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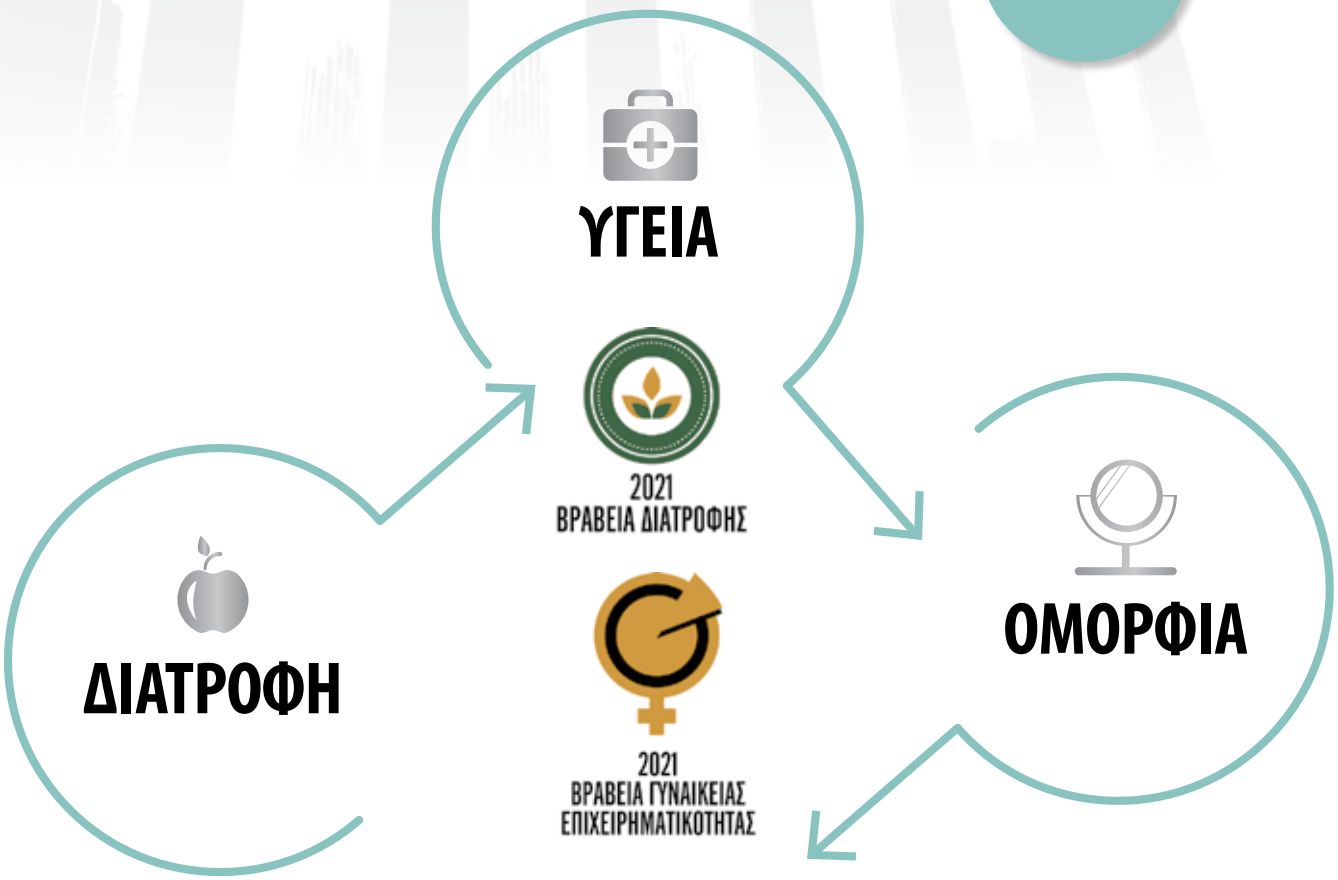


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"Acta Orthopaedica Et Traumatologica" is the official journal of the Hellenic Association of Orthopaedic Surgery and Traumatology, first published in 1948. This revived edition of Acta Orthopaedica Et Traumatologica, published in English, aspires to 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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# LETTER FROM THE EDITOR

It seems that we are growing!!

It has been four years since we published the first issue in English language. During those four years, the Journal keeps a solid policy of a trimester publication with a strictly repetitive range of topics. These topics include basic science, original, review and case report articles.

Additionally, the Journal has its own electronic platform (www.eexot-journal.com) introducing itself to the World Wide Web and the international scientific community.

Furthermore, once yearly, a Special Issue is published. Such issues related to Paediatric Orthopaedics, Foot and Ankle Surgery, Hand Surgery and Microsurgery as well as Spine Surgery have been already published mainly presenting the research and clinical evolutions of the Greek Orthopaedic Society.

Need to mention that a special section, naming The Young Scientists' Pages is added in every issue, including research articles of postgraduate, doctorate and postdoctoral students and fellows.

Finally, the Journal is linked to International Research Platforms such as Bibliovigilance while a registration to Copernicus is in progress.

Having the unwavering support of the HAOST Executive Board and the CHOS Scientific Committee we will always look ahead and keep growing!

On behalf of the Editorial Board

N. Papaioannou

Chief Editor

BASIC SCIENCE

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# The TripAnalyser: a wearable system to assess gait and potential tripping

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## ABSTRACT

A wearable Arduino system (ESP32s) is described that uses optical time of flight (VL6180X) and inertial measurement unit (SENtral EM7180) sensors to estimate the Minimum Foot Clearance (MFC) of participants during gait. It is envisaged that an affordable wearable device that can acquire kinematic data outside the laboratory over periods of several weeks may find application in falls risk assessment in those with ambulatory disorders including the elderly. A geometric model is presented, and a preliminary trial was conducted with able-bodied subjects to test the correlation and agreement of the device with a Vicon 3D motion capture system, consisting of 12 infrared cameras located at the University of Warwick. The correlation between the device and the gait laboratory data yielded a correlation coefficient of r = 0.88. Agreement was tested using the Bland-Altman plot where the line of equality was within the 95% confidence interval of the mean difference suggesting that the device can be used as an alternative to Vicon for estimating MFC.

**KEY WORDS: Elderly, Fall risk, Motion capture systems, Wearable optical systems.**

## 1. Introduction

Tripping is one the most common causes of falling accidents in humans. The cause for a fall ranges from accidentally losing balance during the swing phase of the gait to neurological disorders and ageing. What makes falling an important field to research is that it affects the general populace and most importantly the elderly. One of the most common accidents among the elderly is falling, which results in enormous healthcare costs annually. The Public Health Outcomes Framework reported that between 2013 and 2014, 255,000 people aged 65 and over were admitted to a hospital after a fall-related incident in the UK with the annual healthcare cost for treating these people being at 4.4 billion pounds [1]. The increasingly ageing population will continue to strain the healthcare system. Pin et al. [2] found that patients who had already fallen had negatively associated the fall with social participation, and thus restricted their daily activities. Another study by Liddle et al. [3] conducted in 1995 interviewed 69 elderly people, with an age greater than 65 years old who had suffered a fall, and their carers. They concluded that 25% of the elderly patients had developed a fear of falling and that

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58% of the carers feared that the friend/relative might fall again [3].

One indicator for assessing falls risk is the Minimum Foot Clearance (MFC) which according to Winter [4] is an event during the gait cycle, where the foot travels with the maximum horizontal velocity and the distance between the ground and the base of the foot is the lowest. A typical value of MFC for the healthy elderly (over 60 years old) is around 1.12 cm [4]. Exploring the MFC in a real-world setting can give rise to a better understanding of the cause of falls, and/or strategies to prevent falls in vulnerable populations that will drastically reduce the associated healthcare costs and improve their quality of life. Knowing this value, patients can alter their gait patterns to reduce their likelihood of falling. This can be achieved by either reducing their MFC variability or by increasing the MFC height central tendency [5].

Traditionally, the MFC is measured from kinematic data that are acquired using a gait laboratory. Reflective markers are attached to key locations on the patient's lower body and infrared cameras placed around the laboratory capture the 3-dimensional spatial coordinates of the markers with respect to a global reference system as a time series. The downside of such a laboratory is the cost associated with the formation of one (tens of thousands of pounds) and the limited time patients spend in it. Gait laboratories are usually smooth and level floors and may not accurately represent the everyday surfaces and obstacles that people walk over and occasionally trip on. Furthermore, studies have shown that patients tend to exaggerate their gait patterns when under clinical testing conditions, making the data analysis difficult [6]. On this account, the fall's risks may not be discovered in such an environment, which indicates the need for free range measurement. In the literature there are systems that have been used to collect kinematic data and compare them to a motion capture system [7],[8]. However, the idea to combine both proximity and IMU sensors is novel and provide greater sensitivity to the MFC because foot pose has an important role in the desired measurement. Estimating ground or foot clearance using these devices is usually based on the numerical integration of the vertical acceleration of the foot. However, this approach cannot sense the presence of obstacles or uneven floor surfaces which may present trip hazards and IMU sensors are prone to drift so the need for a Kalman filter to reduce noise is essential, especially when the end goal is to get displacements.

TripAnalyser, the prototype wearable optical system we propose, has the capability to sense the foot's proximity to such obstacles and estimate their distance to the foot. The system uses 2 TOF proximity sensors (VL6180X) one placed on the heel and one in front of the second metatarsal, one IMU (SENtral EM7180) with an in-built Kalman Filter and an ESP32s microcontroller. Preliminary results are presented for the accuracy in estimating MFC in a group of able-bodied subjects walking on an even floor in the Vicon laboratory.

## 2. Determination of MFC

To make use of the TOF and IMU sensors for estimating the distance between the sole of the shoe and the ground, a trigonometric model that accounts for the data from the sensing elements is essential. The model assumptions are as follows:

1. The distance measured from the TOF sensor is perpendicular to the ground.

2. The placement of the IMU and the TOF sensors is parallel to the ground.

3. The shoe creates a plateau from the metatarsal heads to the toes and throughout the calcaneus bone where the vertical distance from the shoe to the ground remains constant.

