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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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- **Letters to the editor:** Communication to the editor is welcomed and will be published if they offer pertinent and/ or constructive comment on articles published in the Acta Orthopaedica Et Traumatologica Hellenica. Letters are published at the discretion of the Editorial team and should be received within three months after on-line publication of an article. Following acceptance, letters will be sent to authors for response. Letter communications should include text of no more than 500 words, up to 2 figures and 10 references, without any abstract or keywords and a maximum of 3 authors.

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Patient anonymity should be ensured. All identifying data (name, identification numbers, initials) must be removed from text, images and tables. If it is mandatory for a patient's face to be included in the manuscript, the eyes should be sufficiently masked. If there is a possibility that a patient may be identified from a photograph or relevant legend and text, the patient's written consent should be submitted.

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All authors (surnames and initials of first name) should be listed when they are three or fewer. If authors are more than three, the first three authors should be listed, then 'et al.' needs to follow the name of the third author.

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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.

■ Book chapters:

Triantafyllopoulos IK, Papaioannou NA. The Effect of Pharmacological Agents on the Bone-Implant Interface. In: Karachalios Th. (ed). Bone-Implant Interface in Orthopaedic Surgery. Springer – Verlag, London 2014, pp 221-237.

■ Online document:

National Institute for Health and Care Excellence. Fractures (Complex): Assessment and Management. Available via www.nice.org.uk/guidance/ng37. Published Feb 2016. Updated Sept 2017. Accessed January 2014.

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Orthopaedic Perspective regarding Operating on COVID-19 Positive Trauma Patients

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ABSTRACT

As most of the orthopaedic procedures are Aerosol Generating Procedures (AGPs), the health care workers are potentially at an increased risk of exposure to COVID-19 during surgical procedures. We have presented the protocol that was followed during this lengthy essential trauma procedure. By meticulous pre-planning and following a comprehensive, robust and protocol-driven infection control workflow, the risk of exposure to the healthcare workers can be kept to a minimum.

KEY WORDS: Orthopaedic procedures, COVID-19 exposure, exposure risk

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Introduction:

The Coronavirus (COVID-19) outbreak was first reported in late December 2019 as many patients in the Wuhan province in China were being diagnosed with pneumonia due to an unknown cause. Later, it was linked to a seafood and wholesale wet market in Wuhan, Hubei Province, China [1]. On 30th January 2020, the World Health Organization (WHO) declared this emerging infectious disease, now known as Coronavirus disease 2019 (COVID-19) as a public health emergency of international concern and on 11th March 2020, declared it a global pandemic [2].

As of 28th May 2020, the coronavirus has infected 5,864,341 patients and claimed 360,319 lives throughout the world [3]. The American continent and Europe have now become the epicentre of this pandemic. In the UK, to date, 269,127 patients have been infected with 37,837 deaths [3]. With daily exponential increase in numbers across the globe, screening and diagnostic tests are being stepped up to contain this pandemic.

Emergency, respiratory, infectious diseases and intensive care physicians are the front-line staff taking a central role in the fight against this pandemic. Although the role of orthopaedic surgeons in controlling this outbreak may appear limited, they also have a crucial role to play, especially while managing suspected or confirmed COVID-19 trauma and orthopaedic patients [4].

Due to the frequent use of high-speed drills, most trauma and orthopaedic procedures are Aerosol Generating Procedures (AGPs); they are therefore classed as high-risk Level 3 interventions (**Table 1**) [7,8]. Public Health England guidelines for the use of full Personal Protective Equipment (PPE) while undertaking Aerosol Generating Procedures (AGPs) have evolved over time and the current guidelines are to use full PPE while undertaking these procedures [5]. Currently, this includes an appropriate Filtering Face Piece Class 3 (FFP3) Respirator mask following a computer-based fit test, a long sleeve fluid repellent disposable gown, a full-face shield or a visor for eye protection, and gloves (**Table 2**).

The aim of this paper is to share our experience and lessons learnt from a major trauma operative procedure. Our main goal is to divide the whole exercise into Pre-operative (including WHO check list), Intra-operative and Post-operative phases, so that the steps are reproducible and easy to follow during the course of the procedure (**Table 3 & Figure 1**).

PRE-OPERATIVE:

The patient was reviewed by the anaesthetic team for anaesthetic fitness. Informed consent was taken and the operative site was marked by the surgical team.

Meticulous pre-operative surgical planning was done to ensure that all the necessary instrumentation and implants/prosthesis were available and checked. Digital templating for prosthesis size was carried out and a printed copy of the images was made available to avoid the need for PACS images in theatre. An appropriate ward pre-operative checklist was completed by the nursing staff. The transfer of the patient between the ward and the theatre complex was meticulously planned and timed in such a way to avoid any unnecessary exposure to others en-route. In our case, due to the proximity of the ward to the theatre complex, a pre-decided path was used.

Theatre Teams:

The theatre team comprised of anaesthetic, scrub and surgical teams with designated specific and shared responsibilities within theatre [7]. Staff with appropriate skill mix and experience was selected to work effectively and efficiently in their respective roles. There was regular communication amongst the teams confirming the agreed protocols and standard operating procedures. All staff members of the theatre team were previously fit tested for fluid repellent surgical respirator face mask (FFP3).

Anaesthetic team included lead Consultant Anaesthetist, Trainee Anaesthetist and Anaesthetic Nurse Practitioner. Another anaesthetic team was on standby in case of an overrun. Scrub team included a lead nurse and two operating room runners in the main theatre. Another staff in the anaesthetic room acted as a communicator between operating room

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TABLE 1

Potentially infectious AGPs [5]:
Intubation, extubation and related procedures, for example, manual ventilation and open suctioning of the respiratory tract (including the upper respiratory tract)
Tracheotomy or tracheostomy procedures (insertion or open suctioning or removal)
Bronchoscopy and upper ENT airway procedures that involve suctioning
Upper gastro-intestinal endoscopy where there is open suctioning of the upper respiratory tract
Surgery and post-mortem procedures involving high-speed devices
Some dental procedures (for example, high-speed drilling)
Non-invasive ventilation (NIV); Bi-level Positive Airway Pressure Ventilation (BiPAP) and Continuous Positive Airway Pressure Ventilation (CPAP)
High Frequency Oscillatory Ventilation (HFOV)
Induction of sputum
High flow nasal oxygen (HFNO)

TABLE 2

Personal protective equipment (PPE)
Plastic apron
FFP3 Respirator mask
Surgical hood that covers the head and neck area
Full Face Shield
Water-resistant Fabric-Reinforced gown
Surgical gloves
Kevlar reinforced gloves
Impervious shoe cover

staff and an experienced runner in the corridor outside the theatre providing any drugs/equipment/instruments/prosthesis needed for the procedure. Surgical team included a lead surgeon and two surgical assistants.

WHO Check listing:
A detailed WHO checklist was performed outside of designated COVID-19 theatre in the corridor and the same documentation was transferred to the white board in theatre. Specific and shared responsibilities of each member of the team was discussed, agreed, and documented. The PPE requirement of each member of the team was confirmed and at this stage, availability of each piece of PPE for the whole team was confirmed (**Table 2**). The donning and doffing sequence for each member of all the teams was reconfirmed (**Table 4 & 5**). The specific anaesthetic and surgical steps were discussed and documented. The availability of previously discussed instruments, prostheses, and additional materials like sutures and drains required for the surgical procedure were reconfirmed so that they could be brought into theatre without any delay. Personal belongings of each member of the team were transferred to individual pouches and securely stored. Duplicate copy of the clearly legible consent form was made available in the operative theatre and rest of the patient's notes were left in the buffer zone 1. Scrub and surgical staff were instructed to carry the required impervious gown and gloves with them so that they were available in the scrub area. The post-operative protocol to be followed by each member of the team

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TABLE 3

Sequence of Pre, Intra and Postoperative Events:
Theatre team fit tested for Fluid resistant face mask (FFP3)
Preoperative planning and check availability of instruments and implants
Anaesthetic review for fitness, preoperative checklist
Patient ready for transfer by porter by a pre-agreed controlled path from ward to theatre
WHO checklist in corridor outside theatre
Personal belongings of staff transferred to a pouch and securely stored
Every team member to enter through the anaesthetic room (Buffer Zone 1) to the Theatre
Agreed PPE Donning and Doffing sequence for each member of staff
Lead nurse scrubbed and sterility of instruments checked
Patient transferred to Theatre through a designated route
Anaesthetic procedure
20-minute break
Patient catheterised and positioned on table
20- minute break: Orthopaedic team to scrub and don sterile impervious gown and gloves
Timeout according to WHO protocol
Surgical procedure according to plan
Sign off and Patient Transfer to bed/ trolley
Surgical team Doff off
Extubation
20-minute break
Patient recovery in theatre
Patient transferred back through designated route to pre-agreed destination

was discussed and reconfirmed.

Theatre Setting:

An operating theatre pre-designated exclusively for all confirmed and suspected COVID-19 cases was used. Entry of every staff member into theatre was through the anaesthetic room which acted as a buffer zone 1 for donning the Personal Protective Equipment (PPE). Patient was brought into theatre through the pre-agreed route. Following the completion of the procedure, all members of the team exited through the sluice room which acted as buffer zone 2 that was used for doffing the PPE. All other entrances were blocked with "No Entrance - COVID 19 Theatre" notification. All the staffs using the theatre complex was made aware of the operating procedure protocols for COVID-19 theatre. Only necessary equipment required for surgical procedure were kept in theatre and all the computer monitors and other equipment were covered with disposable covers to prevent any aerosol contamination.

The surgery was undertaken in a laminar flow theatre with ventilation remaining fully on throughout the procedure. It is important for the team to be aware of the number of air changes per hour (ACH) of each theatre to determine the safe period to enter an aerosol generating zone. In general, in theatres that are fitted with standard HEPA filters, 5 air changes reduce the amount of airborne contamination to less than 1% [6]. With the estates department

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Figure 1

Management of COVID-19 Positive Patient in Operating Theatre				
	OR Charge Nurse & Scrub Staff Team	Anaesthetic Room Runner (Buffer Zone)	Consultant & Trainee Anaesthetist and Anaesthesia Nurse	Orthopaedic Team (Lead surgeon & 2 assistant surgeons)
Pre-operative planning	Activate theatre team ↓ Delegate OR staff ↓ Check availability of: • PPE • Instrumentation • Implants	Check availability of: • PPE • Donning & Doffing Protocol	Pre-operative review of patient ↓ Check anaesthetic equipment & drugs	Pre-operative review of patient ↓ Check consent & site marketing ↓ Check availability of instruments & implants
WHO check list	Staff introduction ↓ Patient briefing ↓ Steps of PPE donning & doffing	Discuss anaesthetic plan		Discuss planned procedure & positioning of patient ↓ Reconfirm availability of PPE, instruments & implants
Intra-operative phase	Helping operating team in surgical procedure and communication with OR runner	Continue with anaesthesia, all unused drugs & consumable discarded		Carry out proposed operative procedure Request orthopaedic implants
		Communication with Operating/Anaesthetic Room runner and corridor runner through walkie-talkie		
Post-operative phase	Signing out of procedure Swabs & instruments check	Extubation and recovery of patient in theatre Twenty minutes delay to settle down aerosols Transfer to ward		Doffing as per established protocol

advice that the theatre had 35 ACH, a waiting period of 10 air changes (20 mins) after each aerosol generating intervention was deemed to be safe.

