 patients were observed in 20 studies and a considerable number of those was followed for a period of time ranging from 1 to 4 years.

Torg et al. examined 117 footballers suffering from cervical spinal stenosis with cord neurapraxia and transient quadriplegia. No correlation was found between stenosis of the spinal canal and irreversible sequelae [13]. It is advisable that patients with cord neurapraxia resulting from transient, reversible compression deformation of the spinal cord refrain from contact activities. Kirshblum & O'Connor (1998) assembled studies that focused on prognosis following traumatic SCI. They concluded that comprehensive physical examination is the most precise method in order to predict neurologic recovery [14].

Several studies have reported that age[15-19]plays an important part in successful recovery, especially when incomplete spinal cord injury is involved [17]. However, race, gender and injury mechanics bear no influence to neurologic recovery [15].

Yale et al. state that neurologic outcome depends on the diameter of the residual spinal canal. In their study involving 200 patients suffering from trauma in cervical spine, the authors reported that those with residual cervical spinal canal diameter <10 mm presented neurologic deterioration, whereas the group with residual cervical spinal canal diameter >10 mm had neurologic recovery [20].

AArabi et al, studied 42 patients with ATCCS due to spinal stenosis. They had a follow up for a year and examined ASIA motor score, midsagittal diameter at the point of maximum compression, MCC, length of parenchymal damage on T2-weighted MR imaging. They also conducted a 10 independent variable gradual regression analysis. Measurements revealed that mean admission ASIA motor score was 63.8, compression was in most cases observed at skeletal segments C3-4 & C4-5 of the spinal cord (71%), mean midsagittal diameter was 5.6 mm in the area of the spinal cord where compression was maximized, maximum canal compromise (MCC) rated 50.5%, spinal cord compression was 16.5% at its maximum point, length of parenchymal damage on T2-weighted MR imaging was 29.4 mm. The period between injury and surgery did not exceed 24 hours in 9 patients. 10 patients were operated within 2 days at most from injury time, 23 patients

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underwent surgery later than 2 days since the injury. At the 1-year follow-up, measurements read: mean ASIA motor score 94.1, FIM 111.1, manual dexterity 64.4% of baseline, pain level 3.5. Regression analysis indicated that ASIA motor score at follow-up and admission ASIA motor score ($p = 0.003$) were considerably connected. The same applied between MCC ($p = 0.02$), and midsagittal diameter ($p = 0.02$). FIM and admission ASIA motor score ($p = 0.03$), MCC ($p = 0.02$), and age ($p = 0.02$) were linked. Manual dexterity and admission ASIA motor score ($p = 0.0002$) as well as length of parenchymal damage on T2-weighted MR imaging ($p = 0.002$) were related. Relationship was observed between pain level and age ($p = 0.02$) and length of parenchymal lesion on T2-weighted MR imaging ($p = 0.04$), as well [21].

In the study of Alpízar-Aguirre et al., 195 patients with cervical stenosis were followed. Female patients at the ages between 46 and 55 were predominant. C5-C6 were the points that suffered at the majority of the cases. Following surgery, they had remarkable improvement of the neck disability. Surgery was demonstrated to be better treatment than physical therapy in other studies, too [22-24].

Kwon et al. (2015) examined 246 patients enduring cervical cord injury. A 1-year follow-up was conducted and a second one was performed at a mean period of 42.2 months. Measurements showed Mean American Spinal Injury Association (ASIA) motor score 38.4 ± 21.9 (range, 2-70) when patients were admitted, ameliorated to 67.7 ± 19.1 (range, 8-94) at the last follow-up ($p < 0.05$). Mean recovery rate of motor score 55.8 ± 19.9%. SI grade 0 was observed in 5 patients, SI grade 1 was recorded in 20 patients, whereas 13 subjects were found with SI grade 2. Age, initial ASIA motor grade, intramedullary SI grade, and SAC bore remarkable relationship with the neurological outcome. The neurological outcome did not seem to be affected by initial cervical alignment, canal diameter, length of SI, period between injury-operation, and OPLL type [25].

In the study of Bonavita et al., 168 patients with Traumatic Spinal Cord Injury and 72 patients with incomplete Spinal Cord Injury were monitored. Patients with an ISCI were older and had fewer cervical lesions than subjects enduring TSCI. Etiology and lesion features were pinpointed as predictors of functional (SCIM improvement and SCIM at discharge) outcome when linear and logistic regression were conducted. Traumatic patients when compared to ischemic ones were found to have greater results. Occurrence of complications, time spent in hospital & discharge dispositions were found to be associated with AIS level, lesion level and age of patients [26].

Park et al. examined 73 patients with cervical spinal cord injury who were treated with one-level decompression and fusion surgery. Of the 73 patients suffering SCI, 27 showed ≥1 grade of AIS immediate improvement and 35 subjects had the same improvement 3 months after surgery. Multivariate analysis revealed that mean arterial blood pressure (MAP) played an important role in recovery of SCI patients during the immediate post-operative period. In the late recovery period at 3 months after surgery, recovery was associated with AIS before surgery and the MAP [27]. On the other hand, Shigematsu et al., in their study, followed 32 patients with cervical spinal canal stenosis. 17 of them underwent decompression and 15 received conservative treatment. At the final follow-up, 3 patients (9.3%) had returned to their pre-injury Frankel grade. 26 patients (83.3%) lost one or more neurological grades. 3 patients (9.3%) passed away. However, in Lee et al. study (29), a 2-year follow-up period was utilized to reveal higher percentages in patients that had undergone surgery than in patients that had received conservative treatment ≥1 grade (90.9% vs. 57.1%, P=0.0051) and 2 grade (30.3% vs. 9.5%) improvements in ASIA grade. In multivariate analysis, solely early surgical treatment resulted in ASIA grade improvement after 2 years (P=0.0044) [28].