For the first assumption, the error introduced to the measurement is

$$Er = |1-\cos(\theta)| \quad (1)$$

where $\theta$ is the angle that the photon detected by the receiver has left the transmitter module. Since it is impossible to know the exact angle of the photon that is detected by the receiver, the theoretical maximum error is calculated instead. The TOF sensor has a field of view of 25 degrees, yet photons that originate from half of the field of view are reflected away from the receiver module thus leaving 12.5 degrees of possible photon detection [10]. From equation (1),

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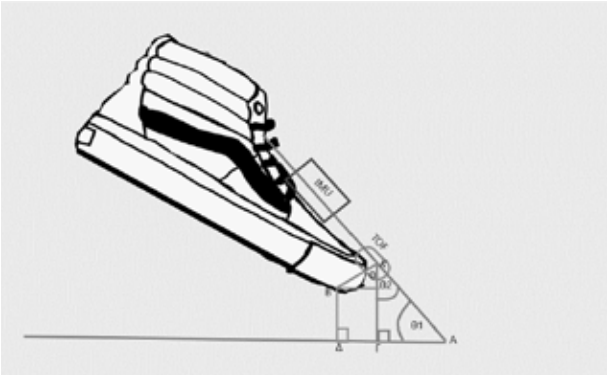

***Figure 1:*** *Visualisation of the foot during the swing phase. The line AK is the virtual line that provides the inclination of the foot with respect to the ground. The line KB is the initial height of the TOF sensor calculated from the static trial. The line KΓ is the vertical distance from the TOF sensor at that instant and the line BΔ is the vertical distance from the sole of the shoe to the ground.*

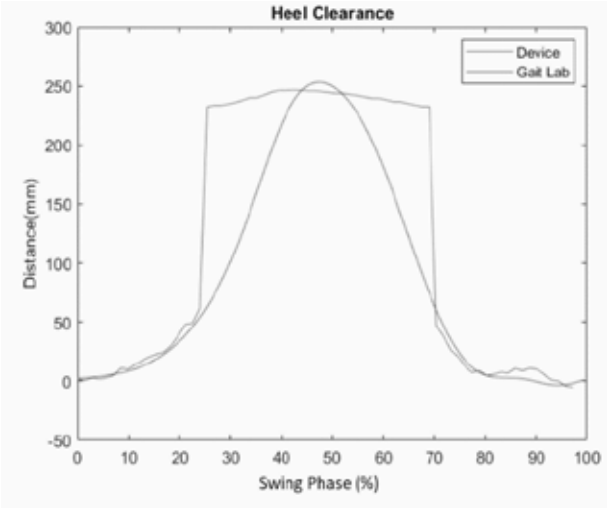


***Figure 2:*** *Heel clearance plot of the device and gait laboratory data against the percentage of the swing phase.*

the maximum theoretical error between the hypotenuse and the vertical distance is calculated to be equal to 2.37%. This error corresponds to differences that are less than the accuracy of the TOF sensor for the predicted MFC distances (around 12 mm). The accuracy of the TOF sensor was found to be 2 ± 0.5 mm during initial testing of the device.

The second assumption is crucial to the extraction of the MFC using the trigonometrical model and the placement of the sensor in the experimental procedure is based on it.

The third assumption allows for the placement of the TOF sensor at the front and the back of the shoe without creating significant variations to the model. The plateau idea provides a good estimate of the MFC point because it conceptualises the foot as a one-dimensional object, during the swing phase, which is consistent with approximations done by others in the literature [7],[8],[9].

The proposed model for the extraction of the distance between the sole of the shoe and the ground is shown in Figure 1.

The extraction of the MFC from the toe sensor is going to be analysed, but the same process was followed for the heel sensor as well. In Figure 2, the point *K* is where the TOF sensor is located, the distance KB is always perpendicular to the line *AK* as it is the vertical position calculated from a static trial and corresponds to the initial height of the TOF sensor. The distance *KΓ* is the vertical distance measured from the TOF sensor during the dynamic trial and the *BΔ* is the instantaneous distance that the foot is clearing the ground. To calculate the MFC, the distance *BΔ* needs to be calculated. From the setup, the angle the IMU sensor reports is the same as the angle which the TOF sensor is positioned at with respect to the ground. From the triangle *AΓK,* the angle $\theta_2$ can be calculated as:

$$\theta_2 = 90^o - \theta_1 \quad (2)$$

and because AK is perpendicular to KB

$$\theta+\theta_2=90^o$$

$$\text{and so } \theta=\theta_1 \quad (3)$$

Hence the angle reported from the IMU is causally related to the angle the TOF sensor is moved from its original vertical position. Finally, the distance *BΔ* can be calculated and it is equal to:

$$B\Delta=K\Gamma-KB*\cos(\theta) \quad (4)$$

Equation 4 is a generalisation of the standard method used in previous MFC measurement experiments where the value was calculated by subtracting the vertical dynamic trial distance of the TOF sensor, from the mean static trial value [9]. The MFC is then calculated from (4) by finding the localised minimum during the mid-swing phase.

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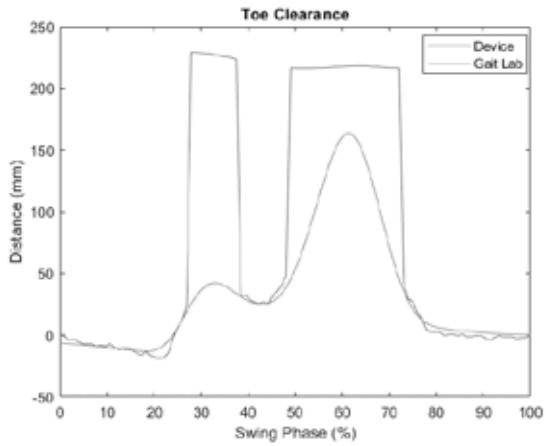


***Figure 3:*** *Toe clearance plot of the device and gait laboratory data against the percentage of the swing phase.*

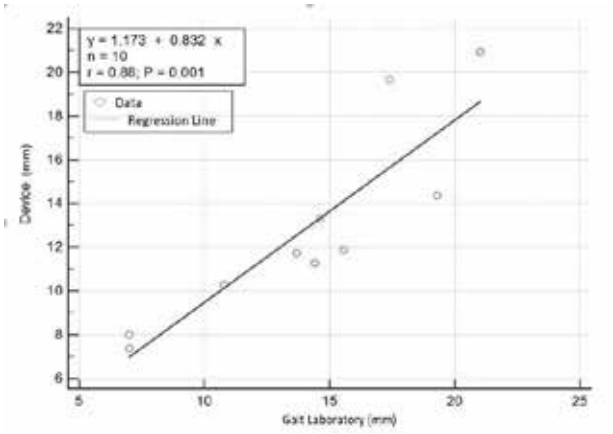


***Figure 4:*** *Regression plot between device and gait laboratory data.*

**3. Results**

Ten able-bodied participants were recruited for the study and one static and 5 dynamic trials were performed. From the static trial the distance *KB* is calculated. This project was granted full approval from the Biomedical and Scientific Research Committee (BSREC) at the University of Warwick (reference number BSREC 53/18-19). The results from the study can be found in Table 1 and the values shown are the average MFC values from the 5 dynamic trials for each participant. The values found under the MFC device column correspond to the data acquired from the developed model only for the toe TOF sensor. The heel clearance data were disregarded because during the instant of MFC the heel is descending towards the ground to prepare for the heel contact portion of the gait cycle. This descending motion does not provide a local minimum value at the MFC point, as shown in Figure 2, and thus was disregarded. The negative regimes shown in Figures 2 and 3 are products of the model. During the initial stage of the swing phase, the toes are pushed downwards to allow the heel to be lifted upwards giving distances lower than the mean static value and resulting in negative portion of Figure 3. Similarly, the heel clearance plot presents a negative region from the moment the heel contacts the ground up until the end of the swing phase. This is attributed to the lower vertical distance of the heel sensor compared to the mean value of the static trial.

For the analysis of the results the MedCalc software was used with the significance level set to 0.05. Linear regression and the Bland-Altman plot were used to test for correlation and agreement between the two methods.

From the linear regression analysis, the coefficient of determination $R^2$ is 0.7760, which determines the goodness-of-fit and the regression equation where $Y$ is the MFC from the device data and $X$ is the MFC from the gait laboratory data is:

$$Y = a + b \cdot X \qquad (5)$$

with $a$=1.173 ± 2.3350 mm with a 95% confidence interval (C.I.) of -4.21 to 6.56 mm with a p-value of 0.6290, $b$=0.8320 ± 0.1580 with a 95% C.I. of 0.476 to 1.1964 with a p-value of 0.0008 and correlation coefficient r = 0.88 with a p-value of 0.001. From the parameters obtained during the analysis, the value of the intercept is not statistically significant because its p-value is greater than 0.05 and there is insufficient evidence in the sample to conclude that a non-zero correlation exists. However, the slope of the equation is statistically significant since its p-value is less than 0.05 suggesting that the null hypothesis can be rejected and that changes in the gait laboratory data are associated with changes in the device data. This effectively shows that there is good correlation between the two methods. This is further supported by the excellent correlation coefficient of the two methods r = 0.88, which is also statistically significant. Figure 4 shows the regression plot.

To assess agreement between the device and gait

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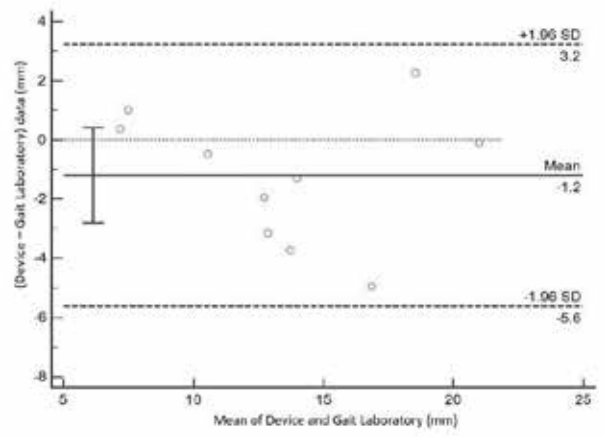


***Figure 5:*** *Bland-Altman plot. The dotted line represents the line of equality and the two dashed lines represent the LoA. The straight line represents the mean difference value and the vertical line represents the 95% C.I. of the mean difference.*

laboratory, the Bland-Altman plot was used. This graphical representation allows quantification of the agreement between two quantitative methods by constructing the limits of agreement [11]. To use the Bland-Altman plot, the differences between the two methods must follow a Gaussian distribution [11]. To verify this requirement, a Shapiro-Wilk test was used, and the analysis yielded that the difference data are normally distributed with a p-value of 0.9728. This allows the use of the Bland-Altman plot analysis. In Figure 6, the Bland-Altman plot can be seen and in the *Y* axis the difference between the MFC values of the device and gait laboratory data is compared against the *X* axis which has the average of these measurements [11]. This allows for the calculation of the Limits of Agreement (*LoA*) from the value of the mean difference and the standard deviation (*sd*) of the differences according to equation (6).

$$LoA = \pm 1.96 \cdot sd \quad (6)$$

By constructing the *LoA*, it is expected that 95% of all data points would lie within these regions [11]. Furthermore, the Bland-Altman plot can assess the existence of bias in any of the methods and whether this is significant. This is done by finding the mean difference and its 95% C.I. If the line of equality, where the mean difference is zero, is within the 95% C.I. of the mean difference, then the estimated bias is not significant, and the mean difference can be considered as being equal to zero [11].