INTRA-OPERATIVE:

Sterility of the instruments was checked by the lead scrub nurse before the patient was transferred to the theatre to reduce the time of exposure. Access to the operating theatre was allowed only through designated entrance and exit doors.

The patient was anaesthetised (Spinal and GA in this case) in the operating room, followed by a break of 20 minutes for the aerosols to settle down.

Any additional procedures and positioning with appropriate supports were undertaken by a PPE donned member of the surgical team with the help of the anaesthetic team (Catheterisation and lateral decubitus in this case). This surgical team member then doffed the surgical gown and gloves. This was followed by a 20-minute break during which the surgical team scrubbed and donned reinforced impervious gowns and triple gloves with Kevlar glove as the inner most layer. Timeout was done according to WHO protocol and consent/site mark form checked for the procedure and confirmed with the staff in buffer zone 1.

Following principles were adhered to during the entire procedure [7,8]:

- Minimum required number of staff in theatre
- Appropriate PPE for all staff in theatre depending on role and risk
- Minimum number of staff during high AGPs like Intubation and Extubation
- Use Smoke Extraction/Capture system for diathermy / other energy sources
- Avoid the use of devices that produce splash/spray secretions, e.g. Pulse Lavage
- Every care was taken to minimise fluid spillage from the operative area
- Consider stand by teams for prolonged procedures in full PPE

Surgical procedure was performed as planned.

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TABLE 4

Donning sequence for PPE (for a sterile procedure)	
STEP 1: Plastic apron	
STEP 2: Protective shoe cover	
STEP 3: - FFP3 respirator mask - Start by placing respirator on your chin first and then over the nose - Secure the elastic bands at the middle of the head and neck - Fit flexible band to nose bridge - Fit snug to face and below chin - Fit check respirator for any air leakage with finger at lower and upper edges	
STEP 4: - Hood covering head and neck	
STEP 5: - Full Face Eye shield; adjust to fit	
STEP 6: - Impervious Gown fully covering torso from neck to knees, arms to end of wrist and wrapped around the back - Tie gown behind the neck and waist	
STEP 7: - 3 pairs of gloves - 1 Kevlar reinforced gloves and 2 sterile surgical gloves	

During surgery there was regular communication between the theatre team with staff in the buffer zone and the runner in the corridor for any consumables, drugs, instruments, and prosthesis needed which were handed to the theatre staff as and when required.

In this case, after 2 hours of patient intubation, a member each from the anaesthetic and surgical teams was relieved by the standby team. Total surgical time was approximately three hours. Lead surgeon and the lead scrub nurse remained scrubbed throughout the procedure.

POST-OPERATIVE

At the conclusion of the procedure, a standard sign out was done including confirmation of the swab count and instruments checklist. Patient was transferred to a trolley after positioning back to supine position. All items of contaminated linen were removed. Surgical team performed doffing with the help of a buddy as per established protocol. Exit out of the theatre was into the sluice room (buffer zone 2).

Patient was extubated and recovered in the operating room. A break of 20 minutes was then taken

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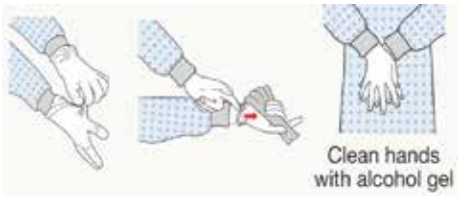
TABLE 5

Doffing sequence for PPE (following a sterile procedure)

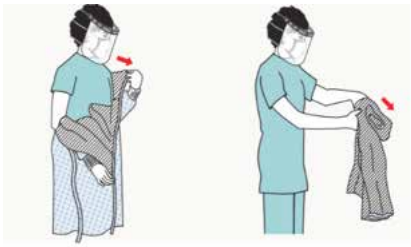
It is important to safely remove PPEs without contaminating your clothes, skin, or mucous membrane with potentially infectious material. All PPEs except respirator mask are doffed in the sluice room (buffer zone2). All doffed contaminated PPEs should be discarded in the orange lined bins for safe disposal. Remove respirator after leaving the sluice room and closing the door.
Following sequence is recommended for doffing the PPE

STEP 1: Gloves
- Outside of gloves are contaminated
- Using a gloved hand, grasp the palm area of the other gloved hand and peel off first glove.
- Hold removed glove in gloved hand
- Slide fingers of removed gloved hand under remaining glove at wrist and peel off second glove over first glove
- Discard gloves
- Repeat same for 2nd pair of gloves. Leave Kevlar reinforced gloves.



STEP 2: Remove shoe covers and discard

STEP 3: Gown
- Gown front and sleeves and the outside of gloves are contaminated!
- Grasp the gown from the front and pull away from your body so that the ties break, touching outside of gown only with gloved hands.
- While removing the gown, fold or roll the gown inside out into a bundle
- As you are removing the gown, peel off your gloves at the same time, only touching inside of gloves and gown with your hands.
- Place gown and gloves into a waste container
- Sanitise hands with alcohol gel



STEP 4: Face and eye shield
- Outside of face shield are contaminated!
- Remove face shield from back by lifting head band and without touching the front of face shield
- If item is reusable, place in designated receptacle for reprocessing otherwise discard in waste container
- Use alcohol gel to clean hands

STEP 5: Surgical hood
- Grab hood at the back and remove the hood and place in the waste container
- Clean hands with alcohol gel

STEP 6: Respirator mask
- Come out of sluice room
- Front of respirator is contaminated!
- Grasp bottom elastic of the respirator and then the ones at the top and remove away from face without touching the front.
- Discard in waste bin
- Wash hands with alcohol gel

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STEP 7: Remove theatre shoes and send for wash
STEP 8: Shower and change to a new theatre dress
AT ANY STEP OF REMOVAL OF PPEs IF HANDS ARE CONTAMINATED, CLEAN WITH ALCOHOL BASED HAND SANITIZER

to allow the aerosols to settle before transferring patient to a pre-agreed destination through a designated route.

All members of the team followed a pre-agreed path to the shower room.

Conflict of interest

The authors declare no conflicts of interest.

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"The role of inflammatory cytokines in the recovery of spinal cord injury: Recent data on NF-κB."

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ABSTRACT

Spinal cord injury is damage to the spinal cord, resulting from physical trauma as well as other pathological conditions, causing temporary or permanent changes in its function. SCI demonstrates increased mortality and morbidity placing a great financial burden to health systems worldwide. The physiology of post-injury spinal cord recovery is complicated and includes primary and secondary damage mechanisms. Inflammation and inflammatory cytokines hold a central role in this procedure. This is a review of the existing literature on the role of inflammatory cytokines in the recovery process following spinal cord injury, with emphasis on the role of the transcriptive factor NF-κB. NF-κB is the ultimate signaling molecule in pathophysiological mechanisms regulated by inflammatory cytokines, such as TNF-α and IL-1β. Its activation includes a complicated network of pathways that interact with one another through several checkpoints. NF-κB modification influences gene expression in the post-injury spinal cord and regulates intracellular procedures that mediate the recovery of the neuronal tissue. These procedures include inflammation, cellular death, oxidative stress and myelination of neuraxons. Therapies that affect NF-κB-mediated pathways influence the functionality and the prognosis of patients who have sustained a spinal cord injury.

KEY WORDS: spinal cord injury, recovery, cytokines, NF-κB

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Introduction

Spinal cord injury, a damage to the spinal cord causing temporary or permanent changes in its function, results to increased mortality and morbidity rates. Globally, it is estimated that approximately 250,000-500,000 people are affected by this condition [1,2]. Spinal cord injury usually affects young males before the 3rd decade of life, while recently there is a marked shift towards persons older than 60 years, mostly attributed to preventive medicine programs aimed at younger ages and to the phenomenon of population ageing in industrialized countries [3].

The most common mechanisms resulting to spinal cord injury include primarily traffic accidents and falls, with national distributions fluctuating according to the country's demographic curve and the existing socioeconomic conditions [4]. An increased percentage of those who suffer acute spinal cord injury die instantly, about 10% die during first hospitalization while the prognosis of patients who finally undergo rehabilitation is influenced by the resulting neurological condition according to ASIA staging [3,5]. About a half of SCI patients are diagnosed with cervical spine lesions and suffer from severe neurological complications, mostly quadriplegia and paraplegia [6].

Despite its low incidence, SCI results in disproportionate burden for health care systems not only in terms of human loss but also financially. Its great cost is an equation of multiple hospital admissions, required for spinal cord injury patients, the expensive and long-lasting rehabilitation programs, as well as the social allowances and the loss of productivity [7]. The existing predicting models describe an increase in healthcare costs resulting from spinal cord injury in the next decade, primarily attributed to an extended hospitalization period and to the treatment of multiple co-morbidities due to the age of the affected population [8].

Up to this moment, there are no existing national studies to evaluate the epidemiology of SCI in Greece. An estimated prevalence of around 34 patients per million is the most realistic scenario according to some sporadic studies that have included Greek patients and this number is considered as increased when compared to other European countries [1,9]. Although detailed data on the exact numbers is still lacking, it can be alleged that the structure of the national healthcare system, the shortage of rehabilitation facilities and the unavailability of effective social policies targeting disabled persons, do not favour the management of SCI patients in Greece [10].

Research on recovery mechanisms following spinal cord injury utilizes animal models to clarify the underlying pathophysiological mechanisms and to test possible treatment regimens that amplify subjects' neurological status [11,12]. Issuing novel guidelines regulating data exchange and increased sharing of acquired knowledge will contribute highly to breakthroughs in the study of spinal cord injury [13].