Khorasanizadeh, et al. [30] conducted a random pooled effect analysis as well as meta-regression analysis in 114. It was concluded that the injury level was related to recovery; recovery rates formed a sequence: lumbar > cervical and thoracolumbar > thoracic. There was high probability that complete injury would be the aftereffect of thoracic SCI and penetrating SCI. Penetrating TSCI showed lower recovery rate than blunt injury (OR 0.76, 95% CI 0.62-0.92; $p = 0.006$). Follow-up duration had a positive relation to recovery rate ($p = 0.001$). Injury factors, namely, the severity, the level and the mechanism of injury affect post TSCI neurological recovery regardless what treatment

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is followed or country of origin of the patients. A follow-up of at least one year period is essential for TSCI studies when patients with neurologically incomplete injury are included.

The most important prognostic factor relating to neurologic recovery in spinal cord injury is contusion plenum. Incomplete cervical spinal cord lesions in younger patients and those with either a central cord or Brown-Sequard syndrome are more likely to recover[15]. SCI clinical syndromes manifest a considerable number of admissions to acute SCI rehabilitation. CCS most frequently occurring, especially in older ages, displays poor admission functional level in comparison with other SCI clinical syndromes. Individuals enduring cervical BSS obtain higher functional improvement, when discharged, as to individuals suffering CCS. The functional outcomes regarding patients with CMS and CES have been proven to be equal. Individuals diagnosed with ACS manifest the longest LOS of the SCI clinical syndromes while inpatient rehabilitation is recommended [16].

According to Rüegg et al., MR measurements of the cord-canal-area ratio (> 0.8) or the space available for the cord (< 1.2 mm) enable reliable identification of patients susceptible to acute CSCI following a minor trauma to the cervical spine. Yet, spinal canal imaging characteristics are not likely to relate to the severity of or recovery from CSCI subsequent to minor trauma [31]. Patients in peril of acute SCI following a minor trauma to the cervical spine are detectable when applying a disc-level canal diameter cutoff value (measured on MR images) of 8 mm. Radiological characteristics of the spinal canal may also determine the severity of acute SCI after a minor trauma to the cervical spine [32]. In the study of Eismond et al., the authors stated that a larger sagittal diameter of the cervical spine is protective of the neural elements [33]. On the other hand, as far as thoracolumbar spine is concerned, Vacaro et al. reported that thoracolumbar spine dimensions do not provide an explanation for the neurologic injury degree subsequent to burst fracture. The authors reported that contrary to what would be inferred, larger canals do not defend neural elements [34].

Neurological recovery after TSCI is definitely reliant on injury factors (i.e., severity, level, and mechanism of injury), yet not affected by type of treatment or country of origin [30]. Marked stenosis of the cervical spinal canal might result in irreversible changes in the spinal cord when combined with indirect minor trauma. It is, therefore, advisable to verify with lateral radiograph of the cervical for early detection of cervical spinal stenosis [20].

Poor neurological recovery is noticed in patients suffering complete thoracic SCI, when levels are above T10. A high SI grade on preoperative T2WI negatively affects neurological outcome. Consequently, the severity of SI change, cord compression ratio, and preoperative neurological status are considered to be important prognostic factors when relation between SCI and OPLL is detected [25].

Age at the time of injury, also, determines prognosis as young patients have better chances to functional recovery. Conversion to a better AIS grade enabled patients to ameliorate concerning self-care and mobility in 12 months [17]. On the other hand, MSCC, spinal cord hemorrhage and cord swelling are prognostic factors for small neurologic recovery. Extent of MSCC is more reliable than presence of canal stenosis for predicting the neurologic outcome after SCI [35].

While preoperative neurological status, cord compression ratio, SI grade and hemodynamic MAP at admission serve for prognosis of recovery [25,27] the MR imaging diagnosis before operation may not always correspond to the intraoperative discoveries, thus failing to provide a comprehensive and accurate diagnosis. Emphasis should be laid on clinical symptoms [36]. It is advisable that acute SCI patients undergo comprehensive physical examination in order to detect the initial level and classification of the injury and predict neurologic recovery. Clinical examination combined with somatosensory evoked potentials, magnetic resonance imaging, transcranial magnetic stimulation and similar tests are likely to define the outcome [14]. Additionally, diagnosis of ischemia and trauma may assist in functional recovery in SCI patients [26].

Samuel et al. (2015) suggest that the majority of patients with SCI do not undergo surgery within the first 24 hours after injury, and the majority of delays occur after inpatient admission which affects the recovery rate later [25]. Early surgery proved to provide better neurological outcomes when compared to conserva-