From Figure 5, the mean difference between the device and gait laboratory data is -1.2 mm with a 95% C.I. of -2.8063 to 0.4194 mm. The yellow dotted line represents the line of equality and the two red dashed lines represent the *LoA*.

The mean difference value suggests that there is a bias of -1.2 mm for the gait laboratory data, meaning that on average the MFC value from the gait laboratory measures 1.2 mm more than the device data. The negative bias is attributed to measurements over 10 mm where a negative trend is apparent from the plot, whereas for measurements below 10 mm the data are closer to each other. However, the estimated bias is not significant because the line of equality is within the 95% C.I of the mean difference value.

## 4. Discussion

From the analysis of the MFC results it becomes apparent that there is an excellent correlation between the two methods from the regression analysis. Furthermore, it has been established that the device can provide adequate results and it can be used as an alternative to the gait laboratory to extract the MFC. An interesting result is the ambiguity of the intercept from the regression analysis. The slope of the line can be estimated with adequate precision b=0.8320 ± 0.1580 with p-value of 0.0008, but the intercept is not well defined, and its value is not statistically significant. This can be attributed to the placement of the device on the foot for each participant. The intercept is linked to the model's initial conditions (IMU inclination, and static value of the sensor's height) and the ambiguity of its value derives from the different position of the sensors and markers in each participant. To acquire a better statistical value for the intercept, the creation of a standardized placement procedure that incorporates the sensors at predetermined positions, which would be the same for each participant, is necessary to reduce the ambiguity. In both Figures 2 and 3, the plateau portion that can be seen at around 240 mm is attributed to the range limitation of the TOF sensor. The TOF sensor used can sense objects from 0-150 mm and in the configuration used outputs a 255 value when nothing is detected within

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TABLE 1.

**Minimum Foot Clearance values from device and gait laboratory data**

| MFC Device (mm) | Standard Deviation (mm) | MFC Gait Laboratory (mm) | Standard Deviation (mm) |
|---|---|---|---|
| 11.87 | 2.49 | 15.57 | 3.62 |
| 11.28 | 3.05 | 14.42 | 2.06 |
| 7.37 | 3.10 | 7.00 | 2.08 |
| 10.30 | 3.15 | 10.78 | 3.60 |
| 11.75 | 2.34 | 13.70 | 5.34 |
| 8.01 | 2.89 | 6.99 | 3.42 |
| 14.37 | 3.23 | 19.31 | 5.42 |
| 19.66 | 8.05 | 17.39 | 5.32 |
| 20.94 | 5.32 | 21.03 | 4.66 |
| 13.33 | 3.59 | 14.62 | 3.80 |

TABLE 2.

**Limits of Agreement from Bland-Altman plot.**

| Lower LoA (mm) | 95% C.I. (mm) | Upper LoA (mm) | 95% C.I. (mm) |
|---|---|---|---|
| -5.6126 | -8.4680 to -2.7572 | 3.2257 | 0.3703 to 6.0811 |

the user specified time window. For the purpose of this experiment having these regions does not provide any error in estimating MFC since they are not considered in the calculations. The plots were used to visualise the motion of the toes and heel during the swing phase. However, it would be advantageous to have a better representation of the curve, so it is suggested that a different TOF sensor be used. At time of writing this paper, similar TOF sensors (VL53L0X, VL53L1X) have greater maximum range detection but the minimum is 50 mm and 40 mm respectively [12],[13]. A case can be made that for the creation of the device these limitations should be taken into consideration and the newest models should be incorporated; however, we feel that an addon solution has to be as small and unobtrusive as possible especially for the elderly population.

## 5. Conclusion

This paper introduced a novel device that measured the MFC from participants and compare its values against the gold standard method of a motion capture system. From the statistical analysis performed it is safe to assume that the proposed device can be used as an alternative to the gait laboratory in order to extract the MFC. This is evident from the excellent correlation and agreement between the two methods presented during the analysis of the results. The potential advantages of using the device as an alternative to a motion capture system are the longer periods of recorded data, outside the gait laboratory, over different terrains and floor textures and the relative low price of such a device compared to expensive motion capture laboratory costs. Such a device may provide clinicians with a better estimation of the patient's MFC and MFC variability.

## 6. Acknowledgments

We would like to thank Dr. Adrian Poulton, Mr. Andrew Jacobs and Mr. Oscar Elliot for their contribution to the project.

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ORIGINAL ARTICLE

# The varied forms of duplicated thumb in infants

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## ABSTRACT

Hand polydactyly is a common congenital anomaly. It appears as a single disorder, or as a separate manifestation of a syndrome. In the Caucasian race, thumb duplication (preaxial polydactyly) is the most common form of hand polydactyly. The purpose of this study was to isolate cases of thumb duplication that were surgically treated during the time period 2008-2018, and to identify diagnostic pitfalls and therapeutic concerns. We studied twelve duplicated thumb cases and classified them according to their severity with Wassel's classification system. All cases were treated by the same surgical team under general anesthesia using pneumatic tourniquet. In a 2-8-year follow-up period, patients were evaluated according to subjective and objective criteria, emphasizing on functional and aesthetic outcomes. On an evaluation scale, results were satisfactory for ten patients (83.34%), while two patients presented moderate results. We analyze the reasons for the moderate results and look for ways of avoiding them. In conclusion, preoperative planning is considered necessary, given the diversity of cases. Choosing the right timing protects both the physician and the patient from practical difficulties. Clinical examination is the patient's first diagnostic approach, while simultaneously studying radiographs helps to identify the problem more accurately. The technique must follow the principles of plastic surgery.

**KEY WORDS: preaxial polydactyly; duplicated thumb; congenital deformity; infants.**

**Introduction**

Preaxial polydactyly is a very common congenital abnormality of the upper limb, which is clinically manifested by a duplication of the thumb, at a frequency ranging from 0.08 to 1.4 per 1000 healthy infant births [1,2]. Its reasoning has not yet been clarified, although an autosomal dominant inheritance transfer was recognized in forms where the supernumerary thumb had three phalanges. This event appears to occur during the first eight fetal weeks as the entire upper extremity and hand develop. Several theories try to explain it as a possible fetal pathogenicity, but they are not reliable enough to be accepted. One of these theories claims that preaxial

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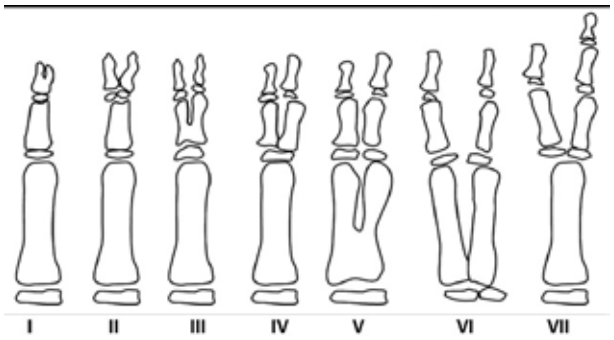


***Figure 1.*** *Wassel's classification system (1969).*

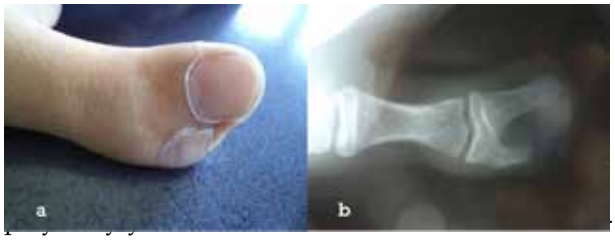


***Figure 2.*** *Incomplete thumb duplication of distal phalanx (type I) a. clinical image b. radiography.*

soderm and ectoderm during cell proliferation [3-5].

This condition may be isolated or may be associated with other manifestations of specific syndromes, such as acrocephalopolysyndactyly type 1 (Noack) and type 2 (Carpenter), Holt-Oram, Fanconi, Rubinstein-Taubi, or Down syndrome [6], brachydactyly, left lip-palpate, imperforated anus, syndactyly, and vertebral anomaly.

Duplicated thumb cases are estimated according to Wassel's classification system [7], exclusively by radiological criteria, depending on the severity of the deformity and the type of phalanx and / or first metacarpal abnormality (**Fig. 1**).

Clinical and radiological evaluation are considered essential for evaluating the outcome of surgical intervention. Cheng et al proposed evaluation of the alignment of the remaining thumb, the range of motion of the interphalangeal and metacarpophalangeal joint, the stability, the interdigital space, the prominence at the point of resection of the supernumerary thumb, and the opposition ability of the remaining thumb [2]. Ogino et al consider as satisfactory parameters for assessing the evolution of surgical repair, the type of deformity, the type of surgery and surgeon's skill [8]. However, Kemnitz observed that the loss of complete thumb mobility is less important than previously thought [1]. Of greater

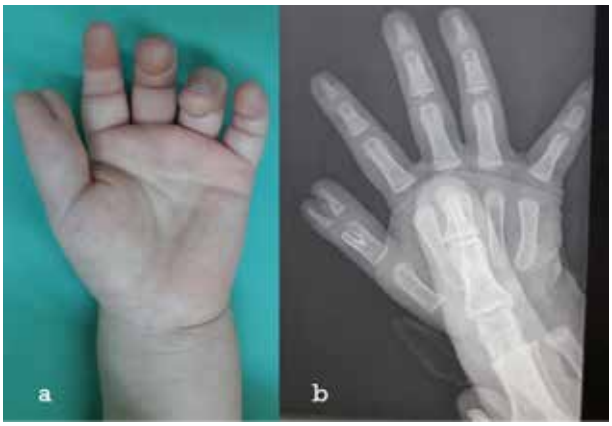


***Figure 3.*** *Incomplete thumb duplication of proximal phalanx (τύπος III) a. clinical image b. radiography, in which the mother's index finger is also obvious.*

value seems to be the aesthetic problem created by the axial deviation.