In the molecular level, the pathophysiological mechanisms that take place following SCI are very complicated. The "primary injury" develops acutely after trauma and includes the direct implications of the injury mechanism to the spinal cord structures [14]. The "secondary injury" follows and is further divided in an acute (0-48 hours), subacute (2-14 days), intermediate (2 weeks-6 months) and chronic phase (>6 months) [15]. This secondary phase includes several pathophysiological mechanisms that promote the expansion of the injury within the spinal cord structures [16]. The most important ones are: deranged blood perfusion, imbalance in the concentration of ions and neurotransmitters, oxidative stress and production of free radicals, cellular death and inflammation [12]. The above mechanisms, primarily represented by the inflammatory one, are mediated by a variety of signaling molecules and develop both in the intra- and extracellular levels. These include cytokines, such as TNF-α, IL-1β, IL-6 andIL-12, which regulate the procedure of secondary spinal cord injury and progressively lead to the recovery of neuronal tissue. The above procedures result in intranuclear modifications and gene expression, primarily mediated by transcription factors, such as NF-κB [17]. Formation of a scar tissue within the spinal cord, is a dynamic balance between the infiltrate of inflammatory cells and molecules of the extracellular matrix. This fibrous

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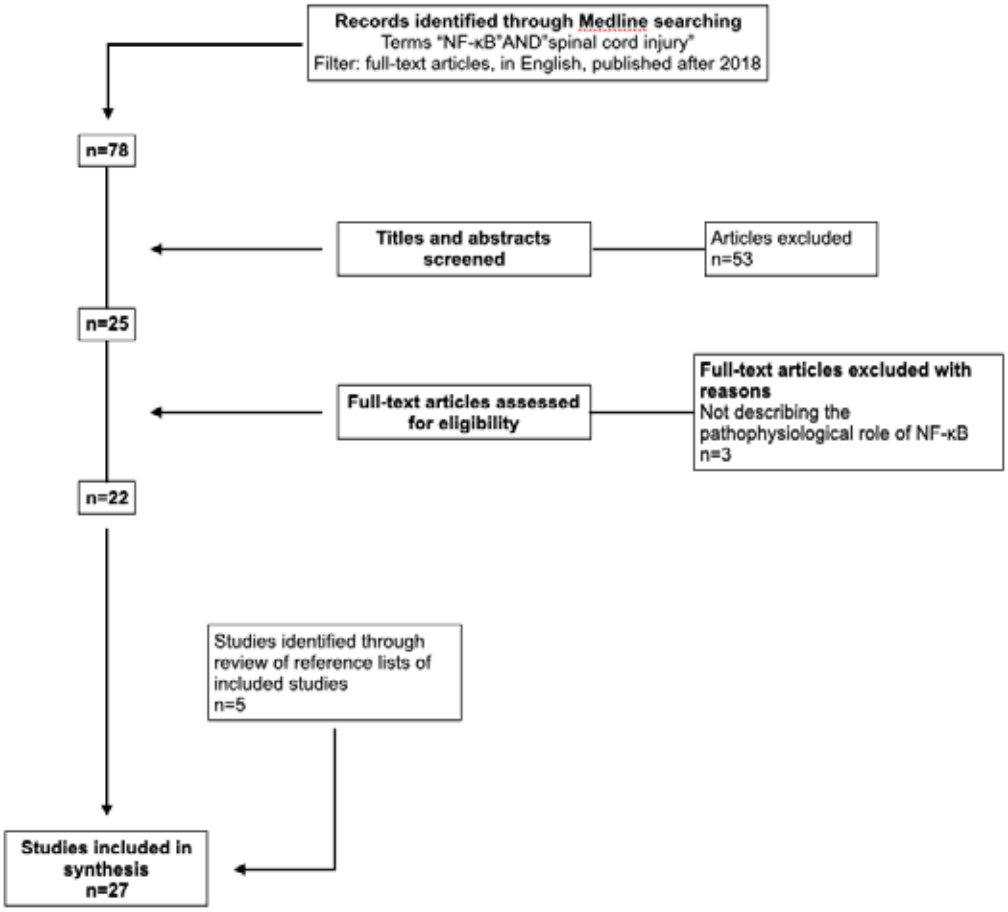
TABLE 1. CURRENT REVIEW FLOW CHART.



tissue surrounding primary injury prevents from spreading through secondary injury mechanisms and partly facilitates the recovery of the neuronal tissue through axial reformation [18].

Given the above facts, the present study is a literature review aiming to summarize the present knowledge on the role of NF-κB in the recovery of spinal cord following injury. In March 2020, an initial search using suitable MeSH terms was performed in the database Medline-Pubmed. From the 78 articles included in the search results only 22 were relevant to the pathophysiological role of NF-κB in SCI after injury. Subsequently, a scan of the articles' reference list was performed to check for more eligible articles to be included in the study. Following the above procedure, 27 articles were finally included in this literature review. (**Table 1**)

Discussion

NF-κB is a transcriptive factor that exists in the nuclei of all eukaryotic cells. In the normal spinal cord, it has been detected both in neuronal cells (neurons, astrocytes, oligodendrocytes) and in microglia [19]. It is a complex molecule that is kept inactive by protein inhibitors (IKK) and by epigenetic modifications [20,21].

Structure of NF-κB

Three molecular complexes contribute to the formation of the entire NF-κB molecule: the NF-κB family proteins, the NF-κB inhibitors (IKB) and the IKK complex.

• The NF-κB family, also described as NF-κB/Rel family, includes the molecules NF-κB1 (p50), NF-κB2 (p52), RelA (p65), c-Rel and RelB.

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• The IκB inhibitor family is comprised of the molecules IκBα, IκBβ and IκBε.

• The IKK complex is a protein with a high molecular weight which regulates the phosphorylation of the NF-κB inhibitors (IκB).

In the deactivated state, IκB inhibitors cover the NF-κB sequencing that facilitate its binding to the nuclear gene promoters and thus its activity as a transcription regulator is annihilated [22]. When activated, NF-κB moves to the nucleus and modifies the transcription of genes which regulate several intracellular procedures and relate to the recovery of neural tissue following spinal cord injury [19].

Activation of NF-κB and signaling

The activation of NF-κB is mediated by many molecules. IL-1β activates NF-κB and enhances inflammation through the TLR/MyD88 or through the TLR4/TRAM/TRIF trail. The first pathway is more rapid and facilitates the acute inflammatory phase by promoting a more acute activation of NF-κB, while the second one leads to a more delayed activation of NF-κB in the subacute inflammatory phase [23,24]. Medicines, such as the natural extract chlorogenic acid, inhibit the IL-1β-mediated activation of NF-κB and result to better neurological outcomes [25]. Other interventions, such as treatment with hyperbaric oxygen (HBO), also deactivate NF-κB by influencing the above pathway and thus ameliorate prognosis after spinal cord injury [26].

Moreover, TNF-α binds to its receptor on the cellular surface (TNFR1) and activates the RIPK1/TAK1/NIK pathway by enhancing the phosphorylation of the inhibitory complex IKK. Prior to binding, the receptor rests in deactivated status connected with ubiquitin molecules. This ubiquitination process is mediated by the TNFAIP3 or A20 molecule. These molecules are possible targets for future therapies that could deactivate TNF-α receptor and thus inhibit inflammation [27]. The unbinding of the RIPK1 molecule from the TNFR1 complex activates the TAK1 molecule, which in turn enables the NEMO-IKK (NIK) molecule to phosphorylate the IKK complex of the NF-κB. Consequently, the inhibitory molecules IκBα, IκBβ are phosphorylated and NF-κB is released. The phosphorylated IκB then binds with ubiquitin and is then decomposed by the 26S proteasome. The free NF-κB inserts the cellular nucleus and enhances the expression of genes which deter cell death and enhance inflammation [28].

Another mechanism of potential activation is the cross-talk between NF-Kb and TWEAK (TNF-like weak inducer of apoptosis). This molecule binds to its Fn14 receptor (Fibroblast growth factor–inducible 14) and activates NF-κB to enter the nucleus and exert its pro inflammatory role through the synthesis of TNF-α and IL-1β[29].

Additionally, Micro-RNAs (miRNAs) regulate the expression of NF-κB by binding on relevant gene promoters that encode signaling molecules included in the mechanisms described above. For example, miR-136-5p and miR-96 induce inflammation by reducing the transcription of IKKβ and by increasing the release of NF-κB [30]. The molecules miR-199b and miR-124 have an opposite action: they increase the transcription of IKKβ and promote the binding of NF-κB to its inhibitor complex. Thus, these molecules could represent targets for the development of novel molecular therapies with the aim to ameliorate neurological burden of SCI patients [31]. The regulatory path is reversible: NF-κB binds to the promoter of certain miRNAs and regulates their activity. For instance, the miRNA-372 has an anti-inflammatory role in the spinal cord following NF-κB binding to its promoter [32].

The presence of free myelin, produced by damaged neuraxons during the primary SCI, has been shown to regulate NF-κB. Literature data support NF-κB activation and the promotion of inflammation through the FAK/P13K/Akt trail initiated by NogoA (neurite outgrowth inhibitor A) and the glycoprotein of oligodendritic myelin [33].

The role of epigenetic modifications is still unclear but they can both enhance and annihilate the activity of NF-κB. In macrophages, methylation and phosphorylation of serine amino-acids in the molecule's promoter (the so-called nuclear localization signals - NLS) enables its traffic to the macrophage nucleus, increases its transcriptive activity and promotes inflammation in the spinal cord [34]. The acetylation of the RelA (p65) molecule in lysine po-

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sitions retains its inactive status and is the output of a subtle balance between histone acetyltransferases (HATs) and histone deacetylases (HDACs) [21]. The AMPK/SIRT1 trail leads to the deacetylation of NF-κB and suppresses inflammation following SCI. Treatment agents, such as resveratrol, enhance neuronal recovery by inducing the early apoptosis of inflammatory cells in the above trail [21,35] and the traditionally used valproic acid has also been reported to suppress SCI inflammation by interacting with these epigenetic modifications [36].

Pathophysiological role of NF-κB

Despite recent progress in the detection of several novel signaling pathways and their cross-talks, associated with NF-κB, their exact pathophysiological roles remain unknown. It is well understood that NF-κB facilitates inflammation by regulating the chemotaxis of inflammatory cells and the intracellular communication during inflammation [16]. NF-κB increases the expression of genes that produce the molecules ICAM and VCAM, which enable the adhesion and immigration of neutrophils through the blood vessel wall. Furthermore, the inflammatory cells that mediate inflammation (astrocytes, T-lymphocytes and macrophages) communicate with chymokines and cytokines, which initiate various signaling mechanisms. Many of these mechanisms end up to the activation of NF-κB. For example, pro-inflammatory cytokines including TNF-α, IL-1β and IL-6 lead to an increased expression of NF-κB, while lower levels of the latter are related to an increased circulation of anti-inflammatory molecules, such as IL-12 [12].