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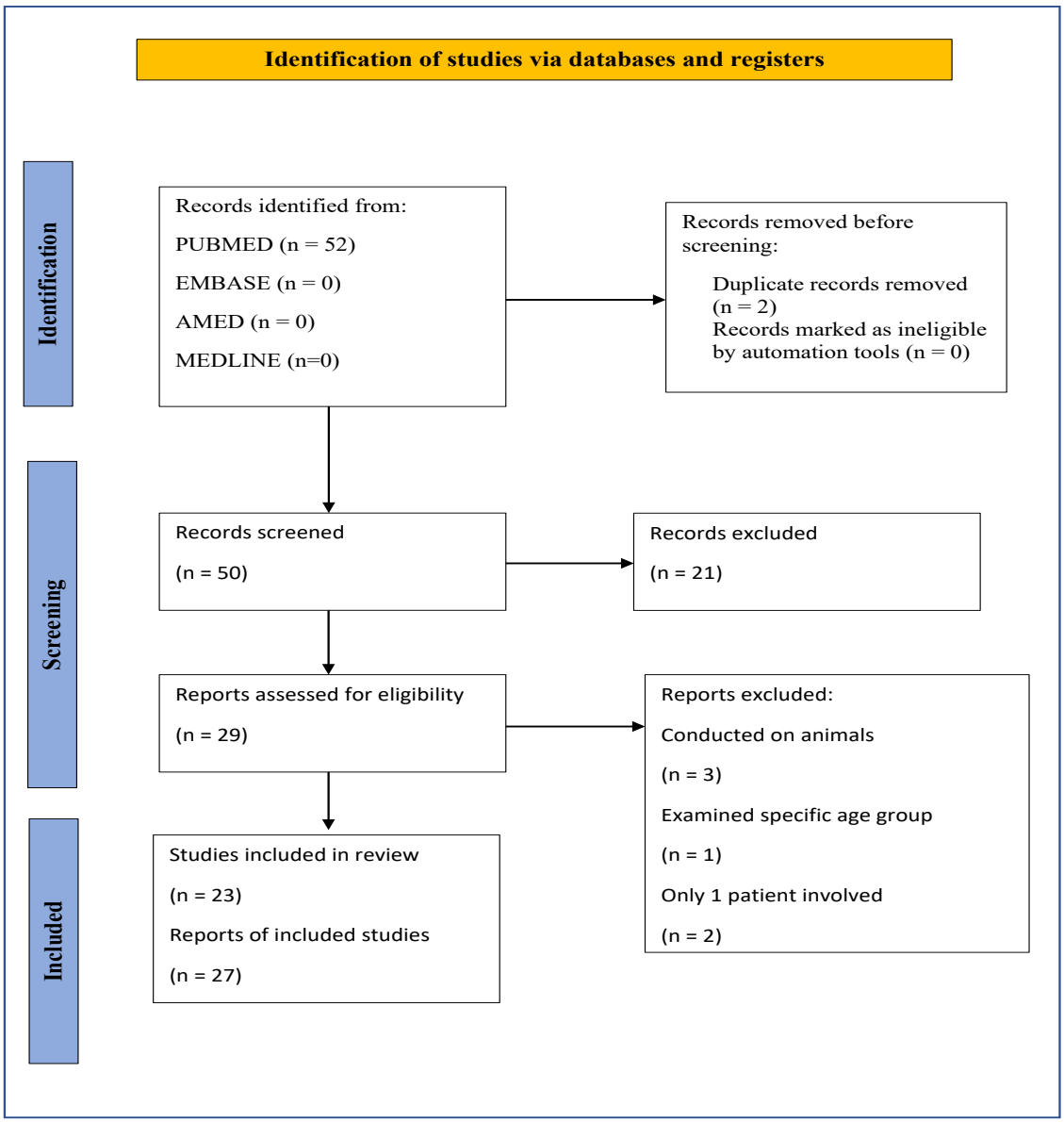

tive treatment received by individuals who suffer from incomplete CSCI without major fracture or dislocation and pre-existing CSCS in the Lee et al. (2021) study as well [22,29]. However, in the Pollard & Apple study, high-dose steroid administration, routine early surgical intervention, or surgical decompression in stenotic patients without fracture were not detected as determinants of the outcome [15]. Park et al. (2017) also state that the interval between decompression surgery and trauma is irrelevant to the neurological outcome [27]. Admission ASIA motor score, midsagittal diameter, MCC, length of parenchymal damage on T2-weighted MR imaging, and age revealed long-term ASIA motor score, FIM, manual dexterity, and dysesthetic pain [27].

According to Shigematsu et al. (2017) "silent" CSCS when combined with cervical cord injuries does not permit return to pre-injury neurological status [21].

No conclusions could be drawn from the review regarding physical therapy treatment[24]. Physiothera-

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TABLE 1.

Description of included studies

No	Study	Population	Intervention	Outcome measures	Results
1	Torg J. S. (1995). Cervical spinal stenosis with cord neurapraxia and transient quadriplegia.	Footballers 117 quadriplegics 45 patients in transient cohort		Ratio Method	No correlation between developmental narrowing (stenosis) of the spinal canal & irreversible sequelae in a spine rendered unstable by football induced trauma. Manifestations of cord neurapraxia resulting from transient, reversible compression deformation of the spinal cord. Athletes with documented episode of cervical cord neurapraxia associated with: • ligamentous instability •intervertebral disc disease with cord compression • significant degenerative changes •magnetic resonance imaging evidence of cord defects or swelling • symptoms of positive neurological findings lasting more than 36 hours •more than one recurrence should avoid continued participation in contact activities
2	Kirshblum, S. C., & O'Connor, K. C. (1998). Predicting neurologic recovery in traumatic cervical spinal cord injury. Review.	Selection of studies in English language that discussed prognosis after traumatic SCI.			Comprehensive physical examination of the acute SCI patient is essential in determining the initial level and classification of the injury and the most accurate method to predict neurologic recovery. Somatosensory evoked potentials, magnetic resonance imaging, and transcranial magnetic stimulation, may be helpful in further determining outcome when used in association with the clinical examination
3	Witzmann A. (2000). Akupuntur und andere Therapieformen beim Patienten mit chronischen Wirbelsäulenschmerzen [Acupuncture and other forms of treatment for patients with chronic back pain]. Review.		Manual therapeutic strategies, application of local anesthetics, Acupuncture. X-ray conducted periradicular infiltration, epidural blockades with local anesthetics and steroids, hiatus sacralis blockade, percutaneous radiofrequency denervation of the facet joint and percutaneous lumbar radiofrequency sympathicotomy	Symptomatology	Pain-producing spinal structures recognized & treatment offered to patients with manual therapeutic strategies. Pain-producing spinal sites treated with local anesthetics. Acupuncture is treatment option for pain relief & has effect upon physical and psychological disturbances.