The purpose of our study was to isolate the cases of thumb duplication that we treated surgically during 2008-2018 time period, to refer to our experience and to identify diagnostic pitfalls and therapeutic concerns. We considered important the subjective evaluation of the surgical outcome, based on a questionnaire completed by the patient's parents at follow-up.

**Patients and Methods**

From January 2008 to December 2018, we treated 92 cases of polydactyly in 43 hands and 49 feet in 69 patients. Twelve cases (7 boys and 5 girls) with an average age of 18 months (range 7 months - 4.5 years) related to duplicated thumb. According to the Wassel's classification, we operated 2 cases of type I (**Fig. 2**), 4 patients of type II, one patient of type III (**Fig. 3**), 4 patients of type IV with duplication of the proximal phalanx (**Fig. 4**) and a patient of type V (**Fig. 5**) with a bifid first metacarpal (**Table 1**).

The majority of cases (83.34%) were operated on over 12 months of age. At these ages, radiographs prove to be safe for bone structures, the risk of anesthesia is lower and manipulations more precise. Preoperatively, the clinical examination was performed in the presence of the parents, hands were photographed with their permission, and they were informed of the planned technique and expected results. Radiological examination was completed in each patient, both in the normal hand

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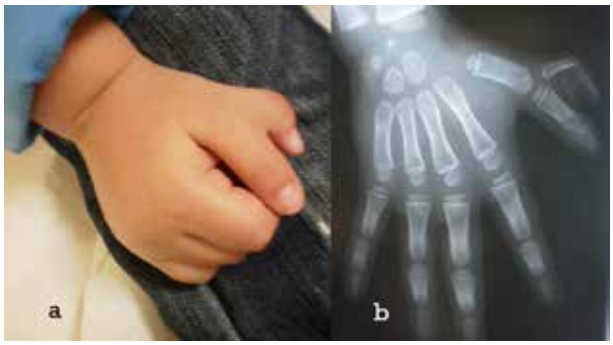


***Figure 4.*** *Complete thumb duplication of proximal phalanx (τύπος IV) a. clinical im-age b. radiography.*

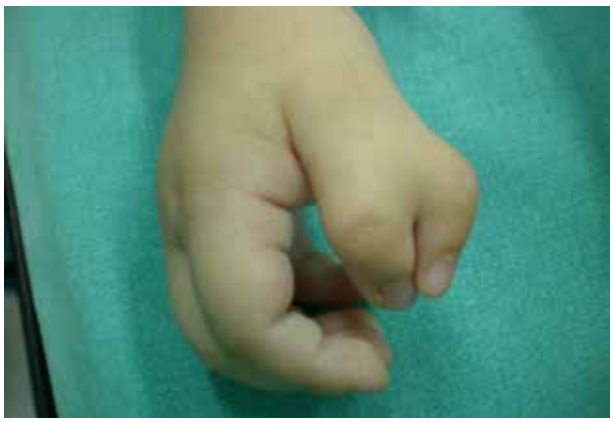

***Figure 5.*** *Clinical image of incomplete thumb duplication of first metacarpal (type V).*

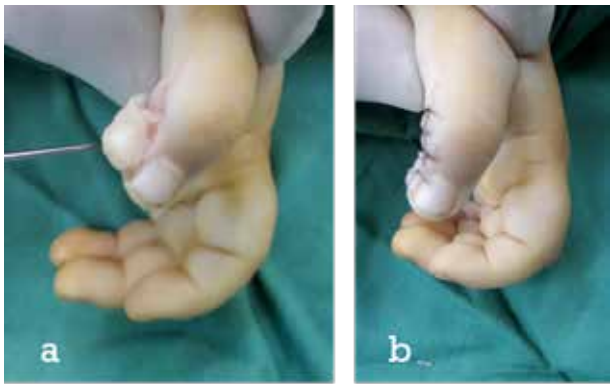


***Figure 6.*** *Careful separation of the nail for the treatment of duplicated thumb in type II (patient 3).*

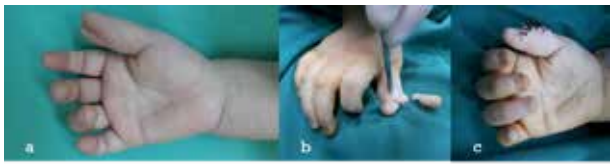


***Figure 7.*** *Prominence of soft tissues in a patient with duplicated thumb of type IV (patient 10) a. preoperative appearance b. surgical image c. postoperative appearance.*

and in the pathological one.

All cases were treated under general anesthesia with the use of pneumatic tourniquet. In type I and II cases, special attention was paid to the nail splitting (**Fig. 6**). The Bilhaut-Cloquet technique was never used, although there were parents who had met it on the Internet and asked for it [9-11]. Also, no Kirschner wires were used to hold the desired axis during the first 3-4 postoperative weeks.

The supernumerary thumb was carefully excluded so that the skin flaps were sufficient to cover the surgical wound. The common neurovascular bundle was also preserved. In Type IV and V cases attention was paid to strengthening the extension of the remaining thumb by the use of connective tissue by the extensor mechanism of the excluded thumb, while the abduction was enhanced by the re-suturing of the abductor pollicis brevis using a slowly absorbable suture 5-0. When phalanx or metacarpal osteotomy was required, a thin metal osteotome was used and bone wax was inserted to control bleeding.

Intraoperatively, the pneumatic tourniquet was removed, to check blood supply before suturing the skin with 4-0 or 5-0 nylon sutures. Gauze dressings, cotton and elastic bandages were applied in a boxing glove form. There were two visits to the outpatient clinics, the first for simple gauze changing and the second for suture removal. The hand was free of bandages at 3 weeks.

Follow-up lasted 2-8 years. At each reassessment, a special form was filled in with the patient's name, age at the time of surgery, Wassel's classification, surgical technique, aesthetic parameters (scarring, pulp or nail hypoplasia, axial deviation, phalangeal or metacarpal prominence), as well as functional parameters (hyposensitivity or numbness, ability to grasp small objects, thumb to index and thumb to little finger opposition). Grades 9-10 rated the score as satisfactory, 5-8 moderate and below 5 poor.

**Results**

In no case did the postoperative scar create a problem while the residual thumb pulp presented a satisfactory

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***Figure 8.*** *Despite the excellent surgical technique in the treatment of duplicated thumb type IV (patient 8), the fair result could not be avoided due to prominent soft tissues and opposition inability of the remaining thumb.*

image in all cases. On the contrary, nail hypoplasia to a degree that was aesthetically problematic was observed in two patients with type I duplicated thumb (**Table 2**). Slight axial deviation was found in one type II patient and in one with type V duplicated thumb. Prominence of the soft tissue, or the head of the first phalanx, or metacarpal, was found in one type II patient (**Fig. 7**) and two type IV patients.

The ability to grasp small objects was normal in all cases, as well as the opposition ability of the remaining thumb to the index finger. However, the opposition of the thumb to the little finger was problematic in one type II patient and two type IV patients, probably due to stiffness of the interphalangeal or the metacarpophalangeal joint.

Looking closely at Table 2, we observe that ten patients (83.34%) scored 9-10, with satisfactory results. One type IV patient (**Fig. 8**) was assessed with grade 8 and another type II patient with grade 7 (moderate results). The patient with the lowest score was the one with the highest age. In no case did the parents suggest re-operation to improve the aesthetic or functional outcome.

| Patient | Sex | Age | Type |
|---|---|---|---|
| 1 | Male | 7 months | I |
| 2 | Male | 12 months | I |
| 3 | Female | 15 months | II |
| 4 | Female | 18 months | II |
| 5 | Male | 4 y and 6 m | II |
| 6 | Female | 12 months | II |
| 7 | Male | 18 months | III |
| 8 | Male | 20 months | IV |
| 9 | Female | 22 months | IV |
| 10 | Male | 17 months | IV |
| 11 | Female | 10 months | IV |
| 12 | Male | 11 months | V |

***Table 1.*** *The patients of the study according Wassel's classification*

## Discussion

In our study, all cases were unilateral. The presence of bilateral deformity would force us to look for a syndrome such as Townes-Brocks syndrome [12]. There was also no frequency difference according to gender, and most authors agree with this conclusion [1-5,7,8].

Most of the cases in this study belong to forms II and IV. There are other researchers who agree with this finding [13], although Naasan and Page claim that type VII is the most common [14]. However, Wassel's classification system is often inadequate to present details related to surgical design, or to describe common subtypes that require separate surgical treatment.

In an attempt to solve this problem, Hung et al [15] propose for Wassel's Type IV a new classification with four subtypes to avoid possible post-operative complications: IV/A (hypo-plastic supernumerary finger), IV/B (supernumerary finger with ulnar deviation), IV/C (divergent duplication), and IV/D (convergent duplication). For cases where coexists a supernumerary thumb with three phalanges (Type VII), Wood [16] proposes four subtypes: VII/A (radial hypoplastic triphalangeal finger); VII/B (consisting of two complete triphalangeal thumbs); VII/C (ulnar hypoplastic triphalangeal finger); VII/D (triphalangeal finger accompanied by a hypoplastic ulnar digit).

Chung et al [17] adopt a new classification, based on the anatomical features of the deformation, with the aim of facilitating surgical times and avoiding complications: type I (joint type) where the supernumerary thumb has its own joint; type II (single epiphyseal type) where both thumbs share the same epiphysis; type III (osteochondroma-like type) where the supernumerary thumb resembles to osteochondroma; type IV (hypoplastic type) where the supernumerary thumb is associated with the normal one via soft tissue. In a series of 159 cases, 134 duplicated thumbs (84%) were treated with excellent results, 17 (11%) with moderate and 8 (5%) with poor results.

Recently, Wassel's classification system has been im-

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| Patient | Scar | Pulp | Nail | Deviation | Prominence | Hypoesthesia | Numbness | Pinch | Thumb-index | Opposition |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | - | - | + | - | - | - | - | yes | yes | yes |
| 2 | - | - | + | - | - | - | - | yes | yes | yes |
| 3 | - | - | - | - | - | - | - | yes | yes | yes |
| 4 | - | - | - | - | - | - | - | yes | yes | yes |
| 5 | - | - | - | + | + | - | - | yes | yes | no |
| 6 | - | - | - | - | - | - | - | yes | yes | yes |
| 7 | - | - | - | - | - | - | - | yes | yes | yes |
| 8 | - | - | - | - | + | - | - | yes | yes | no |
| 9 | - | - | - | - | - | - | - | yes | yes | yes |
| 10 | - | - | - | - | + | - | - | yes | yes | yes |
| 11 | - | - | - | - | - | - | - | yes | yes | no |
| 12 | - | - | - | + | - | - | - | yes | yes | yes |

***Table 2.*** *Treatment results in twelve patients based on subjective and objective crite-ria, regarding aesthetic and functional parameters.*

proved with the Rotterdam classification, which consists of 8 types and uses letters to indicate anomalous elements and their location, such as thumb with three phalanges or triple-thumb variants [18,19]. In a study [20] where 520 cases were examined, only 60% were estimated with the Wassel's classification, whereas they could be evaluated with the Rotterdam classification at 100%.