Free oxygen and nitrate radicals (ROS, NOS) activate NF-κB and preserve inflammation in the spinal cord by preventing autophagy and apoptosis of inflammatory cells [37,38]. The mechanism includes an increase in the expression of the mitochondrial enzyme MnSOD and a decrease in the production of free radicals through a reverse feedback mechanism. As a result, the free-radical-mediated apoptosis of inflammatory cells is inhibited, a phenomenon which exacerbates inflammation in the spinal cord [37]. Another mechanism includes the activation of kinase JNK1 by NOS and the consequent phosphorylation of Bcl-2 (Beclin 1 / B-cell lymphoma-2) and of IKKb of the NF-κB complex. The free NF-κB increases the expression of genes that annihilate the autophagy of inflammatory cells (c-Fos, c-Jun) [38]. In animal models, the commencement of ketotic diet (rich in fat, poor in carbohydrates, medium protein intake) reduces oxidative stress and prevents inflammation as early as the 4th week after injury. This procedure is mediated by NF-κB [39].

Moreover, cellular death associated with NF-κB is regulated by TNF-α and by the TWEAK molecule. A study performed by Xu et al in 2016 proved the anti-apoptotic role of TWEAK in inflammatory cells following spinal cord injury in a procedure mediated by RIPK1/caspase 8. Through this mechanism, TWEAK preserves inflammation within the spinal cord by binding to its Fn14 receptor that leads to the activation of NF-κB [26]. TNF-α also activates RIPK1/caspase 8 after binding to its receptor in the membrane of inflammatory cells that appear in the acutely damaged spinal cord. Through the RIPK1/RIPK3/MLKL complex ("necrosome") TNF-α promotes the necroptosis of inflammatory cells in a strictly regulated procedure that includes gene transcription mediated by NF-κB [28]. This anti-apoptotic role of TNF-α through NF-κB-mediated gene transcription is further supported by experimental data that show an increase in the cell death rates of inflammatory cells within the spinal cord when gene transcription was inhibited by using actinomycin D or cycloheximide [40]. Medications, such as the natural extract Paeoniflorin, influence the above pathway, by deactivating NF-κB, thus deterring inflammation and exerting a neuroprotective influence [41]. Other molecules, such as DUSP19, inhibit apoptosis by enhancing the transcription of NF-κB and are suitable targets for future therapies [42]. Last, resveratrol is a polyphenol of red wine that promotes the recovery of neuronal tissue after spinal cord injury. Its role is performed by an increase in the expression of SIRT1 and AMPK in the spinal cord macrophages. Resveratrol deters inflammation by rendering inflammatory cells vulnerable to apoptosis, a procedure which relates to a decrease in the expression of NF-κB, decreased levels of

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TNF-α and increased levels of IL-12 [43].

Axon demyelination and remyelination are also under NF-kB modulation. The phagocytosis of free myelin by microglia cells promotes the activation NF-κB and preserves inflammation. Rat models that underwent intrathecal infusion of E6020, a factor that activates NF-κB through the TLR pathway of the precursor oligodendritic cells (OPCs), showed an estimated increase in the levels of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 and the percentage of remyelinated neuraxons increased [44,45].

In conclusion, the transcriptive factor NF-κB is a central regulatory molecule in the recovery process following SCI and is included in several pathophysiological pathways. More research is required to clarify the exact role of NF-κB in the cellular functions and for the development of targeted therapies against molecules that affect its functionality, to ameliorate the neurological function of patients suffering from SCI.

Conflict of interest

The authors declare no conflicts of interest.

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Metabolic bone diseases and parenteral nutrition in pediatric patients: clinical and nursing aspects

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ABSTRACT

Total parenteral nutrition is a feeding strategy widely used in children and, particularly, in preterm infants, due to a variety of pathological conditions that hinder enteral feeding. Parenteral feeding has been associated with the development of metabolic bone diseases. These can manifest as rickets and/or pediatric osteoporosis, with a prevalence reaching 40%, while the nutritional limitations of parenteral feeding, along with the increased metabolic needs of the bones at this growth stage, further deteriorate the problem. There are plenty of theories regarding the underlying mechanisms. Deficiency or toxicity of nutrients, such as calcium, phosphorus and vitamin D, and cholestasis have been identified as risk factors. Another contributing factor is the contamination with aluminum, with its numerous deleterious effects, along with the composition of the fatty acid emulsions administered. Appropriate enrichment of parenteral nutrition solutions with specific nutrients plays a key role in managing or preventing the disease. High standards in the use of this method, including the restriction of aluminum contamination, are of high importance. The role of clinicians and nurses is crucial, since a significant level of alert for malnutrition signs is required, as well as high professional standards for applying and maintaining the parenteral nutrition setting.

KEY WORDS: Bone, Metabolic disease, Parenteral nutrition, Pediatric, Nursing

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Introduction

Total Parenteral Nutrition (TPN) constitutes a landmark therapeutic strategy for providing the necessary nutrients and energy, usually through a central vein, to neonates, children and adults, suffering from a condition that hinders normal enteric food intake [1]. While TPN was firstly introduced to the pediatric patient population in the 1960s, it was not until 1980 when the TPN-associated complications were firstly described [2, 3]. Among them lie the TPN-induced Metabolic Bone Diseases (MBD), developed through a variety of speculated mechanisms and manifesting either as rickets (in children) and osteomalacia (in adults) or as osteoporosis [4-8].

Although a significant amount of research has provided valuable knowledge on the clinical manifestations and laboratory findings of these diseases, as well as on the distinct molecular pathways leading to them, the prevalence of MBD in children assisted with TPN is still high, up to 40% [9]. Therefore, exploring these fields at a greater extent, could not only lead the way for a deeper understanding of these conditions, but also for their more effective management. Additionally, it is of paramount importance to enable clinicians and nurses to be informed for the details of these conditions, stay alert for any alarming signs and respond successfully in case needed. Presumably, this study aims, on the one hand, to review the various aspects of TPN-induced MBD, with an emphasis on the speculated mechanisms of development, and, on the other hand, to present a framework for a proper clinical approach by the clinician and the nurse.

Tpn in children

Indications

TPN administered to children differs from that of adults, with respect to the timeframe of the administration, the dosage of various nutrients provided depending on the child's growth needs and the various technical issues associated with the intravenous access [10]. Any gastrointestinal (GI) tract condition that does not permit enteral feeding, such as severe inflammatory bowel disease and GI reflux, generally requires TPN [6-8]. TPN is particularly indicated for preterm and low birth weight infants, immediately after birth, to compensate for the low nutrient reserves, in the face of increased energy consumption due to prematurity diseases and high developmental needs. Since the GI tract is still premature to take up its role, parenteral feeding is usually unavoidable. These issues arise predominantly when birth weight is less than 1.500 kg or the age is lower than 34 weeks [11]. In this cases, TPN is usually applied if it is anticipated that enteral feeding will not be achieved for at least two days [6-8].

Administration regimens

The pattern of TPN usage depends on several factors. Principally, TPN solutions must contain adequate sources of energy (carbohydrates and fats), abundant amino-acids, electrolytes, vitamins, minerals and trace elements. Moreover, solutions might also contain further additives, such as heparin, cysteine and carnitine. In particular, dextrose is used for covering the needs for carbohydrates, while there are specialized amino acid solutions, such as TrophAmine 6% and 10%, Premasol 6% and 10% and Aminosyn-PF 7% and 10%, rich in essential amino-acids and tailored for the needs of infants and children. These solution regimes display a lower pH, permitting the dilution of larger amounts of calcium (Ca^{+2}) and phosphate (P^{+4}) [6-8]. Fats are provided in the form of Intravenous Fat Emulsions (IVFE), which consist either of soybean oil alone or of a combination of soybean with safflower oil. Highly concentrated IVFE are preferred, since they provide abundant calories in relatively small solution volumes. Infants and children must receive at least 0.5–1.0 gr/kg of IVFE per day, while preterm require more than 0.6–0.8 g/kg/day [12].

Frequent electrolyte monitoring to adjust the daily intake is necessary. Preterm and full-term have similar needs in electrolytes, except for Ca^{+2} and P^{+4}, which are higher for preterm, since they lack in the maternal supply of the third gestational trimester, while their growth needs are increased [12]. Despite the ongoing research on optimizing the TPN supplementation strategies, pediatric vitamin products have not evolved and, often, the increased dietary

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needs of malnourished and severe patients are not met [6-8].

Adverse effects

TPN, as a potentially long-term strategy that intervenes with normal physiological procedures, is not exempt from undesired events. Among them, toxicity or deficiency of certain minerals, vitamins and trace elements is a major consideration [6-8, 13]. Cholestasis is another serious complication that requires close attention, as it further obstructs the natural nutrients intake and leads to extended metabolic imbalance [14]. Finally, contamination of TPN fluids with substances, such as aluminum (Al) has also been reported. Al contamination, along with cholestasis and several other distinct causes, have been reported to drive the development MBD in children treated with TPN [15-17].

MBD IN CHILDREN

Classification and clinical manifestations

MBD in neonates and children refers to the reduction of bone mineral content, with respect to the body size or gestational age, presenting with particular radiological and biochemical findings [9]. Rickets and pediatric osteoporosis are the main clinical entities falling under the MBD umbrella term. Osteoporosis in children usually occurs between 1 and 13 years of age and presents with hip and back pain. Long bone and vertebral compression fractures, along with other deformities, can also occur [18]. Osteoporosis is characterized by low net bone mass and normal mineral-to-collagen ratio, leading to microarchitectural lesions that make the bones susceptible to fractures [19].

On the contrary, rickets is characterized by insufficient mineralization of the epiphyseal plates. The deformed open epiphyseal plates lead to architectural changes affecting the bone sized and shape, finally resulting to instability and, possibly, deformities such as chest bone softening, cranial bossing, bowing and craniotabes [20]. After the closure of the epiphyseal plates, the ineffective bone mineralization, once developed, leads to a similar syndrome of "soft" bones called osteomalacia. Osteomalacia, as well as rickets, is characterized by reduced mineral-to-collagen ratio.