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					X-ray conducted periradicular infiltration, epidural blockades with local anesthetics and steroids, hiatus sacralis blockade, percutaneous radiofrequency denervation of the facet joint and percutaneous lumbar radiofrequency sympathicotomy preferable when the aforementioned methods fail. Disc herniation with radicular symptoms, spinal canal stenosis, cervical stenotic myelopathy and degenerative spinal instability may be indications for surgical intervention.
4	Pollard, M. E., & Apple, D. F. (2003). Factors associated with improved neurologic outcomes in patients with incomplete tetraplegia.	412 patients with traumatic, incomplete, cervical spinal cord injuries.	intravenous steroids (NASCIS II protocol), early definitive surgery (<24 hours after injury), early anterior decompression for burst fractures or disc herniations (<24 hours after injury), and surgical decompression for stenosis without fracture.	change in motor score, change in sensory score, final motor score, and final sensory score data recorded at the time of injury, on admission to rehabilitation, on discharge from rehabilitation, and at 1, 2, and final year of follow-up evaluation.	Neurologic recovery not related to the following factors: gender, race, type of fracture, or mechanism of injury. Neurologic recovery also not related to the following interventions: high-dose methylprednisolone administration, early definitive surgery, early anterior decompression for burst fractures or disc herniations, or decompression of stenotic canals without fracture. Improved neurologic outcomes noted in younger patients (= 0.002), and those with either a central cord or Brown-Sequard syndrome (= 0.019).
5	McKinley, W., Santos, K., Meade, M., & Brooke, K. (2007). Incidence and outcomes of spinal cord injury clinical syndromes.	839 consecutive admissions with acute SCIs.	Tertiary care, level 1 trauma center inpatient rehabilitation unit.	Functional independence measure (FIM), FIM subgroups (motor, self-care, sphincter control), length of stay (LOS), and discharge disposition	175 patients (20.9%) diagnosed with SCI clinical syndromes. CCS the most common (44.0%), followed by CES (25.1%) and BSS (17.1%). Significant differences (P < or = 0.01) found between groups with regard to age, race, etiology, total admission FIM, motor admission FIM, self-care admission and discharge FIM, and LOS. Statistical analysis between tetraplegic BSS and CCS revealed significant differences (P < or = 0.01) with respect to age (39.7 vs 53.2 years) and a trend toward significance (P < or = 0.05) with regard to self-care admission and discharge FIM. No significant differences (P < or = 0.01) were found when comparing CMS to CES.

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6	Miyanji, F., Furlan, J. C., Aarabi, B., Arnold, P. M., & Fehlings, M. G. (2007). Acute cervical traumatic spinal cord injury: MR imaging findings correlated with neurologic outcome--prospective study with 100 consecutive patients.	100 patients (79 male, 21 female; mean age, 45 years; age range, 17-96 years) with traumatic cervical SCI.		American Spinal Injury Association (ASIA) motor score at admission and follow-up ASIA impairment scale for injury severity classification. 3 quantitative (maximum spinal cord compression [MSCC], maximum canal compromise [MCC], and lesion length) and 6 qualitative (intramedullary hemorrhage, edema, cord swelling, soft-tissue injury [STI], canal stenosis, & disk herniation) imaging parameters. Data analyzed with Fisher exact test, the Mantel-Haenszel chi(2) test, analysis of variance, analysis of covariance, stepwise multivariable linear regression.	Patients with complete motor and sensory SCIs had more substantial MCC (P=.005), MSCC (P=.002), and lesion length (P=.005) than did patients with incomplete SCIs and those with no SCIs. Patients with complete SCIs also had higher frequencies of hemorrhage (P<.001), edema (P<.001), cord swelling (P=.001), stenosis (P=.01), and STI (P=.001). MCC (P=.012), MSCC (P=.014), and cord swelling (P<.001) correlated with baseline ASIA motor scores. MSCC (P=.028), hemorrhage (P<.001), and cord swelling (P=.029) predictive of the neurologic outcome at follow-up. Hemorrhage (P<.001) and cord swelling (P=.002) correlated significantly with follow-up ASIA score after controlling for the baseline neurologic assessment.
7	Cao, J., Wang, Q., Wang, G., Lv, F., & Zhong, D. (2009). [Diagnostic value of MR imaging in cervical spinal canal stenosis combined with spinal cord injury]	41 patients with cervical spinal canal stenosis and spinal cord injury: 34 males and 7 females aged 32-71 years (average 53.4 years, 27 patients older than 60 years). 12 cases of anterior spinal cord injury syndrome, 23 of central spinal cord syndrome and 6 of Brown-Sequard syndrome.	operation	MRI data, JOA score of spinal cord function	MR imaging diagnosis before operation showed abnormal signal changes within the spinal cord in 37 cases (41 sites), anterior and posterior longitudinal ligaments and discs (APLLD) injury in 28 cases (30 sites) and signal of edema and hematoma signals in anterior surface of cervical spines (EBC) in 34 cases (36 sites). Diagnosis during operation revealed edemas raises, contusions tears of posterior soft tissue in 18 cases (20 sites), appendix fracture in 6 cases (7 sites), formation of EBC in 20 cases (23 sites), APLLD injury in 34 cases (44 sites), intervertebral instability without the rupture of ligament and intervertebral disc in 7 cases (10 sites). Significant difference between MRI diagnosis before operation and intraoperative discoveries ($P < 0.05$).