The patient's age on the day of surgery positively or negatively affects the postoperative outcome. Proper timing should be the first care of the Surgeon. However, there is controversy among the researchers. Although some claim the deformity to be repaired at ages younger than 6 months, most recommend surgery later, at around 12 months, when the anesthetic risk is lower, the patient may progressively improve hand functionality, and before social effects occur which would adversely affect his confidence [21]. Cabrera Gonzáles et al recommend that surgery be performed at ages 7-12 months, based on their experience with the least complications [22]. Dobyns et al recommend the age of 6-18 months [6], while Goffin et al suggest that the ideal age is between the first and second year [23]. Excellent results appear to arise when surgery is performed under the age of 3 years, with the ultimate goal of preventing postoperative deformities. This is probably the reason for the moderate outcome in our patient aged 4 years and 6 months.

The extensor tendon of the supernumerary thumb strengthened the action of the extensor of the remaining thumb in type II cases in our study, but we did not move the flexor tendon centrally as described by Miura [24], nor did we use the extensor tendon of the index finger to stabilize the interphalangeal joint and correct the extension deficit as described by Kawabata et al [25]. Our view was that we should not seek to improve axis deviations, as suggested by Goffin et al [23], in order not to disrupt the growth plate of the epiphysis and not to limit joint mobility.

The goal of the procedure should be to provide a stable and flexible thumb of sufficient size and shape. Stability and size are related to strength, both for strong and fine grip [26]. Thumb mobility depends on the integrity of the carpometacarpal joint, which is guaranteed in duplicated thumb types I, II, III and IV but not in types V and VI. The mobility of the metacarpophalangeal and interphalangeal joints, although considered essential for proper thumb function, is of less importance.

The ingenuity of the various authors to overcome complex problems during surgery is remarkable. It is a rule that both thumbs have both flexor pollicis longus (FPL) and extensor pollicis longus (EPL), but the more functional thumb has better tendons and a wider range of active motion. However, the eccentric adhesion of these tendons poses a problem that is seeking its solu-

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tion. Also the shape of the remaining thumb is often not the desired one. Pulp and nail are also smaller than normal in most cases [13].

Chang et al [27] propose transport of the duplicated thumb, provided that none of the thumbs is superior to the other, where one having a better central section and the other a better peripheral section. According to the authors, this technique is simple, safe, and effective for remaining thumb functionality in type IV cases.

Various techniques have been proposed for subtype IV/D (convergent duplication). Abid et al recommend a modified Bilhaut-Cloquet technique, in cases where both thumbs are hypoplastic, with their divergence at the level of the metacarpophalangeal joint and convergence at the level of the interphalangeal joint [28]. The purpose is to avoid the usual complications of the classic Bilhaut-Cloquet technique (coaptation of equal parts of bone, soft tissue, and nail tissue after resection of the central segment of the duplicated thumb), like nail dystrophy, axial deviation and instability. Hung recommends the use of an epiphyseal segment of the proximal phalanx with insertion of the abductor pollicis brevis tendon into the radial side of the epiphyseal proximal phalanx of the ulnar thumb [29]. Xu Yun-Ian et al support the ablation of the radial thumb and reconstruction of the ulnar thumb by a series of soft tissues procedures, including FPL rebalancing [30].

We did not use the Bilhaut-Cloquet technique because we considered it useless for the specific cases we had to deal with. This kind of operation presents a real challenge, as long as thumb duplication is absolutely symmetrical. However, it often leads to nail splinting [9-11,13,31]. An innovative technique to avoid this complication was described by Back et al in 2008, modifying the Bilhaut-Cloquet technique. Indications of this technique were concerning cases of type II or III, where both thumbs were symmetrical and the nail size was less than two-thirds of the normal thumb of the other hand, or smaller than the index finger size in patients with bilateral deformity [ 32].

Regarding the evaluation method used in this study, we preferred subjective and objective criteria, giving importance to the appearance and functionality of the remaining thumb. In 1998, Cohen was the first to classify residual deformities after duplicated thumb repair [5]. In the same year, Mih [33] distinguished residual deformities into three categories: joint abnormality (stiffness, deviation, and instability); bone abnormality (angled bone growth and presence of a delta-bone); soft tissue abnormality (reduction of the first space, hypoplasia of the thenar muscles and anomalous insertion of the flexor and extensor tendons).

We are pleased with the results of our research. However, the cases we faced were relatively simple and less complex. A disadvantage of our study is the short follow-up as well as the small number of patients. A study that will include the cases we have described, along with other new ones, is the next challenge for the future.

**Conclusion**

Preoperative planning in the case of duplicated thumb treatment is considered necessary given the diversity of the deformity. The day before surgery, decisions are made about the surgical approach, the creation of flaps and how to protect the thumb which will be preserved, while informing parents. Choosing the right timing protects both physicians (orthopedist and anesthesiologist) and patients of appropriate age to redefine the functionality of their hand. Clinical examination is the first diagnostic approach in any case. It is recommended to take a hand photograph as a reminder of the original thumb image, which can help parents appreciate the value of the end result. The study of x-rays helps to identify the problem more accurately. The technique must follow the principles of plastic surgery *lege artis*.

***Conflict of interest***

*The authors declare no conflicts of interest.*

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REVIEW

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# The role of therapeutic hypothermia in acute spinal cord injury

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## ABSTRACT

Ancient Egyptians were the first to use therapeutic hypothermia; thus, it is not a new concept. The term "hypothermia" is defined as a core temperature < 35° C (95° F). A spinal cord injury (SCI) is considered as one of the most significant injuries someone can endure since damage to just a small area of the body could implicate multiple body systems. A wide range of different mechanisms leading to tissue damage in the cord could cause injury.

Various early clinical SCI studies have investigated therapeutic hypothermia as a treatment strategy and have shown that if applied according to certain optimized parameters, the clinical use of hypothermia is most successful. Such parameters are temperature, time from injury to initiation of cooling, and rewarming time. Both local hypothermia and systemic hypothermia could be beneficial for acute SCI according to experimental evidence and some clinical evidence. The underlying mechanisms by which small reductions in central nervous system temperature can improve outcomes in brain and spinal cord injury models are still under investigation.

**KEY WORDS: therapeutic hypothermia, spinal cord injury**

**Introduction**

Ancient Egyptians were the first to use therapeutic hypothermia; thus, it is not a new concept. Hippocrates had the idea that cooling a person can slow biological processes that lead to death and thus he advised packing wounded soldiers in the snow (circa 450 B.C). During the French invasion of Russia (decade of 1800), a battlefield surgeon noticed that wounded soldiers placed closer to fire died sooner than those placed in colder bunks. At that time, surgeons used cryoanalgesia for amputations and noticed that hypothermia acted as an analgesic and at the same time slowed bleeding. The clinical interest of therapeutic hypothermia began in the 1930s with case reports on drowning victims who were resuscitated successfully despite prolonged asphyxia.[1]. One of the first scientific papers referring to therapeutic hypothermia was

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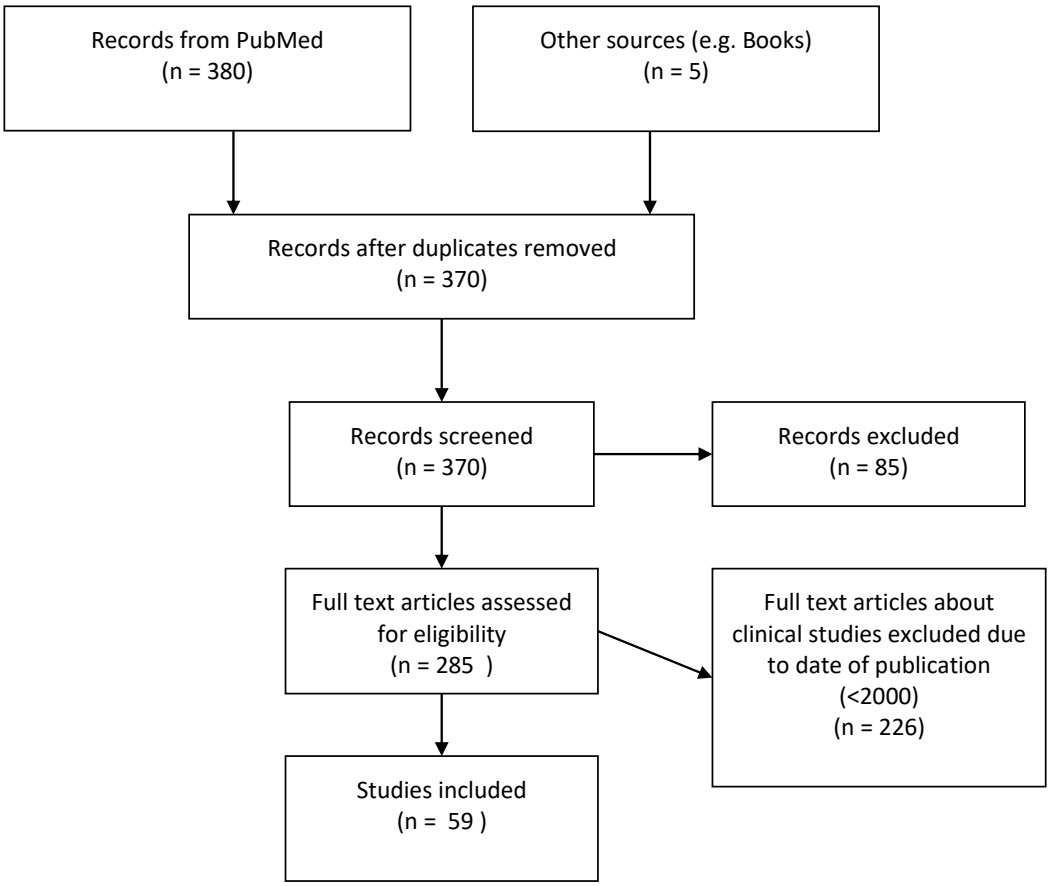
**Flowchart**
**THE ROLE OF THERAPEUTIC HYPOTHERMIA IN ACUTE SPINAL CORD INJURY**
TABLE 1




published in 1943 and described improvement after traumatic brain injury when temperatures were lowered to 32.7° C. In the decades of 1950 and 1960, clinical trials using deep hypothermia were started but abandoned soon because of adverse effects. During the decade of 1990, mild hypothermia was applicated in three cases of cardiac arrest after successful resuscitation, and all three made a complete recovery without residual neurological damage [2].