Risk factors and disease-causing mechanisms

Osteoporosis can be secondary due to several illnesses and nutritional deficiencies that disrupt the balance between osteoblastic and osteoclastic activity. Inflammatory diseases, such as Crohn's disease, have been found to contribute to the onset of osteoporosis through a cytokine-mediated mechanism. Glucocorticosteroids and hormonal disturbances also have a detrimental effect on the development of bone tissue. Inadequate nutritional intake of Ca^{+2}, P^{+4}, vitamin D and other elements also leads to osteopenia and finally osteoporosis. A predominant cause of rickets/osteomalacia is vitamin D deficiency, leading to diminished intestinal absorption of Ca^{+2} and P^{+4}, and also to their lower usage in bone mineralization. Any disruption in the metabolic pathway of vitamin D up to its bioactive form (1,25-dihydroxycholecalciferol) can result in rickets. Dietary sources provide approximately 20% of the required vitamin D, and the exclusion of these food types can be a cause. The rest amount is produced by the sunlight-mediated transformation of 7-dihydro-cholesterol to cholecalciferol, which is then gradually hydroxylated into its final form in the liver and the kidneys. Abstinence from sun exposure, as well as severe renal diseases can block this pathway, leading the way for the disease [21]. Finally, rare genetic causes have been reported. CYP27B1 and CYP2R1 mutations were shown to cause vitamin D deficiency, as they hinder the hydroxylation process [22].

Premature neonates experience decreased mineralization as a multifactorial disorder. Although several pathways have been described, the reduced placental transfer of Ca^{+2} and P^{+4} in prematurity is the predominant reason. Since most of the mineral accretion happens in the last trimester of pregnancy, preterm infants fail to achieve this critical accumulation [15]. This leads to both decreased bone mass and/or low mineral deposition. Therefore, rickets and osteoporosis can exist in isolation or co-exist. The extended use of TPN constitutes another risk factor in preterms with chronic diseases or prema-

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turity-associated conditions, by promoting MBD through several mechanisms [1, 17, 23].

Laboratory and imaging findings

Diagnosis partly relies on the estimation of certain biochemical markers: Serum Ca^{+2}, P^{+4}, Alkaline Phosphatase (ALP), urinary Ca^{+2} and blood Parathormone (PTH) levels. The earliest finding is the decreased P^{+4} levels. Low P^{+4} levels occur due to nutritional deficiency or/and due to elevated PTH levels, as a response to abnormally low Ca^{+2} levels. In the case of nutritional deficiency, hypophosphatemia can trigger the vitamin D upregulation at such an extent that Ca^{+2} increases and PTH production is suppressed. Cut-off values for estimating ALP vary across studies from 500 IU/L to 1200 IU/L [24-27]. A sharp increase in ALP levels (above 900 IU/L) displays excellent sensitivity and high specificity in diagnosing MBD, since ALP can be 5-fold higher than the normal range [28]. Liver and GI diseases must also be excluded in the face of an abnormally high level of ALP. When PTH is considered together with ALP (over PTH>180 pg/mL or ALP<4.6 mg/dL at 3 weeks) the sensitivity and specificity reach 100% and 94%, respectively [29, 30]. These markers should be monitored weekly or biweekly to estimate the disease progress and achieving normal values should serve as a therapeutic target [31].

Dual Energy X-Ray Absorptiometry (DEXA) is the gold standard technique to reveal even small changes in Bone Mineral Content (BMC) and Bone Mineral Density (BMD), as markers for MBD. In neonates, this method applies ionizing radiation preferably to the lumbar spine, the forearm or the calcaneus. A BMD greater than 0.068 g/cm^2 in preterm infants of <31 weeks, has been associated with low probability of developing MBD [24]. Although a precise method, standardized for the pediatric population, it exposes neonates and older children to radiation and also holds the risk of imprecise measurements due to movement artifacts [32]. A revolutionary novel method employs ultrasounds to estimate the bone speed of sound, usually over the tibia shaft. This method eliminates the risk of radiation, is applicable bedside and has also been standardized for both term and preterm infants at various ages [33]. A study has found that ALP levels are inversely correlated with the ultrasound signal over the tibia, indicating the promising diagnostic value of this method [15].

TPN-induced MBD display the same diagnostic markers as the ones of other causes. In preterm infants, MBD can be diagnosed as early as 2-4 months from birth, as they tend to develop during a 'catch-up' growth period following the recovery from prematurity illnesses [34, 35]. In 40-100% of newborns receiving prolonged TPN, histologic findings of MBD can be found, although the disease usually remains asymptomatic [36].

TPN-INDUCED MBD

Various conditions in neonates and older children, including prematurity with its satellite anomalies, require the use of TPN, which has been associated with the onset of MBD [37]. TPN-associated MBD was initially described with hypercalciuria, normal vitamin D, increased Ca^{+2} and normal P^{+4} levels [38]. Since then, many studies have shown the characteristics of the MBD following the use of TPN and explored the underlying mechanisms [15-17, 23, 39-41]. Lack of nutrients, such as Ca^{+2} and P^{+4}, in the TPN solution, insufficient or excessive amount of exogenously administered vitamin D, altered administration of certain fatty acids, cholestasis and, predominantly, the risk of aluminum (Al) accumulation with its deleterious actions, have been identified as key factors.

Ca^{+2} and P^{+4}

Over 80% of the fetal required amount of Ca^{+2} is accumulated during the last trimester of pregnancy in order to fill 99% of term neonates' stores. Similarly, around 80% of fetal P^{+4} stores are accumulated in the bones by term gestation. Consequently, preterm neonates are deprived of this abundant supply and have an increased need for exogenous compensation [42]. Studies have shown that low intake of Ca^{+2}, P^{+4}, vitamin D and proteins for the first weeks of life, in extremely low weight preterm neonates, is correlated with MBD [43].

It has been reported that TPN solutions often fail

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to achieve adequate concentrations in Ca^{+2} and P^{+4} [44]. This is usually unavoidable due to the limited quantities of Ca^{2+} and P that can be diluted in the small TPN volumes required for pediatric patients and, especially, for preterm neonates [45]. Large amounts of Ca^{+2} and P^{+4} in relatively small TPN volumes hold the risk of precipitation, especially when the amino acid concentration is low, the environmental temperature is high and the pH of the amino acid solution is high [46]. Of note, the available amino acid solutions for children (TrophAmine and Aminosyn-PF) have a relatively low pH to allow the dilution of larger amounts of Ca^{+2} and P^{+4} [47]. Addition of alkaline agents, such as aminophylline, or lipid emulsions in a TPN mixture further increases the risk of precipitation [48]. The Ca^{+2}/P^{+4} weight ratio is crucial for achieving optimal retention and Ca^{+2}/P^{+4} homeostasis in TPN-assisted infants, and has an optimal range from 1.3:1 to 1.7:1 [2, 49, 50].

Vitamin D

Deficiency of the fat-soluble vitamin D has been associated with rickets or osteomalacia in older ages, as its role is to mediate the intra- and extracellular Ca^{+2} concentrations [51]. It stimulates intestinal Ca^{+2} and P^{+4} absorption, as well as bone turnover and, indirectly, mineralization [52]. Due to the underlying illnesses that deter oral vitamin D intake, but also due to the limited exposure to sunlight of patients under TPN, low levels of vitamin D are often observed [53]. On the other hand, excessive administration of vitamin D, especially in the absence of need for Ca^{2+} enteral absorption, might be unneeded or even deleterious for the bones [2]. A study showed that withdrawing vitamin D from TPN in children resulted in normal serum concentrations of the active form of vitamin D (1,25-dihydroxycholecalciferol), Ca^{+2} and P^{+4}, no changes in Ca^{+2} and P^{+4} urine excretion and no significant clinical effects [54]. Another study demonstrated absence of MBD signs in patients receiving extremely small amounts of vitamin D [55]. Even very low amounts of daily administered vitamin D suffice to achieve normal values of serum vitamin D levels in preterm infants [56].

Aluminum

Another crucial risk factor for the development of MBD, associated with the use of TPN, is the contamination of the administered solution with aluminum (Al). Relatively early, an Al-dependent clinical syndrome presenting with hypercalciuria, hypocalcemia and low to normal vitamin D levels was described [2, 57].

A study by Lidor *et al*. (1991) reported a case of Al poisoning with concomitant rickets/osteomalacia and osteopenia, where Al was detected on the bone surface [58]. Another study by Hamilton *et al*. (2004) supported the same theory about the relationship between long-term TPN and MBD [59]. Interestingly, Fewtrell *et al*. (2009) published a study claiming that TPN-associated Al contamination can have a long-term impact on children's bone health. The study showed that, after a 13-to-15-year follow-up, DEXA revealed signs of BMD of the hip and the lumbar spine [60].

The aforementioned findings led the way for many theories attempting to explain the underlying mechanisms of the Al-induced bone lesions. Al comes particularly from the salts of Ca^{+2} and P^{+4}, present in TPN solutions. It is believed that about 20-40 mcg/kg are administered to neonates each day, depending on the mineral content of TPN [61]. Prematurity itself, or any other condition that impairs renal function, deteriorates the Al accumulation in infants [40]. Premature infants on TPN present with negative Ca^{+2} balance and hypercalciuria, which is believed to be a compensatory mechanism, rather than the origin of the condition. High bone Al loading, as well as low bone turnover have been observed, designating the Al-triggered decreased bone uptake of circulating Ca^{+2}, which, in return, leads to hypercalciuria. Moreover, reduced Al levels in PTN solutions were associated with normal levels of vitamin D, while the same result was found in patients with end-stage renal disease treated with the Al-chelation agent deferoxamine. These outcomes suggest the Al contamination as the culprit for the low vitamin D levels of patients on TPN. Finally, the Al accumulation on the mineralization front of the bones indicates that Al has a direct, suppressing impact on bone mineralization [40].

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Cholestasis

PTN typically predisposes infants and older children to cholestasis, which might occur after two to four weeks. PTN-associated cholestasis is a product of reduced or delayed enteral nutrition and leads to decreased enteral absorption of many nutrients, including the fat-soluble vitamin D [62]. However, evidence shows that, despite the adequate replacement of nutrients and vitamin D with TPN, MBD may still persists, suggesting a yet unknown, vitamin D-independent mechanism for its development [63].

Fatty acids

Long-term employment of TPN has been found to induce deficiencies in specific omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), and particularly in docosahexaenoic (DHA) and arachidonic (ARA) acids. It has been shown that these fatty acids are significant modulators of bone formation, with DHA promoting the differentiation of mesenchymal cells into osteoblasts, while ARA enforces the activity of osteoclasts [64]. Animal studies have revealed a beneficial effect of omega-3 PUFA on bone health during the growth period [65]. It has been speculated that there might be a unique window during the first stages of bone formation, when PUFAs exert their effect on osteoblasts/osteoclasts differentiation and activity. More studies evaluating the effect of PUFAs during gestation and lactation are needed [64].

CLINICAL AND NURSING APPROACH

Management of nutritional deficiencies

The first step toward mitigation of the TPN-induced MBD, is to ensure sufficient amounts of all related nutrients, including amino-acids, fatty acids, minerals and vitamin D [6-8]. Specialized amino-acid solutions, highly concentrated in essential amino-acids, are commercially available for infants and children. These include TrophAmine, Premasol and Aminosyn-PF. They are especially designed to display low pH values, appropriate for diluting higher quantities of minerals. Both soybean oil and a mixture of safflower and soybean oil can be used as IVFE, to provide 10 kcal per gram of solution. IVFE not only play a central role in bone metabolism, but also their lower osmolality contributes to the integrity of peripheral lines [6-8].