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8	Yoo, D. S., Lee, S. B., Huh, P. W., Kang, S. G., & Cho, K. S. (2010). Spinal cord injury in cervical spinal stenosis by minor trauma.	200 cases (98 cervical OPLLs and 102 CSMs) of cervical spinal stenosis for 8 years. 63 (33.5%) minor trauma cases to the cervical spine in 200 patients. Patients divided into 2 groups according to the residual cervical spinal canal diameter: group I (<10 mm cervical spinal canal) and group II (> or =10 mm cervical spinal canal).	surgical decompression	Neurologic status assessed by JOA score.	Neurologic outcome depended on the diameter of the residual spinal canal; 22 of 25 patients in group I developed neurologic deterioration, that occurred in 8 of the 38 patients in group II (P < .05). After surgical decompression, 8 patients in group I and 30 patients in group II came out with an improved JOA score of more than 50% (P < .05).
9	Aarabi, B., Alexander, M., Mirvis, S. E., Shanmuganathan, K., Chesler, D., Maulucci, C., Iguchi, M., Aresco, C., & Blacklock, T. (2011). Predictors of outcome in acute traumatic central cord syndrome due to spinal stenosis.	42 patients treated for ATCCS due to spinal stenosis	surgical decompression	follow-up for at least 12 months, ASIA motor score, midsagittal diameter at the point of maximum compression, MCC, length of parenchymal damage on T2-weighted MR imaging. Stepwise regression analysis of 10 independent variables.	Mean admission ASIA motor score 63.8, spinal cord most frequently compressed at skeletal segments C3-4 & C4-5 (71%), mean midsagittal diameter at the point of maximum compression 5.6 mm, maximum canal compromise (MCC) 50.5%, maximum spinal cord compression 16.5%, length of parenchymal damage on T2-weighted MR imaging 29.4 mm. Time after injury until surgery: within 24 hours in 9 patients, 24-48 hours in 10 patients, more than 48 hours in 23 patients. At the 1-year follow-up, mean ASIA motor score 94.1, FIM 111.1, manual dexterity 64.4% of baseline, pain level 3.5. Regression analysis indicated significant relationships between ASIA motor score at follow-up and admission ASIA motor score (p = 0.003), MCC (p = 0.02), and midsagittal diameter (p = 0.02); FIM and admission ASIA motor score (p = 0.03), MCC (p = 0.02), and age (p = 0.02); manual dexterity and admission ASIA motor score (p = 0.0002) and length of parenchymal damage on T2-weighted MR imaging (p = 0.002); and pain level and age (p = 0.02) and length of parenchymal lesion on T2-weighted MR imaging (p = 0.04).

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10	Aebli, N., Rüegg, T. B., Wicki, A. G., Petrou, N., & Krebs, J. (2013). Predicting the risk and severity of acute spinal cord injury after a minor trauma to the cervical spine.	52 patients suffering from acute cervical SCI & 131 patients showing no neurologic deficits after minor trauma to cervical spine.		On sagittal MR images: vertebral body diameter, midvertebral canal diameter, disc-level canal diameter, and spinal cord diameter. On lateral conventional radiographs: vertebral body diameter and midvertebral canal diameter.	All investigated MR image parameters in the SCI group significantly ($p<.001$) smaller compared to control group. No significant ($p>.9$) difference in any parameter among the different American Spinal Injury Association impairment score groups. A cutoff value of 8.0 mm for the minimal sagittal disc-level canal diameter yielded the largest positive predictive value and likelihood ratio for predicting SCI.
11	Alpízar-Aguirre, A., Solano-Vargas, J. D., Zárate-Kalfopulus, B., Rosales-Olivares, L. M., Sánchez-Bringas, G., & Reyes-Sánchez, A. A. (2013). Resultados funcionales de la cirugía del conducto cervical estrecho [Functional results of surgery for cervical stenosis].	195 patients with cervical stenosis	surgical treatment	neck disability index questionnaire, the Nurick scale. Descriptive statistics.	Females were predominant. The most affected age group was 46-55 years. The most frequently affected level was C5-C6. A significant improvement was seen in the neck disability index due to pain and the Nurick scale.
12	Macedo, L. G., Hum, A., Kuleba, L., Mo, J., Truong, L., Yeung, M., & Battié, M. C. (2013). Physical therapy interventions for degenerative lumbar spinal stenosis: a systematic review.	Ten studies included: 5 RCTs, 2 controlled trials, 2 mixed-design studies, and 1 longitudinal cohort study.			Pooled effects of 2 studies revealed that addition of physical therapy modality to exercise had no statistically significant effect on outcome. Pooled effects results of RCTs evaluating surgery versus physical therapy demonstrated surgery better than physical therapy for pain and disability at long term (2 years) only. Exercise is significantly better than no exercise, cycling and body-weight-supported treadmill walking have similar effects, and corsets are better than no corsets.
13	Kwon, S. Y., Shin, J. J., Lee, J. H., & Cho, W. H. (2015). Prognostic factors for surgical outcome in spinal cord injury associated with ossification of the posterior longitudinal ligament (OPLL).	246 patients with cervical cord injury.	cervical laminoplasty (8) and cervical decompression and fixation (30).	1-year follow-up, with mean follow-up period 42.2 months. OPLL type, cause of injury, cervical sagittal angle, cervical spine stenosis, cord compression ratio (space available for the spinal cord (SAC)), grade of intramedullary SI (grade 0, none; grade 1, light; grade 2, intense T2WI) were assessed.	Mean American Spinal Injury Association (ASIA) motor score at admission 38.4 ± 21.9 (range, 2-70) and improved to 67.7 ± 19.1 (range, 8-94) at last follow-up ($p < 0.05$). Mean recovery rate of motor score 55.8 ± 19.9%. Five patients had SI grade 0, 20 patients SI grade 1, and 13 patients SI grade 2. Age, initial ASIA motor grade, intramedullary SI grade, and SAC significantly related to neurological outcome.