Definition of hypothermia is as a core temperature below 35° C. A more detailed classification of hypothermia is the following

- mild 35° C to 32° C
- moderate 32° C to 28° C
- severe 28° C to 20° C
- profound < 20° C [3].

Spinal cord injury refers to the damage of spinal cord due to trauma or disease. Immediately after the injury, different mechanisms lead to tissue damage in the cord. These include destruction of spinal cord neurons from direct trauma, compression by bone fragments or hematoma, ischemia from damage or compression of the spinal arteries and swelling of the cord tissue.

Patients with SCI experienced deficits in motor, sensory or autonomic functions. These clinical outcomes are closely related to the level of the injury.

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The International Standards for Neurological and Functional Classification of Spinal Cord Injury published by American Spinal Injury Association (ASIA) are based on clinical examination and evaluation of motor function and sensory. Depending of the level of SCI, patients experience tetraplegia or paraplegia. Tetraplegia is the injury to the spinal cord in the cervical level that result to partial or complete loss of motor or sensory in all four limbs. On the other hand, paraplegia is defined as loss of motor or sensory in lower extremities. Another significant classification is the complete or incomplete SCI. Patients are classified as having a complete SCI when no voluntary motor or sensory is described below the level of SCI. According to ASIA, a SCI is complete when the patient has any spinal level below, which there is no neurological function. [4,5].

In this paper we review the literature considering therapeutic hypothermia and acute spinal coed injury. The database that we mostly used was PUBMED and the keywords for our search were therapeutic hypothermia, systemic and local and spinal cord injury. We investigate all studies published from 1980 until 2020 containing the above terms, with both clinical and experimental evidence. Our study included also papers with animal trials. We excluded the studies about therapeutic hypothermia that were performed before 2000.

(Table 1)

## Discussion

### *Therapeutic hypothermia*

Therapeutic hypothermia has been investigated in many clinical studies [6]. During the decade of 1960, local hypothermia was induced in patients by administering cold saline to the exposed spinal cord after laminectomy and during decompression surgeries [7, 8]. These studies combined with experimental observations described that local hypothermia resulted in neurological improvement [8-10].

The bias of the previews studies was the fact that hypothermia was combined with surgical techniques, such as decompression. Furthermore, the administration of corticosteroids such as methylprednisolone in SCI as anti-inflammatory therapy is probably also a bias error [8, 12,13]. Another difficult issue in analysis and interpretation of the results of therapeutic hypothermia was the kinds of methods that the researchers choose to apply to the patients with SCI. Different approaches were used to improve reduction of the temperature such as cold fluids, ice baths and cooling blankets. These techniques were very inefficient, and therefore difficult to maintain therapeutic levels and adequate time of hypothermia. [14, 15].

Hypothermia is believed to have neuroprotective role against periods of ischemia that occur during time of spinal cord compression or aortic reconstruction surgery [16-18]. In other studies, therapeutic hypothermia has been shown to improve neurological outcome and recovery of motor and sensory function, when applied in models of compression injury [19]. Both local and systemic hypothermia has as a result the reduction of neurological deficits caused by spinal cord ischemia in studies which the aorta is clamped for specific period of time [20, 21].

Methods of local cooling lead to low levels of hypothermia without adverse effects, such as hypotension, bradycardia, and respiratory infection that can be seen in cases where systemic hypothermia is used [22-24]. The disadvantage of local cooling is that the procedure cannot be initiated until rather invasive surgical approaches are completed to allow the application of cold fluid onto the surface of the injured spinal cord. The realization that only relatively moderate levels of hypothermia are required to produce improved outcome has allowed for systemic hypothermia to be evaluated in clinically relevant animal models, as well as targeted patient populations [24, 25]. During the decades of 1960 and 1970, the interest in therapeutic hypothermia for the treatment of acute neurological disorders had decreased because new pharmacological agents were developed with similar and in some case better neuroprotective results.

Studies with animal models showed that local hypothermia improved recovery and improvement of motor and sensory function after

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SCI. Latest clinical research findings did not match with the results of these animal trials, and thus the role of local hypothermia in therapy of SCI had gradually underestimated. Since the 1980s, systemic hypothermia has been successfully used to treat SCI in both animals and humans. [26].

Therapeutic hypothermia decreases free radical production, inflammation and intracranial pressure, and improves cerebral metabolism after traumatic brain injury and cerebral ischemia, thus protecting against central nervous system damage [27].

The clinical use of hypothermia is most successful if applied according to certain optimized parameters (e.g., duration, temperature, time from injury to initiation of cooling, and rewarming time). Experimental evidence and some clinical evidence suggest that both local hypothermia and systemic hypothermia are beneficial for acute SCI [27].

Many researchers have approved that the use of hypothermia provides neuroprotection after SCI. The clinical studies that were mostly focused on local cooling techniques had mixed and complicated results. More recent data for the therapeutic role of systemic hypothermia proved its safety and its benefits. Methods used to induce systemic hypothermia such as endovascular cooling seemed to be safe and reliable [27].

Local cooling was utilized to cool areas of the damaged spinal cord. In those investigations, relatively profound levels of hypothermia were shown to produce marked neurological and functional recovery after spinal cord trauma [28]. Modest hypothermia (32°C–34°C) can deliver the potential benefits of hypothermia without incurring the complications associated with deep hypothermia. Mild hypothermia introduced after a traumatic or compressive spinal cord injury improved function and reduced histopathological damage [27,29-32]. Moderate hypothermia introduced after cervical spinal cord injury improved histopathological and behavioral outcomes. Likewise, improved forelimb function, preservation of motor neurons, and decreased contusion volumes occur in rats cooled after cervical traumatic insult [33]. This evidence shows that mild to moderate hypothermia improves outcome in models of both cervical and thoracic spinal cord injury [32].

Histologically, the application of hypothermia after spinal cord injury significantly increased normal-appearing white matter (31% increase) and gray matter (38% increase) volumes, greater preservation (four-fold) of neurons immediately rostral and caudal to the injury epicenter, and enhanced sparing of axonal connections from retrogradely traced reticulospinal neurons (127% increase) compared to normothermic controls[32]. Case reports and clinical studies have provided encouraging results regarding the safety and efficacy of moderate hypothermia following severe spinal cord injury [34]. In compression injury models, hypothermia reduced blood flow to the focal area of the injured spinal cord [29]. Also, when used before decompressive surgeries, hypothermia can prevent neurological decline [35].

Numerous studies have investigated the underlying mechanisms by which small reductions in central nervous system temperature can improve outcomes in brain and spinal cord injury models [36].

**Mechanisms of hypothermic protection**

The following will summarize the current thinking regarding basic mechanisms of hypothermic protection:

***(i) Reduced cerebral metabolism:*** Cerebral metabolism decreases by 6% to 10% for each 1°C reduction in body temperature during cooling. However, reduced metabolic rates are only one of many mechanisms underlying hypothermia's protective effects [37, 38].

***(ii) Apoptosis, calpain-mediated proteolysis, and mitochondrial dysfunction:*** Hypothermia can interrupt the apoptotic pathway, thereby preventing cellular-injury-induced apoptosis. Effects of hypothermia include inhibition of caspase enzyme activationprevention of mitochondrial dysfunction, modification of intracellular ion concentrations, and reduce overload of excitatory neurotransmitters. The c-Jun NH2-terminal kinase pathway mediates traumatic injury-induced apoptosis in astrocytes. Prolonged hyperthermia as

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a secondary insult worsens apoptosis by increasing c-Jun $NH_2$-terminal kinase activation. These studies indicate that apoptotic cell death is another important target by which temperature may affect long-term outcome in various models of central nervous system injury [39,40].

***(iii) Ion pumps and neuroexcitotoxicity:*** Reperfusion and ischemia interrupt the delicate balance between calcium influx and sequestration at the cellular level. Even a relatively small decrease in temperature can significantly improve ion homeostasis, whereas the occurrence of fever can trigger and stimulate these destructive processes [41].

***(iv) Immune and inflammatory responses:*** Numerous animal experiments and clinical studies have shown that hypothermia suppresses ischemia-induced inflammatory reactions and the release of proinflammatory cytokines. Hypothermia may block ischemic damage by blocking cytochrome c release or caspase activity after both transient focal and global ischemia. It also prevents or mitigates reperfusion-related DNA damage, lipid peroxidation, and leukotriene production, and decreases the production of nitric oxide, which is a key agent in the development of post-ischemic brain injury. Moreover, the proinflammatory response of stimulated microglial cells is significantly reduced after moderate hypothermia [42-43].

***(v) Free radical production:*** Free radicals can oxidize and damage numerous cellular components. ascorbate is known to be involved in many neurochemical processes. It is one of the most significant antioxidants and free radical scavengers that relieve oxidative stress in the central nervous system. Compared with other tissues, the high concentration of ascorbate in the nerve tissue also strongly suggests that ascorbate plays a very important role in neurophysiological and pathological processes. Preliminary conclusions are drawn that a significant reduction in spinal cord ascorbate concentration in rats with spinal cord injury under mild hypothermia may be related to protective mechanisms associated with secondary spinal cord injury. Thus, under hypothermic conditions, significantly fewer free radicals are generated, even though free radical production is not completely prevented. This allows the endogenous antioxidative (protective) mechanisms to better cope with free radicals that are being released, thereby preventing or significantly mitigating oxidative damage [44].

***(vi) Vascular permeability, blood-brain barrier disruption, edema formation, tolerance to ischemia:*** Mild hypothermia significantly reduces blood-brain barrier disruptions and also decreases vascular permeability following ischemia-reperfusion, further decreasing edema formation [45].

***(vii) Intracellular and extracellular acidosis and cellular metabolism:*** The diminished integrity of cell membranes, the failure of various ion pumps, development of mitochondrial dysfunction, inappropriate activation of numerous enzyme systems with cellular hyperactivity, and the disruption of various other intracellular processes all contribute to the development of intracellular acidosis, a factor that powerfully stimulates the abovementioned destructive processes. All of these factors can be significantly attenuated by hypothermia. Hypothermia during or after reperfusion increases the speed of metabolic recovery, with a better preservation of high-energy phosphates and reduced accumulation of toxic metabolites [46,47].