Unlike the other minerals and electrolytes, the requirements for Ca^{2+} and P differ between preterm and term infants [6-8]. The minimum amounts of Ca^{+2} and P^{+4} to be administered in preterm infants, are 150 mg/kg/d and 75 mg/kg/d, respectively, with a Ca^{+2} to P^{+4} ratio equal to 1.7:1, reflecting the intrauterine mineral accretion in the last gestational trimester [66]. Since the solubility of these substances is severely influenced by temperature, amino-acid concentrations, pH and other factors, close attention must be paid to the proper preparation and storage of these solutions. Adding high amounts of protein in TPN within the first days, along with the earliest possible initiation of enteral feeding, has become the main practice in neonatal care, as it also increases the cellular uptake of P^{+4} [67].

Vitamin D supplementation products for infants and children on TPN have not been drastically reformulated for decades and may lack in covering the augmented needs of these patients [6-8]. Apart from the evidence showing the toxic effect of vitamin D oversupply, it can battle the corticosteroid-induced detrimental effect on osteoblasts and improve the intestinal Ca^{+2} absorption when the enteral feeding is established [68]. The recommended dose by the American Academy of Pediatrics is 400 IU/d, while the European guidelines suggest 800-1000 IU/d for preterm infants [69, 70].

There is also some evidence of the beneficial effect of physical activity on bone mineralization in infants. Particularly, passive range of motion and joint compression performed for 5–15 min/d for 4–8 weeks, improved the ultrasonographic and biochemical markers of bone turnover in preterm infants [71].

Proper use of TPN

TPN is usually administered through a central venous line (CVL), which delivers the TPN content to the superior vena cava or the right atrium of the heart. A CVL offers the ability for a far higher osmolality compared to that of the peripheral ve-

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nous line (PVL), which is limited to 900 mOsm/kg, with a significant concomitant risk of phlebitis and infiltration [72]. Some basic laboratory diagnostics should be made prior to the initiation of a TPN, but also be constantly monitored during its use. These parameters include Ca^{+2}, P^{+4}, magnesium, ALP, hepatic enzymes, total and conjugated/direct bilirubin, albumin and lipid panel. After the initial phase of TPN induction, the monitoring pace can be adjusted according to the stability signs of the patient. Young patients on prolonged TPN call for continuous monitoring to protect the sensitive vitamin and mineral balance [6-8].

It is generally recommended to replace TPN with enteral feeding as soon as possible, not only to eliminate the risk of certain TPN-placement complications, but also to surpass the inherent nutritional limitations of TPN. Weaning from TPN is introduced with human milk, ideally mother's own milk or a pasteurized donor substitute [73]. However, human milk does contain all the required mineral content and, therefore, must be fortified with Ca^{+2}, P^{+4}, vitamin D and other nutrients [74].

Further clinical and nursing considerations

The multilevel risk of MBD in infants (predominantly premature) and children under TPN, requires a constant alert by clinicians and nurses. The weight of the child must be measured daily, under standard conditions, and evaluated against standardized weight velocity charts. In this way, growth, body size and other somatometric parameters are estimated, and nutrient needs are assessed. Clinicians should also be cautious for potential adverse effects of TPN, including infection, hyperglycemia, hypertriglyceridemia, disturbance of acid-base balance, electrolyte abnormalities and phlebitis [6-8]. Osteopenia and vitamin D/mineral deficiency or toxicity are frequent long-term adverse effects and lead to the onset of MBD. Therefore, the corresponding laboratory and radiological markers must be checked and assessed frequently. As for Al contamination, the Food and Drug Administration has set a maximum limit for the tolerable amount of Al to 5 mcg/kg/d [75].

Site infections can be induced by the improper care of the catheter or by its unorthodox use (medication administration, blood draws). Regular skin disinfection and dressing changes are a common practice to prevent these events. Chlorhexidine gluconate is the most widespread disinfectant used in patients older than 7 days. Transparent dressings are replaced every week or when wet or damaged. Moreover, laboratory specimens must be frequently obtained and appropriate flushing performed [6-8].

In 2007, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) published its standards for nutrition support nurses [76]. According to this manual, nurses are recommended to have an active role in the assessment of TPN-assisted patients who are at risk or already diagnosed with TPN-related complications. This includes the identification of signs or markers of imbalanced nutrition, fluid volume deficit/excess, delayed growth and low body weight. This procedure has to be data-driven, relying upon physical examination, interviewing (if possible) and diagnostic procedures. Nurses should also be involved in the development of an individualized nutrition care plan and also monitor its implementation, periodically reassess the route of administration and suggest a plan for transition to enteral feeding. They can also make suggestions on the equipment and supplies needed, as well as on the type of feeding device, the infusion rate and other technical parameters. Moreover, nurses should be alert for signs of complications, such as catheterization site infections, and contribute efficiently to their resolution. The A.S.P.E.N. guidelines emphasize the importance of high quality qualifications and encourage the continuous evaluation of practice skills. They also point out the importance of productive collaboration with colleagues, as well as with the patient, other clinicians and caregivers. Quality and cost-efficiency (efficacy, safety, availability, cost, outcomes) of the nutrition strategies are also considered as important, as well as the focus on research and ethics around this clinical field.

The shift from TPN to breastfeeding can also be aided by specialized nurses. A recent study demonstrates the high awareness of breastfeeding among nurses and their existing efforts in promoting it

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[77]. Psychological support to the family is also of paramount importance and can be, at least partly, provided by the caregiving nurses. High quality education and training, possibly encompassing modern simulation technologies, can accelerate the learning curve and preserve high professional standards [78].

Conclusively, TPN in infants and children is a multidisciplinary field, with the contribution of nurses being of crucial importance. MBD still continue to manifest frequently in these patients, and the high level of alert is necessary for detecting and mitigating them, while ongoing research on the underlying mechanisms, risk factors and successful management strategies is promising.

Conflict of interest

The authors declare no conflicts of interest.

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VOLUME 71 | ISSUE 4 | OCTOBER - DECEMBER 2020 ORIGINAL ARTICLE

Correlation of limping during walking with pain, oedema and restriction of ankle range of motion after ankle sprains

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ABSTRACT

Purpose. The correlation of the degree of ankle sprain, pain, oedema and the restriction of the range of motion of the ankle with limping during walking after ankle sprain in the acute post-traumatic period.
Material and method. The sample consisted of 68 individuals, 18-50 years old, with 1st and 2nd degree ankle sprain. We evaluated the degree of sprain with clinical examination, the pain with VaScale, the oedema with figure of eight method as well as the restriction of the range of motion of the ankle with a digital goniometer. The limping concerning the difference in support time at each leg while walking was evaluated too.
Results. Statistically, the degree of ankle sprain was found to be significantly correlated with pain (Spearman's rho = 0.660, p = 0.000), oedema (Spearman's rho = 0.672, p = 0.000) and restriction on its range of motion (Spearman's rho = 0.564, p = 0.000). The difference in walking support time was significantly correlated with pain (Spearman's rho = 0.297, p = 0.014) and the degree of sprain (Spearman's rho = 0.362, p = 0.002) but not with oedema and restriction on the range of motion of the ankle.
Conclusion. The intensity of the pain and the ankle sprain degree can be evaluated by the degree of limping during walking. However, the swelling and the restriction on the range of the ankle motion cannot be evaluated by the degree of limping during walking after an ankle sprain.

KEY WORDS: Ankle Sprain, Pain, Oedema, Limping, Plantogram

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Figure 1: *Parameter measurements*

Introduction

A sprain is one of the most common sport injuries where there is a stretch or rupture of ligaments which stabilize a joint [1]. The ankle and the knee are the most susceptible joints in sprains although the shoulder and the hip have a greater range of motion. The most frequent mechanism of injury is a forceful ankle plantar flexion and inversion of the foot in a plantar flexion [1]. The ankle sprains are clinically classified in three degrees depending on their severity.

In the 1st degree sprains what can be observed is stretching or slight tearing of the ligament with mild tenderness, swelling and stiffness. The ankle feels stable and it is usually possible to walk with minimal pain. In the 2nd degree or moderate sprains there is an incomplete tear with moderate pain, swelling and bruising. Although the ankle at times feels stable, the damaged areas are tender to the touch and walking is painful. In 3rd degree sprains there is a complete tear of the affected ligaments with severe swelling and bruising. The ankle is unstable and walking is usually impossible because of the pain. The clinical classification of the degree of sprain is clearer because of the oedema and pain after 4-5 days [2]. Although sprains are considered to be the result of sport activities, they are also common in daily activities [1]. After a sprain there is pain, oedema and less functional ability. The functional ability is restricted because of the inability of full weight bearing, which is clinically expressed with limping during walking. The full weight bearing ability is the ability to load equally on both legs during walking.

Restriction of the weight bearing ability is related with the person's functionality. However, other factors such as reduced daily physical activity, fear of falling and reduced static balance may also prove important for weight bearing ability [3]. Partial or not full weight bearing ability refers to walking with less support on the leg, while weight bearing inability refers to walking only with the use of helpful equipment. The reason for restriction of weight bearing and limping during walk is the pain and the fear of further tissue injury. Less loading during walking results in more energy consumption of the body [4]. The weight bearing ability, age, the ankle sprain degree and the mechanism of injury are indicators of the time of rehabilitation after ankle sprains [5]. Most investigations of sprains evaluate different factors such as pain, oedema, range of motion of ankle, the functional disability and returning time to activities. There are no studies about weight bearing ability during walking after an ankle sprain. The aim of the present study is to record the levels of pain, the extent of edema, the restriction of the range of motion and weight bearing ability when walking after an ankle sprain, as well as examining the correlations between the above parameters in the acute post traumatic period.

Material – Methods

68 individuals, 18 to 50 years old, with an ankle sprain of 1st and 2nd degree participate in this study. The ankle sprain degree with medical examination, the pain during walking using the VAScale and the oedema with figure of eight method. Furthermore, the range of motion with a digital goniometer and the limping during walking by the support time with dynamic plantogram were assessed **(Fig. 1).**

The statistical analysis of the sample was performed with SPSS version 20.0 statistical package.

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TABLE 1.