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					Initial cervical alignment, canal diameter, length of SI, time interval between injury and operation, and OPLL type had no significant effect on neurological outcome.
14	Rüegg, T. B., Wicki, A. G., Aebli, N., Wisianowsky, C., & Krebs, J. (2015). The diagnostic value of magnetic resonance imaging measurements for assessing cervical spinal canal stenosis.	52 CSCI patients & 77 control patients	single-center retrospective radiological case-control study of patients with CSCI after a minor trauma to the cervical spine from 2000 to 2010	axial T2-weighted MR images, motor index scores of 10 key muscles at different time points (initially, 1, 3, and 12 months after injury), Receiver operating characteristic curves.	The intra- and interobserver reliability regarding the MRI measurements ranged from good (0.72) to perfect (0.99). Significant differences between CSCI group and control group ($p < 0.001$) for all parameters, except for cord area. Prominent differences between the groups for the spinal canal area, cord-canal-area ratio, and space available for the cord. Classification accuracy best for cord-canal-area ratio and space available for the cord; areas under the curve were 0.99 (95% CI 0.97-1.0) and 0.98 (95% CI 0.95-0.99), respectively. No significant ($p > 0.05$) correlation between any of the imaging parameters and the motor index score at any time point.
15	Samuel, A. M., Bohl, D. D., Basques, B. A., Diaz-Collado, P. J., Lukasiewicz, A. M., Webb, M. L., & Grauer, J. N. (2015). Analysis of Delays to Surgery for Cervical Spinal Cord Injuries.	2636 patients with cervical SCI: 803 with complete SCI, 950 with incomplete SCI, and 883 with central SCI.	surgery	Relationships between surgical timing and patient and injury characteristics	Average time to surgery was 51.1 hours for patients with complete SCI, 55.3 hours for patients with incomplete SCI, and 83.1 hours for patients with central SCI. Only 44% of patients with SCI underwent surgery within the first 24 hours after injury, including only 49% of patients with incomplete SCI. The vast majority of time between injury and surgery was after admission, rather than in the emergency department or in the field. Upper cervical SCIs and greater Charlson Comorbidity Index were associated with later surgery in all 3 SCI subpopulations.
16	Burns, S. P., Weaver, F., Chin, A., Svircev, J., & Carbone, L. (2016). Cervical stenosis in spinal cord injury and disorders.	1954 Veterans with onset of traumatic or non-traumatic tetraplegia during FY 1999-2007		Demographics, etiologies of SCI/D and comorbidities by CSS status.	Veterans with SCI/D and CSS were older, more likely to have incomplete injuries and more likely to be Black than those with SCI/D and no CSS.

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					Of patients with traumatic etiologies for SCI, 35.1% had a diagnosis of CSS at the time of or in the 2 years prior to SCI onset. Of those with tetraplegia due to falls, 40.0% had CSS. For other traumatic etiologies the percentages with CSS were lower: vehicular (25.0%); sports (16.1%); and acts of violence (10.2%). Total comorbidity scores measured by the Charlson co morbidity index and CMS Hierarchical Condition Category (CMS-HCC) were higher in those with CSS and SCI/D compared to those with SCI/D without CSS ($P < 0.0001$ respectively).
17	Harvey L. A. (2016). Physiotherapy rehabilitation for people with spinal cord injuries.	60 clinical trials	Physiotherapy		Absence of high-quality trials involving people with SCI to guide treatment, lack of high-quality direct evidence, extensive scope of practice Physiotherapy interventions to increase strength, treat and prevent contractures, improve performance of motor tasks Physiotherapists need to resort to previous knowledge from other areas of physiotherapy to decide upon treatment.
18	Lee, B. A., Leiby, B. E., & Marino, R. J. (2016). Neurological and functional recovery after thoracic spinal cord injury.	661patients enrolled in Spinal Cord Injury Model Systems database, injured between 2000 and 2011, with initial neurological level of injury from T2-12. 265 patients had second neurological exams & 400 patients had Functional Independence Measure (FIM) scores ≥6 months after injury.	Retrospective analysis of longitudinal database	American Spinal Injury Association Impairment Scale (AIS) grade, sensory level (SL), lower extremity motor scores (LEMS), and FIM.	At baseline, 73% of subjects were AIS A, of them, 15.5% converted to motor incomplete. The mean SL increase for subjects with an AIS A grade was 0.33 ± 0.21; 86% remained within two levels of baseline. Subjects with low thoracic paraplegia (T10-12) demonstrated greater LEMS gain than high paraplegia (T2-9), and had higher 1-year FIM scores. Better FIM scores were correlated with better AIS grades, younger age and increase in AIS grade. Ability to walk at 1 year associated with low thoracic injury, higher initial LEMS, incomplete injury and increase in AIS grade.

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19	Bonavita, J., Torre, M., Capirossi, R., Baroncini, I., Brunelli, E., Chiarottini, G., Maietti, E., Olivi, S., Molinari, M., & Scivoletto, G. (2017). Outcomes Following Ischemic Myelopathies and Traumatic Spinal Injury.	168 patients with a TSCI and 72 with an ISCI.	-	American Spinal Injury Association Impairment Scale (AIS) standards and Spinal Cord Independence Measure (SCIM). Linear and logistic regression models to analyze the effects of the etiology of the lesion, AIS level at admission, and level of the lesion.	Patients with an ISCI were older and had fewer cervical lesions and fewer complete lesions than patients with TSCI. By linear and logistic regression, etiology was a predictor (together with lesion features) of functional (SCIM improvement and SCIM at discharge) outcome. Traumatic patients had better outcome than ischemic ones. Age, AIS level, and lesion level were chief predictors of length of stay, occurrence of complications & discharge dispositions.
20	Park, J. H., Kim, J. H., Roh, S. W., Rhim, S. C., & Jeon, S. R. (2017). Prognostic factor analysis after surgical decompression and stabilization for cervical spinal-cord injury.	73 patients with cervical SCI.	one-level decompression and fusion surgery	American Spinal Injury Association Impairment scale (AIS) before surgery, blood pressure at admission, the amount of cord compression, surgical time, estimated blood loss during surgery, and steroid use. Considered improvement if AIS improvement ≥1 grade.	Of 73 patients with SCI, 27 and 35 showed ≥1 grade of AIS improvement immediately and 3 months after surgery, respectively. In multivariate analysis, the mean arterial blood pressure (MAP) was a significant prognostic factor affecting recovery in the SCI patients during the immediate post-operative period. In the late recovery period at 3 months after surgery, the AIS before surgery and the MAP were significant prognostic factors affecting recovery.
21	Shigematsu, H., Cheung, J. P., Mak, K. C., Bruzzone, M., & Luk, K. D. (2017). Cervical spinal canal stenosis first presenting after spinal cord injury due to minor trauma: An insight into the value of preventive decompression.	32 patients with CSCS 47 asymptomatic individuals from general population	Decompression in 17 patients & conservative treatment in 15.	MRI measurements, Frankel classification,	At the final follow-up, 3 patients (9.3%) returned to their pre-injury Frankel grade, whereas 26 patients (83.3%) lost one or more neurological grade. 3 patients (9.3%) died.
22	Khorasanizadeh, M., Yousefifard, M., Eskian, M., Lu, Y., Chalangari, M., Harrop, J. S., Jazayeri, S. B., Seyedpour, S., Khodaei, B., Hosseini, M., & Rahimi-Movaghar, V. (2019). Neurological recovery following traumatic spinal cord injury: a systematic review and meta-analysis.	114 studies		random pooled effect analysis, meta-regression analysis.	Level of injury was a significant predictor of recovery; recovery rates followed this pattern: lumbar > cervical and thoracolumbar > thoracic. Thoracic SCI and penetrating SCI were significantly more likely to result in complete injury. Penetrating TSCI had a significantly lower recovery rate compared to blunt injury (OR 0.76, 95% CI 0.62-0.92; p = 0.006). Recovery rate was positively correlated with longer follow-up duration (p = 0.001).