***(viii) Coagulation activation and formation of microthrombi:*** Hypothermia has some anticoagulatory effects. Mild platelet dysfunction occurs at temperature ≤ 35°C, and inhibition of the coagulation cascade develops at temperature ≤ 33°C; platelet count can also decrease during cooling. In theory, this anticoagulation effect may constitute yet another neuroprotective mechanism. This remains speculative given that no studies directly addressing this issue have been performed [48].

***(ix) Vasoactive mediators:*** Hypothermia affects local secretion of vasoactive substances such as endothelin, thromboxane A2, and prostaglandin I2 in the brain and other organs. The predominance of local vasoconstrictors can be corrected or modified by hypothermia [49].

***(x) Influence on genetic expression:*** Hypothermia

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increases the expression of immediate early genes, which are a part of the protective cellular stress response to injury, and stimulates the induction of cold-shock proteins, which can protect the cell from ischemic and traumatic injury [50].

***Combination with other therapies***

Because of the benefit of therapeutic hypothermia in SCI, many researchers proceed to a next level and carried out clinical studies with combination of hypothermia with other therapeutic methods [51]. These therapies can be divided into three general categories: cell therapy, pharmaceutical therapy and other alternative therapies [52].

For cell therapy, stem cells are differentiated into a variety of cells within the nervous system in order to be used for the treatment of nerve diseases. Wang and coworkers found that combination treatment with therapeutic hypothermia produced synergistic effects in transplantation to promote the recovery of spinal cord injury [53].

Additionally, many drugs enhanced therapeutic hypothermia neuroprotection in nerve injury. They included chemical drugs, hormones, neuroprotectants and others. For example, valproic acid is a histone deacetylase inhibitor. Valproic acid also enhanced neuroprotective effect of hypothermia against ethanol-mediated neuronal injury, and improved survival in a rat cardiac arrest model [54]. Early post-hypoxia-ischemia administration of phenobarbital may augment the neuroprotective efficacy of therapeutic hypothermia [55]. In a study a series of neuroprotectants including albumin, atorvastatin, baclofen, brain-derived neurotrophic factor, bumetanide, citicoline sodium salt hydrate and cyclosporine A were applied to an oxygen-glucose deprivation and re-oxygenation-mediated neuronal injury. This research showed that combination of therapeutic hypothermia with brain derived neurotrophic factor, glibenclamide, dizocilpine, HUK or neuroglobin provided a better protection compared with a single treatment method [56]. Xenon, $MgSO_4$ and Chinese traditional bloodletting treatment also offered better neuroprotection when combined with hypothermia [57-59].

Overall, an accumulating body of clinical evidence along with several decades of animal research and mathematical simulations has documented that the efficacy of hypothermia is dependent on achieving a reduced temperature in the target tissue before or soon after the injury-precipitating event. Mild hypothermia with temperature reduction of several degrees Celsius is as effective as modest or deep hypothermia in providing therapeutic benefit without introducing collateral/systemic complications. In the past several decades, many different cooling methods and devices have been designed, tested, and used in medical treatments with mixed results. Accurately designing treatment protocols to achieve specific cooling outcomes requires collaboration among engineers, researchers, and clinicians. Although this problem is quite challenging, it presents a major opportunity for bioengineers to create methods and devices that quickly and safely produce hypothermia in targeted tissue regions without interfering with routine medical treatment.

***Conflict of Interest Statement***

*The authors declared no conflicts of interest*

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REVIEW

# Cervical spinal cord injury: comparative study on the optimal surgical approach based on the level of injury

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## ABSTRACT

Anterior and posterior surgical approaches are used for immobilization of the unstable features of the cervical spine. The choice for optimal approach is still under discussion. Each procedure has advantages and disadvantages and the surgeon must be aware to make the right decision to assure patient's safety.
Intraoperative evaluation of reduction is essential to ensure satisfactory postoperative outcomes. However, immediate postoperative neurologic improvement is rare for patients with preoperative neurologic deficit and thus postoperative rehabilitation for improvement of motor and neurologic dysfunctions is imperative. Literature data report minor or severe intraoperative and postoperative complications for cervical spine surgery. The purpose of this mini review is to provide literature data on cervical spinal cord injuries and assess optimal surgical treatment based on cervical injury level. Moreover, the rate of postoperative complications and recovery time will be discussed.

**KEY WORDS: Cervical spine injuries, Fusion, Instrumentation, Spinal cord injury, Rehabilitation**

**Introduction**

The Cervical Spine consists of seven vertebrae (C1-C7) and supports the weight of the head (approximately 14 pounds). The first and second vertebrae, the "atlas" and "axis", do not have a disc between them, but are tightly bound together by a ligamentous complex [2]. The C1 (atlas) 'ring' rotates around the odontoid or 'peg' of C2 (axis), allowing for almost 50% of total cervical rotation. The spinal canal is housed within the cervical vertebrae and is widest between the C1 and C3 levels (A-P diameter 16-30 mm) and narrows as it progresses caudally (14-23mm). When the neck is fully extended, this canal can narrow an additional 2-3mm.

Traumatic spinal cord injuries (SCI) cause high morbidity and mortality worldwide. Common mechanisms include vehicular crashes, followed by falls, violence and sports and/or other recreational activities. Up to 80% of patients with SCI suffer multisystem trauma and require special considerations due to the risk of secondary cord injury from hypoperfusion and hypoxemia. Upon stabilization,

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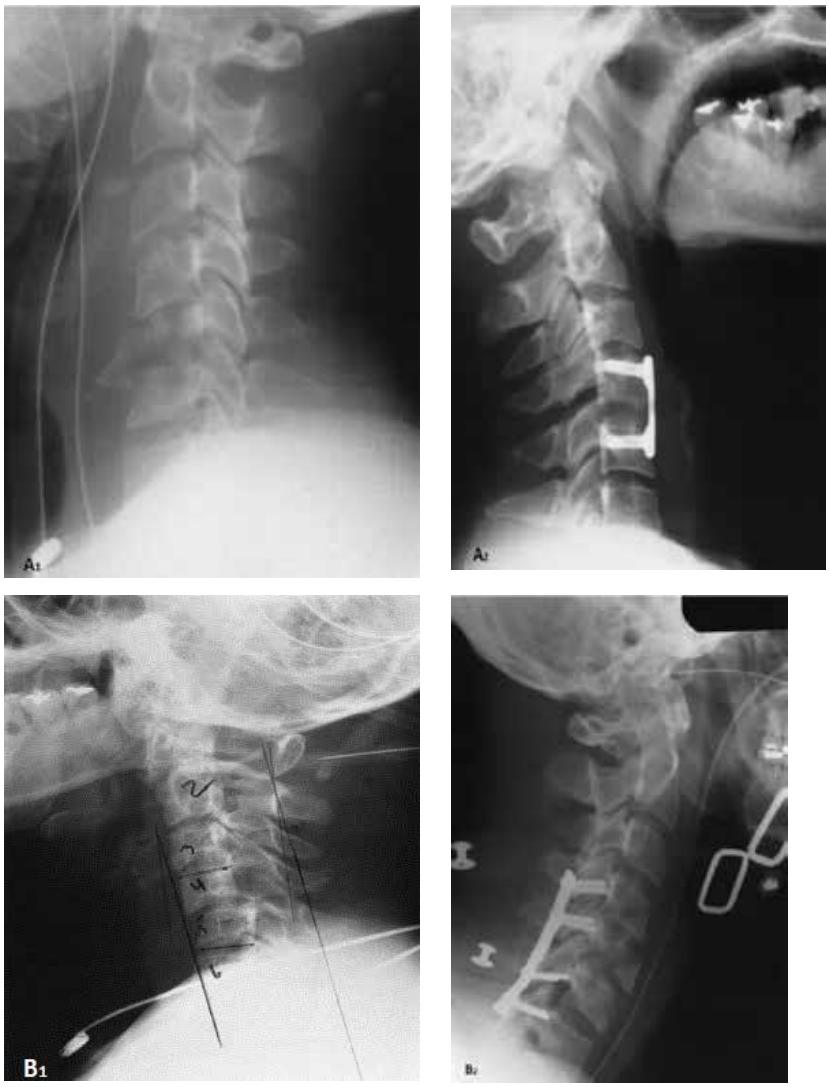

***Figure 1.*** *Cervical Spine Injuries. Dislocated Facets with posterior lateral mass screws and rods (A1 & A2). Burst fracture of C5 and anterior plating with screws (B1& B2).*

decisions for surgical decompression and/or spinal column stabilization remain especially challenging for polytrauma patients. In these situations, the management of the patient must be careful, and the surgeon must decide the perfect timing and approach of decompression for acute spinal cord injury [4].

Injury to the cervical spine is highly related to SCI (whether complete or incomplete). Two major issues must be addressed once the patient sustains an SCI: (i) the neurologic dysfunction due to persisting compression of neuronal structures and (ii) the residual instability that impairs early mobilization and rehabilitation. Primary treatment mandates decompression of the nervous structures either conservatively through traction, or surgically [3].Even if adequate decompression is achieved by closed means, operation may still be indicated to achieve segmental stability and allow patient's early mobilization [1].

Depending on the level of injury, different complications may emerge. Injuries from C1 to C4 may cause tetraplegia or quadriplegia, leading to trunk and upper and lower limb paralysis, impaired breathing and bladder and bowel disorders [4]. Such patients require continuous assistance for daily activities, such as eating, dressing, bathing, and getting in or out of bed. On the other hand, patients

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with injuries at the level of C5, preserve diaphragm function as well as some shoulder and elbow movement (mainly flexion) [5]. These patients will probably require assistance with most daily activities, but once in a power wheelchair, they can move from one place to another independently. Injuries at the level of C6 affect wrist extension and patient typically present with trunk, legs and hand paralysis. They will most probably be able to move in and out of wheelchair and bed with assistive equipment and drive an adapted vehicle. These patients demonstrated limited bowel or bladder control [7]. Injuries at C7 may maintain elbow and some finger extension. They can perform most daily living activities; however, they require assistance with more difficult tasks as well as for bowel or bladder control. Finally, injuries at C8 allow some hand movement and grasp. Patients can perform most daily living activities but will need assistance with more elective tasks as well as for bowel or bladder control [9].

The main goals of surgical treatment following SCI are: (i) achieve decompression of neuronal structures and (ii) provide segmental stability to the cervical spine. Surgery can be performed either through anterior approaches by means of plating and screws or through posterior approaches by means of lateral mass screws and plates or rods [6].