Correlation of sprain degree with other parameters

		Sprain Degree
pain	Spearman's rho	0.660
	Sig (2-tailed)	**0.000***
	N	68
oedema	Spearman's rho	0.672
	Sig (2-tailed)	**0.000***
	N	68
range of motion	Spearman's rho	0.564
	Sig (2-tailed)	**0.000***
	N	68

The Paired Sample t-test was applied as there was regularity in the distribution of data after the coding, but also the Spearman's rho correlation coefficient, because there was no regularity in the data distribution. The significance level was set as 5% and bilateral.

Results

The degree of ankle sprain was found to be statistically associated with pain (Spearman's rho=0.660, p=0,000), oedema (Spearman's rho=0.672, p=0,000) and range of motion of joint (Spearman's rho=0.564, p=0,000) **(Table 1).** More specifically, the correlation was positive, because the higher the degree of sprain, the more intense the pain was. The swelling and the limitation in the range of motion increased as well.

The difference of the support time during walking between the two legs, namely limping is significantly associated with pain (Spearman's rho = 0.297, p = 0.014), sprain degree (Spearman's rho = 0.362, p = 0.002), oedema (Spearman's rho = 0.166, p = 0.176) and restriction of the ankle's range of motion (Spearman's rho = 0.232, p = 0.057) **(Table 2).** The difference in weight bearing ability between the two legs during walking was greater in the second degree of sprains and the pain was more intense.

Discussion

Ankle sprains are frequent injuries and are usually due to an ankle inversion injury. Male gender and participation in high-level sport activities are risk factors for ankle joint injuries [6]. The main symptoms that characterize a sprain are pain, oedema, the restriction of ankle range of motion and the inability to full leg weight bearing ability. The main goal of the ankle sprains treatment is to reduce pain and oedema and protect the ligaments from further injury.

Striding is the basic unit of measurement in walking and running analysis [7]. On the other hand, stepping is part of the stride and is defined by the contact of one leg with the ground until contact of the opposite one [7]. The walking cycle is divided into the support phase where the tread is in contact with the ground and the suspension phase [8]. In a normal walk there is symmetry of the phases between the two legs.

The assessment of pain in this study was done as in other studies with the VAScale or otherwise a

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TABLE 2.

Correlation of difference in support time with other parameters

		Difference in support time with other parameters
pain	Spearman's rho	0.297
	Sig (2-tailed)	**0.014***
	N	68
oedema	Spearman's rho	0.166
	Sig (2-tailed)	**0.176**
	N	68
restriction of the ankle range of motion	Spearman's rho	0.232
	Sig (2-tailed)	**0.057**
	N	**68**
ankle sprain degree	Spearman's rho	0.362
	Sig (2-tailed)	**0.002***
	N	68

visual analogue scale for pain. The levels of pain after a sprain vary depending on the degree of sprain. A further factor is that the perception of pain may vary among patients, but the validity and reliability of pain assessment is ensured by scientific studies that evaluate the method of diseases of the musculoskeletal system [9]. Analgesics and NSAIDs can be used for the reduction of pain after sprains with good efficacy [10,11]. The ankle pain was found to correlate statistically significantly with the restriction in the range of motion, swelling and degree of sprain. Greater correlation was found to exist with the degree of sprain. The greater the pain is, the greater the degree of the sprain is, and there is more restriction to the range of motion of the ankle movement. Also, with regard to the degree of sprain, the higher it is, the higher is the level of the pain, the oedema increases and the reduction in the range of motion as reported in the literature and confirmed by the measurements in the present study [12].

Oedema is one of the clinical features of the sprain. The figure-of-eight method used in this study is a valid and reliable method, as it is described in other scientific studies [13]. In bibliographic reports the volume of oedema was not found to be associated with functional disability after an ankle sprain [14]. In our study the ankle oedema was related to the degree of sprain, but not to limp during walking.

The restriction of the ankle range of motion may be due to oedema or pain. Local pain during pressure with fingers helps us locate injured structures which typically involve the joint, while the pain during active or against resistance movement usually involves muscles, tendons or ligaments [15]. In many studies, only ankle flexion is evaluated [16]. Moselay and Adam (1991) used photography to measure the angle of ankle [17]. The restriction of ankle motion was found to correlate with pain rather than ankle swell-

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ing after sprains. Most studies concerned the assessment of people with chronic anxiety disorder [18].

Weight bearing for a shorter time in one leg during walking is clinically manifested by lameness. Limiting the loading capacity is due to the fear that excessive loading on an injured or surgical arm will lead to a deterioration of the condition or failure of the operation [19]. A plantogram is a measurement of plantar pressures and walking time support. It can be performed with plantografs, which are expensive devices and are usually found in medical centers [20]. It is a reliable way of assessing the charging capacity and body balance without any attachment of cables or reflectors. As consequence, no individual preparation is needed and there is no difficulty in doing it [3]. Nevertheless, because of the cost, it is difficult to use it in everyday clinical practice.

Conclusion

The difference in support time between legs during walking was found to be related to the sprain degree and the pain after an ankle sprain. Consequently, we can evaluate the severity of an ankle sprain with the regard of the degree of sprain and the intensity of the pain by the support time during walking.

Conflict of interest

The authors declare no conflicts of interest.

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CASE REPORT

Intraosseous lipoma of the calcaneus: A rare case report

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ABSTRACT

Aim: The aim of this study is the presentation of a rare case of an intraosseous lipoma of the calcaneus in a middle-aged woman, the therapeutic surgical treatment and the post-operative results.
Material and Methods: A 49 years old female patient presented with pain in the area of the calcaneus for the past three years, localized at the plantar region. The patient had no previous history of trauma, and described the pain as progressively increasing. Furthermore, she reported tenderness at the calcaneus region during the clinical examination and soft tissue swelling. The patient was subjected to a routine radiographic control of the foot (anteroposterior and lateral views) and a computed tomography (CT) scan of the calcaneus.
Results: The CT scan showed an osteolytic lesion with density equal to that of adipose tissue, marginal sclerosis without cortical breakthrough and a central nidus of calcification, giving the diagnosis of an intraosseous lipoma of the calcaneus. The patient underwent curettage, surgical debridement and bone grafting of the lesion in the operating room. The histological findings included the presence of fatty tissue with various areas of fat necrosis, consistent with a grade 2 lesion according to Milgram. Three months postoperatively the bone graft had been fully incorporated and the heel pain had resolved.
Conclusion: Intraosseous lipoma is one of the rarest benign primary bone tumors. The lesions are often asymptomatic, but if symptoms occur, as in our case, mild pain and swelling are described. The potential of the lesion for a pathological fracture made the surgical intervention necessary with excellent short- and medium-term functional and roentengraphic results.

KEY WORDS: Intraosseous lipoma, calcaneus, bone grafting

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Introduction

Intraosseous lipomas are benign lesions, accounting for less than 0.1% of all bone tumors [1]. They are composed mainly of mature adipocytes and atrophic bone trabeculae and may contain varying areas of necrosis [2]. They are mainly found in the lower limb, with the calcaneus being involved in approximately 30% of the cases [3]. In this report we present a case of this rare tumor, the therapeutic treatment used and the short- and medium-term post-operative results.

Case report

A 49-year-old female patient visited our outpatient department complaining of left heel pain, localized at the plantar region. The pain had started approximately 3 years before and was progressively getting worse, making her unable to perform her everyday work. She reported no previous history of trauma in the aforementioned area. The clinical examination revealed tenderness at the region of the calcaneus with concomitant soft tissue edema. The patient had no familial history of malignancy, was a recreational smoker and was receiving tibolone and paroxetine for the last 3 years. She was subjected to routine anteroposterior and lateral radiographs and a computed tomography (CT) scan of the calcaneus. The radiographs showed a 3.2cm x 2.2cm osteolytic lesion of the calcaneus with well-defined borders containing a central sclerotic nidus with a diameter of 5mm (**Fig. 1**). The CT scan revealed sclerotic margins demarcating the lesion from the surrounding healthy bone tissue, without any signs of cortical perforation. The density within the lesion was consistent with adipose tissue, which led to the diagnosis of an intraosseous lipoma (**Fig. 2**). Due to the duration of the symptoms and the risk of a pathological fracture the patient underwent curettage and surgical debridement of the lesion, which was subsequently packed with heterologous bone grafts. The histological examination revealed the presence of adipose tissue with varying areas of necrosis. Three months postoperatively the graft had been fully incorporated and the patient was able to full weight bear without pain (**Fig. 3**). Eight years postoperatively the patient continues to be free of symptoms.

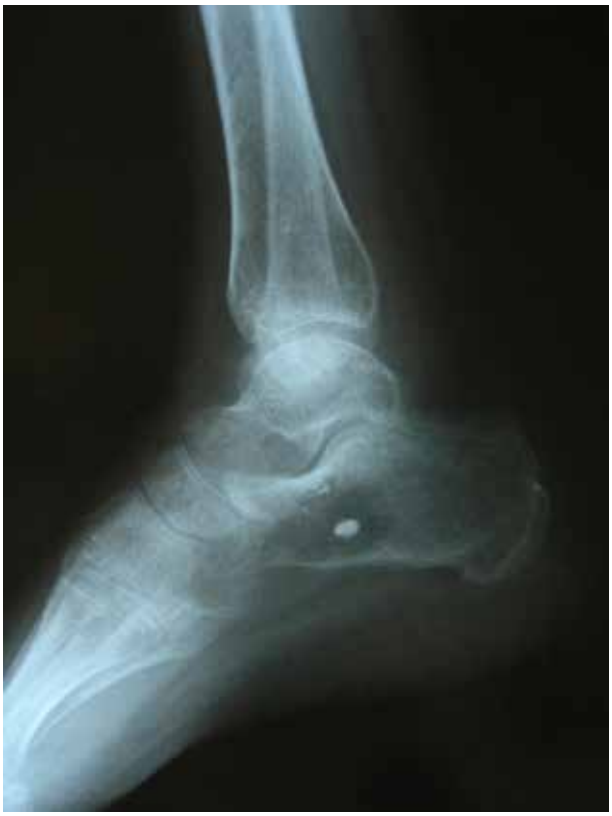

Figure 1. *Lateral radiography of the calcaneus. A radiolucent area covering the 2/3 of the calcaneal body is documented.*

Discussion

Intraosseous lipomas are considered to be amongst the rarest primary bone tumors with an incidence of approximately 0.1% [1]. They are most commonly found in the lower limb (72%), and especially in the os calcis (30%) and femur (20%) [3]. Other sites include the fibula, the upper limb, the mandible, the spine and the pelvis [4-6]. They are mainly observed between the ages of 40 and 60 and show a slight male predominance [2]. They usually present with pain, which is extravagated by walking, tenderness and soft tissue edema [3]. Pathological fractures have also been reported [7]. However, almost one third of the cases is asymptomatic and is diagnosed incidentally on radiographs performed for other pathologic modalities. This has led many researchers to believe that intraosseous lipomas are actually not so rare, as many cases are undiagnosed due to lack of symptoms [8].