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					Neurological recovery after TSCI is significantly dependent on injury factors (i.e., severity, level, and mechanism of injury), but is not associated with type of treatment or country of origin. A minimum follow-up of 12 months is recommended for TSCI studies that include patients with neurologically incomplete injury.
23	Lee, S., Kim, C., Ha, J. K., Jung, S. K., & Park, J. H. (2021). Comparison of Early Surgical Treatment with Conservative Treatment of Incomplete Cervical Spinal Cord Injury Without Major Fracture or Dislocation in Patients with Pre-existing Cervical Spinal Stenosis.	54 patients	early surgical treatment (<24 h) (S group), conservative treatment (C group)	degree of improvement in ASIA grade after 2 years, medical records and radiographic data.	During the 2-year follow-up period, higher percentages of patients in the S group than in the C group showed ≥1 grade (90.9% vs. 57.1%, P=0.0051) and 2 grade (30.3% vs. 9.5%) improvements in ASIA grade. Multivariate analysis showed that early surgical treatment, was the only factor significantly associated with ASIA grade improvement after 2 years (P=0.0044).

py interventions tend to improve strength, treat and protect from contractures, raise performance of motor tasks, however, physiotherapists need to resort to previous knowledge from other areas of physiotherapy to decide upon treatment [37].

Conclusion

According to Table 1, which successfully summarizes the data presented in the 23 articles included in this research, it is clearly indicated that a comprehensive physical examination of an acute SCI patient is of the outmost importance in defining initial level and classification of the injury. The aforementioned method is the most accurate available to predict a possible neurologic recovery using immediate surgical treatment. An invaluable tool, which can be used as a prognostic criterium towards neurological recovery, is the level of completion of the lesion caused by a spinal cord injury. Even though several studies have already indicated that age, race and other similar demographic statistics may not be indicative of the success of the neurological recovery, younger patients with an incomplete lesion bear better chances to recover.

Spinal cord hemorrhage and cord swelling are associated with a poor prognosis for neurologic recovery since they inhibit the comprehensive physical examination prior to an invasive surgery treatment. Unfortunately, the literature review has already demonstrated that MR imaging diagnosis before operation do not correspond to the intraoperative discoveries, indicating that MRI diagnosis fails to make a relatively comprehensive and accurate diagnosis. Therefore, a clinical diagnosis is imperative, which in turn corroborates further with the previous assessment.

Although the waiting time between the inflicted injury and the surgery is not a crucial factor for a successful surgery and neurological rehabilitation - at least not as crucial as the physical examination and diagnosis itself - the majority of patients with SCI do not undergo surgery within the first 24 hours after injury. In fact, most delays are observed after inpatient admission.

Several studies have illustrated that subjects with pre-existing canal stenosis may present a lower threshold for surgery due to the poor neurological outcome of CSCS. Patients that have considerably good preoperative neurological status, are more likely to neurologically recover after surgery.

Incomplete cervical spinal cord lesions when inflicted on patients young at age are most likely to result in neurologic recovery.

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No conclusions could be drawn from the review regarding the most appropriate physical therapy treatment for LSS. Despite not playing an important part in rehabilitation, exercise and corsets contribute to the patient's recovery.

The best prognostic factors lie with patients suffering incomplete CSCI without major fracture or pre-existing CSCS when undergoing early surgery. A