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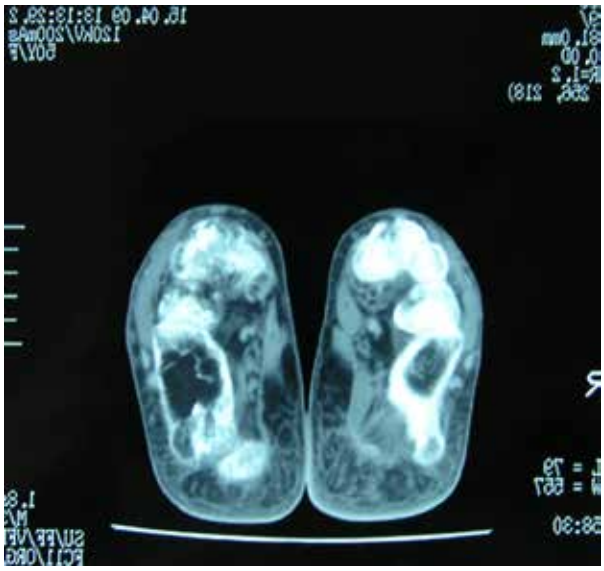

Figure 2. *Computed Tomography reveals extensive bone destruction. No pathological fracture is observed.*

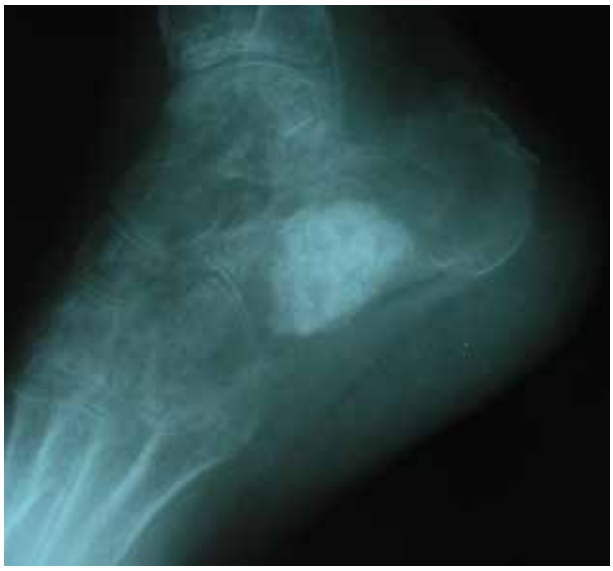

Figure 3. *Lateral radiography of the calcaneus at 3 months postoperatively.*

The pathogenesis of this tumor is poorly understood and certain theories have been proposed. One hypothesis suggests that these tumors arise as a result of bone reaction secondary to trauma [9]. However, less than 10% of the patients report injury and more than 30% of the cases are asymptomatic. Another hypothesis suggests that lipomas arise during the healing of a bone infarct. This is possible, although unlikely, as calcification in bone infarcts is located usually in the periphery, in contrast to lipomas where it is always found centrally [10]. Also up to 50% of lipomas show bone expansion, which is impossible for infarctions, as they cannot expand beyond their original location [11]. Last but not least many researchers believe bone lipomas to be true primary benign tumors, which seem to be the most plausible explanation [9].

The lesion usually appears on plain radiographs as a well circumscribed osteolytic lesion with a sclerotic rim which may contain a central nidus of calcification [9]. In CT scans the lesion displays negative Hounsfield units (ranging for -110 to -40) equivalent to those of fat [12]. Bone expansion is frequently seen and areas of pathological fractures may be noted [8]. Magnetic resonance imaging (MRI) studies demonstrate high signal intensity in both T1-weighted and T2-weighted images, which becomes extinguished in fat-suppression sequences [13]. The sclerotic margins and the central areas of calcification appear with a low intensity signal in both T1- and T2-weighted images. Fluid filled cavities are found in over 60% of the cases and appear with a low to medium signal intensity in T1-weighted and a very high signal intensity in T2-weighted images. No contrast enhancement is observed within the lesions [8].

Milgram has categorized intraosseous lipomas in 3 stages according to radiological and histological findings [2]. Stage 1 is characterized by pure osteolytic lesions containing viable adipocytes intermingled with bony trabeculae which appear thin due to pressure atrophy. Stage 2 lesions appear as osteolytic areas containing sites of increased density due to central calcification and ossification. Histologically both viable adipocytes as well as areas of necrosis and calcification are observed. Stage 3 lesions are characterized by a reactive ossified rim and contain central cysts and calcified areas. Histologically extensive fat necrosis is seen throughout the specimen.

The differential diagnosis of an intraosseous lipoma is wide and depends on the stage of the disease. In stage 1 one should consider other benign osteolytic lesions like pseudocysts or simple bone cysts [14]. Even

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though these lesions appear similar in plain radiographs, studies with CT or MRI can quite accurately differentiate between them, making surgical biopsy usually unnecessary [15]. Stage 2 and 3 lesions can appear similar to both benign and malignant conditions. Benign ones include bone infarcts, enchondromas, non-ossifying fibromas, giant-cell bone tumors, chondromyxoid fibromas and fibrous dysplacia, while malignant ones include mainly liposarcoma and malignant fibrous histiocytoma (MFH) [7,16]. Even though malignant lesions usually appear less homogenous in CT or MRI studies, biopsy is many times needed in order to establish the correct diagnosis [9].

As a general rule asymptomatic lesions are best left untreated with a close follow-up, as a number of them have been shown to regress spontaneously [17,18]. Care though has to be taken when they affect weight-bearing areas in order to avoid a pathological fracture [19]. Symptomatic lesions on the other hand are usually treated with an extensive curettage and a tight bone grafting [20]. Both homologous and heterologous grafts have been used with equal great results [9,21]. Recurrence rate after surgical excision is unknown, but it appears to be extremely low [3].

Malignant transformation of intraosseous lipomas is a matter for discussion. Milgram is the only one having published 4 cases, in which intraosseous lipomas were transformed to either MFH or liposarcoma [22]. Given the fact that bone infarcts, which as mentioned before mimic intraosseous lipomas, have a potential for transformation to tumors of mesenchymal origin, one should consider Milgram`s report with skepticism [23,24]. Were those cases true malignant transformation, or were they actually misdiagnosed bony infarcts? This question remains to be answered.

Conclusion

Intraosseous lipomas are rare benign tumors usually found in the lower limbs. Their diagnosis can be made quite accurately using CT or MRI studies and surgical treatment with curettage and bone grafting is usually reserved for symptomatic or suspicious lesions with excellent postoperative results. Whether these lesions have any malignant potential remains still a mystery.

Conflict of interest

The authors declare no conflicts of interest.

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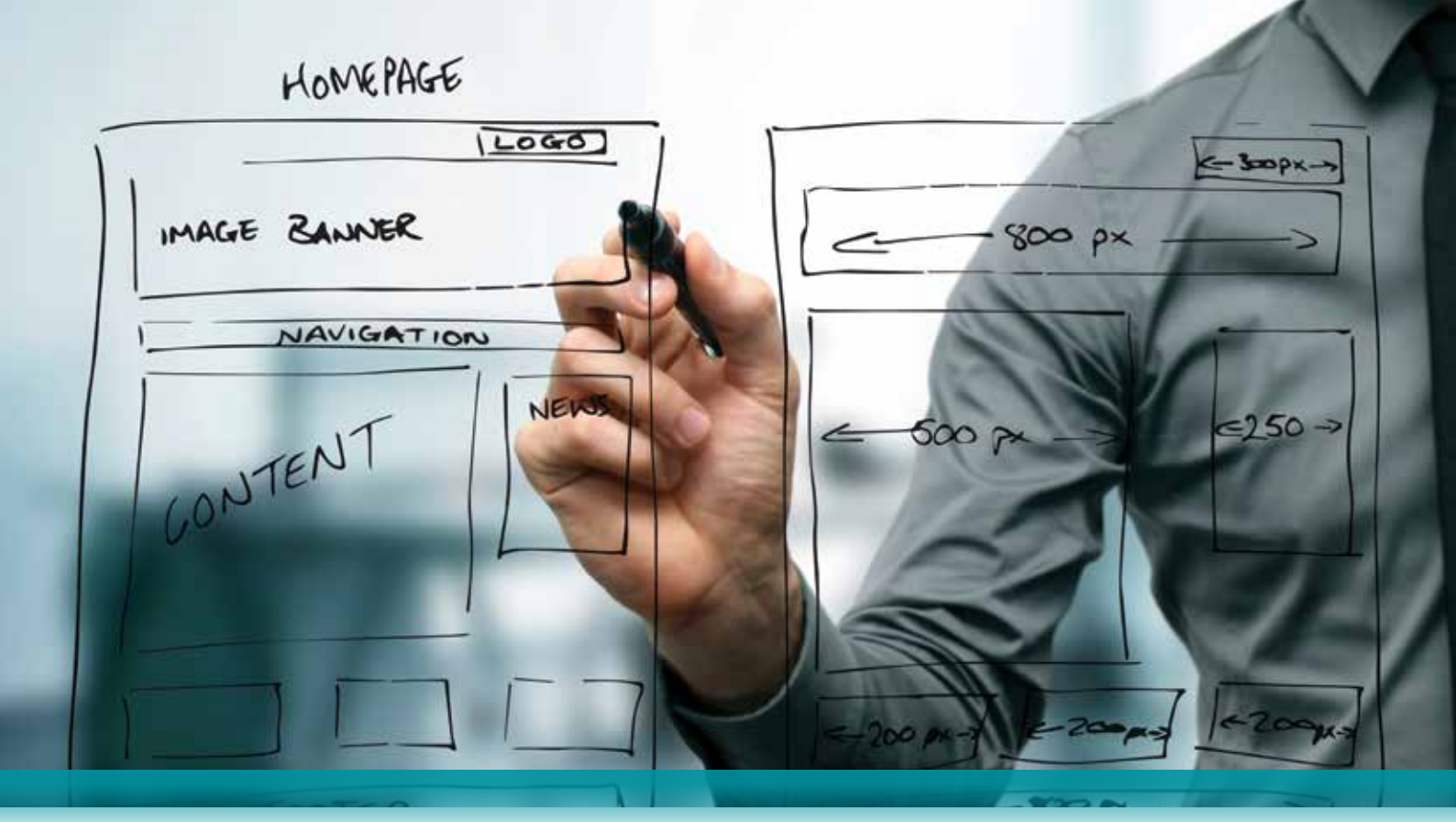

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