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REFERENCES

1. Edwards CC, Riew KD, Anderson PA et al. Cervical myelopathy. Current diagnostic and treatment strategies. Spine J. 2003;3(1):68-81.
2. Rao RD, Currier BL, Albert TJ et al. Degenerative cervical spondylosis: clinical syndromes, pathogenesis, and management. J Bone Joint Surg Am. 2007;89(6):1360-78.
3. National Spinal Cord Injury Statistical Center. Facts and Figures at a Glance. Birmingham, AL: University of Alabama at Birmingham.2020. Available at: https://www.nscisc.uab.edu/Public/Facts%20and%20Figures%202020.pdf
4. Badhiwala JH, Wilson JR, Fehlings MG. Global burden of traumatic brain and spinal cord injury. Lancet Neurol. 2019;18(1):24-5.
5. Lee BB, Cripps RA, Fitzharris M, Wing PC. The global map for traumatic spinal cord injury epidemiology: update 2011, global incidence rate. Spinal Cord. 2014;52(2):110-6.
6. Cripps RA, Lee BB, Wing P et al. A global map for traumatic spinal cord injury epidemiology: towards a living data repository for injury prevention. Spinal Cord. 2011;49(4):493-501.
7. Hagen EM. Acute complications of spinal cord injuries. World J Orthop. 2015;6(1):17-23.
8. Schneider RC, Cherry G, Pantek H. The syndrome of acute central cervical spinal cord injury; with special reference to the mechanisms involved in hyperextension injuries of cervical spine. J Neurosurg. 1954;11(6):546-77.
9. The Burden of Traumatic Spinal Cord Injury in the United States: Disability-Adjusted Life Years – Science Direct [Internet]. [cited 2022 Feb 15]. Available from: https://www.sciencedirect.com/science/article/abs/pii/S000399931831298X?via%3Dihub.
10. Middleton JW, Dayton A, Walsh J et al. Life expectancy after spinal cord injury: a 50-year study. Spinal Cord. 2012, 50:803–11.
11. Deyo RA. Treatment of lumbar spinal stenosis: a balancing act. Spine J. 2010;10(7):625-7.
12. Page M J, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews BMJ 2021;372:71
13. Torg JS. Cervical spinal stenosis with cord neurapraxia and transient quadriplegia. Sports Med. 1995;20(6):429-34.
14. Kirshblum SC, O'Connor KC. Predicting neurologic recovery in traumatic cervical spinal cord injury. Arch Phys Med Rehabil. 1998;79(11):1456-66.
15. Pollard ME, Apple DF. Factors associated with improved neurologic outcomes in patients with incomplete tetraplegia. Spine (Phila Pa 1976). 2003;28(1):33-9.
16. McKinley W, Santos K, Meade M et al. Incidence and outcomes of spinal cord injury clinical syndromes. J Spinal Cord Med. 2007;30(3):215-24.
17. Lee BA, Leiby BE, Marino RJ. Neurological and functional recovery after thoracic spinal cord injury. J Spinal Cord Med. 2016;39(1):67-76.
18. Witzmann A. Akupuntur und andere Therapieformen beim Patienten mit chronischen Wirbelsäulenschmerzen. Wien Med Wochenschr. 2000;150(13-14):286-94.
19. Burns SP, Weaver F, Chin A et al. Cervical stenosis in spinal cord injury and disorders. J Spinal Cord Med. 2016;39(4):471-5.

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20. Yoo DS, Lee SB, Huh PW et al. Spinal cord injury in cervical spinal stenosis by minor trauma. World Neurosurg. 2010;73(1):50-2; discussion e4.
21. Aarabi B, Alexander M, Mirvis SE et al. Predictors of outcome in acute traumatic central cord syndrome due to spinal stenosis. J Neurosurg Spine. 2011;14(1):122-30.
22. Alpízar-Aguirre A, Solano-Vargas JD, Zárate-Kalfopulus B et al. Resultados funcionales de la cirugía del conducto cervical estrecho [Functional results of surgery for cervical stenosis]. Acta Ortop Mex. 2013;27(1):4-8.
23. Samuel AM, Bohl DD, Basques BA et al. Analysis of Delays to Surgery for Cervical Spinal Cord Injuries. Spine (Phila Pa 1976). 2015;40(13):992-1000.
24. Macedo LG, Hum A, Kuleba L et al. Physical therapy interventions for degenerative lumbar spinal stenosis: a systematic review. Phys Ther. 2013;93(12):1646-60.
25. Kwon SY, Shin JJ, Lee JH et al. Prognostic factors for surgical outcome in spinal cord injury associated with ossification of the posterior longitudinal ligament (OPLL). J Orthop Surg Res. 2015;10:94.
26. Bonavita J, Torre M, Capirossi R et al. Outcomes Following Ischemic Myelopathies and Traumatic Spinal Injury. Top Spinal Cord Inj Rehabil. 2017;23(4):368-76.
27. Park JH, Kim JH, Roh SW et al. Prognostic factor analysis after surgical decompression and stabilization for cervical spinal-cord injury. Br J Neurosurg. 2017;31(2):194-8.
28. Shigematsu H, Cheung JP, Mak KC et al. Cervical spinal canal stenosis first presenting after spinal cord injury due to minor trauma: An insight into the value of preventive decompression. J Orthop Sci. 2017;22(1):22-6.
29. Lee S, Kim C, Ha JK et al. Comparison of Early Surgical Treatment with Conservative Treatment of Incomplete Cervical Spinal Cord Injury Without Major Fracture or Dislocation in Patients with Pre-existing Cervical Spinal Stenosis. Clin Spine Surg. 2021;34(3): E141-E146.
30. Khorasanizadeh M, Yousefifard M, Eskian M, et al. Neurological recovery following traumatic spinal cord injury: a systematic review and meta-analysis. J Neurosurg Spine. 2019:1-17.
31. Rüegg TB, Wicki AG, Aebli N et al. The diagnostic value of magnetic resonance imaging measurements for assessing cervical spinal canal stenosis. J Neurosurg Spine. 2015;22(3):230-6.
32. Aebli N, Rüegg TB, Wicki AG et al. Predicting the risk and severity of acute spinal cord injury after a minor trauma to the cervical spine. Spine J. 2013;13(6):597-604.
33. Eismont FJ, Clifford S, Goldberg M, et al. Cervical sagittal spinal canal size in spine injury. Spine 1984;9:663-6.
34. Vaccaro A, Nachwalter R, Klein, G et al. The Significance of Thoracolumbar Spinal Canal Size in Spinal Cord Injury Patients. Spine, 2001;26(4):371-76
35. Miyanji F, Furlan JC, Aarabi et al. Acute cervical traumatic spinal cord injury: MR imaging findings correlated with neurologic outcome--prospective study with 100 consecutive patients. Radiology. 2007;243(3):820-7.
36. Cao J, Wang Q, Wang G, Lv F et al. Diagnostic value of MR imaging in cervical spinal canal stenosis combined with spinal cord injury]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2009;23(7):800-2.
37. Harvey LA. Physiotherapy rehabilitation for people with spinal cord injuries. J Physiother. 2016;62(1):4-11.

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