There is limited literature data to provide reliable guidelines on the choice of optimal surgical approach and instrumentation for the treatment of SCI according to the level of the cervical lesion [10, 15]. Even though both approaches may provide adequate stability, each one displays certain advantages and disadvantages that should be considered for assessing an optimal preoperative planning.

A thorough literature search was conducted in Pub Med, Web of Science, Cochrane, SCOPUS and EMBASE databases on anterior and posterior decompression for the treatment of cervical fractures with SCI [13]. Examined parameters included operative time, intraoperative blood loss, postoperative tactile score, postoperative motor score, postoperative vertebral height, hospitalization time, neurological function recovery, treatment efficiency, postoperative complications. References of included articles were reviewed to find additional studies [11]. Inclusion criteria comprised: (i) age between 18-65 years old, (ii) traumatic SCI of the Cervical Spine (C1-C7), (iii) traumatic SCI of the Cervical Spine associated with preexisting degenerative changes, (iv) absence of comorbidities, (v) anterior decompression-stabilization, (vi) posterior decompression-stabilization and (vii) combined approaches [17]. Exclusion criteria comprised: (i) animal studies, (ii) systematic reviews, (iii) SCIs receiving conservative treatment (iv) cervical trauma associated with Thoracic spine injuries and (v) cervical trauma associated with infection or tumor (Figure 1).

All patients were submitted to thorough preoperative assessment [16,18]. Applied procedures included anterior, posterior or a combination of these two approaches [19]. Neurologic recovery in most of the articles was evaluated with ASIA score and Barthel scale [20]. Most often complications comprised infection, dysphagia and neurologic recrudescence and postoperative kyphotic angulation.

**Discussion**

The treatment of an unstable cervical spine is still under discussion. Darrel et al support that decision for optimal procedure is mainly based on the "personality" of the cervical trauma. The term "personality" includes all the unique characteristics of a lesion: (i) the level of the neurologic compression, (ii) the type of fracture, (iii) the presence of irreducible dislocated facets, (iv) ligamentous instability and (v) the presence of disc herniation [3].

Based on Abitbol's findings, anterior approaches require less muscle splitting, providing easier approach to the cervical spine. Thus, reconstruction of the anterior column may be performed under direct visualization. On the other hand, posterior approaches may ensure anatomic reduction and increased stability of the facet joints due to higher biomechanical strength [13]. Surgical stabilization of the cervical spine has developed remarkably over the last 40 years since Robinson and Smith first depicted their approach and procedure for an anterior discectomy and fusion [12]. Since then, anterior plates with fixed angle unicortical screws, replaced older bicortical screw plate systems providing con-

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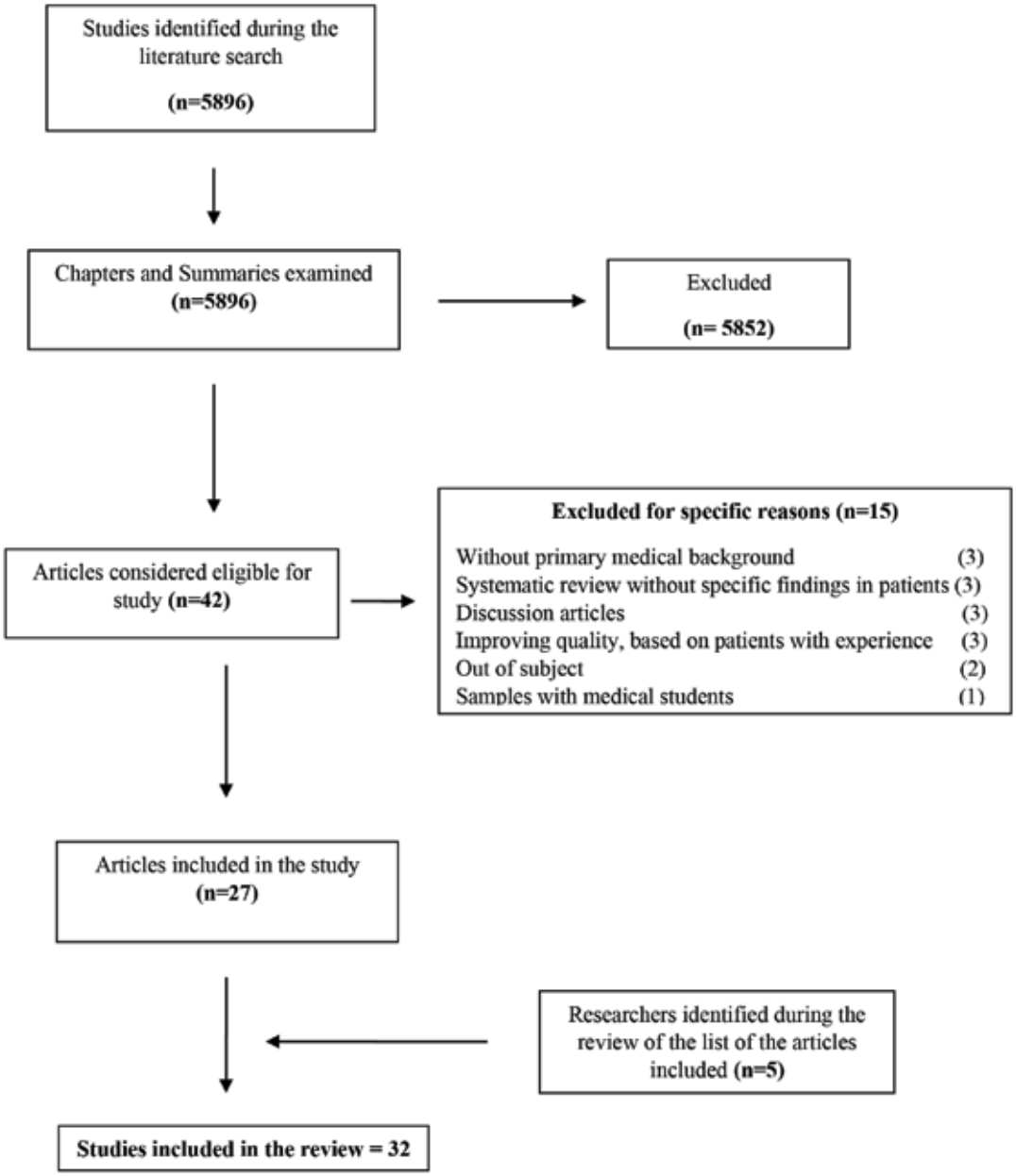


***Figure 2.*** *Flowchart.*

venience in practice, adequate stability and reliable results [13-16]. They bring back normal or supernormal stiffness in flexion, extension, rotation and axial loading. More recently, posterior cervical fixation with lateral mass screws and plates or rods has been developed for the treatment of cervical spinal cord injuries [17]. *Ex vivo* studies, report increased stiffness in flexion, extension, and rotation as contrasted with anterior plates [13, 15].

Cao et al suggest that surgical treatment for cervical spine lesions aims to: (i) decompress spinal cord, (ii) reconstruct vertebral canal morphology, (iii) restore vertebral canal volume, (iv) restore physiological cervical angulation, and (v) manage intervertebral bony fusion [34].Surgeons must choose optimal approach based on the type of injury and the level in the cervical spine (Table 1).

Based on biomechanical studies related to stabil-

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TABLE 1. **The Surgical Approach to Cervical Spine Injuries**

| Approaches / Level of injury | Anterior | Posterior | Combination |
|---|---|---|---|
| **Upper Cervical Spine** | • Type II odontoid fractures | • Type II/III odontoid fractures<br>• Atlantoaxial instability<br>• Atlantoaxial rotatory displacement<br>• Type II/III Jefferson unstable fractures | None |
| **Subaxial Cervical Spine** | • Compression and Burst fractures<br>• Unilateral or Bilateral Facet subluxation or Perched Facets<br>• Unilateral or Bilateral Facet Fracture Dislocation/ Subluxation (when there is no anterior vertebral disruption) | • Unilateral or Bilateral Facet subluxation or Perched Facets (when MRI shows disc and posterior ligament disruption without herniation)<br>• Unilateral or Bilateral Facet Fracture Dislocation/ Subluxation | • Unilateral or Bilateral Facet Fracture Dislocation/ Subluxation<br>• Vertebral Burst Fracture or Dislocation (Teardrop Fracture) |

ity following traumatic injury, Dennis divided the vertebral column into 3 vertical parallel columns. The anterior column comprises the anterior longitudinal ligament and the anterior half of the vertebral body. The middle column comprises the posterior half of the vertebral body and the posterior longitudinal ligament [35]. Finally, the posterior column comprises the pedicles, the facet joints and the supraspinous ligaments. Instability occurs when injuries affect 2 contiguous columns (i.e. anterior and middle or middle and posterior column). Obviously a 3-column injury is considered unstable [34]. There are many different types of spinal fractures: compression, burst, flexion-distraction, and fracture-dislocation [33]. Analyzing the three-column concept, a flexion-distraction fracture usually damages the posterior and the middle column while flexion-dislocation fractures usually involve all three columns [36].

Although there are guidelines for the cervical fractures and dislocations, Marcel et al suggest that the specific treatment of a cervical fracture and/or dislocation ultimately depends on a number of factors: (i) type and location, (ii) severity and amount of displacement, (iii) presence of spinal cord/nerve compression, (iv) presence of neurologic dysfunction or spinal cord injury, and (v) patient's age, medical condition and associated injuries [33].

Sethy et al reported that disc protrusion or vertebral body fragments displaced into the spinal canal require an anterior approach [37].On the other hand, Liu et al suggested that injury to the cervical spine associated with an irreducible facet dislocation mandates a posterior procedure [22]. Li et al claim that anterior approach is associated with fast recovery and improved neurologic outcomes [34]. Hatta et al state that posterior approaches provide higher postoperative stability [18], while Wang et al insist on the combination of both approaches to achieve optimal results [15].

**Anterior Approaches**

For burst fractures with compression of the spinal cord in subaxial area (C3-C7), an anterior approach and fusion is preferred. The only case that an anterior approach is recommended at the upper cervical spine is for the type II odontoid fractures. According to Theodotou et al, a surgeon prefers the anterior approach mostly in the subaxial cervical spine for: (i) compression fractures with 11 degrees of angulation or 25% loss of vertebral body height, (ii) unstable burst fractures with cord compression, (iii) unstable tear-drop fractures with cord compression, (iv) minimal injury to posterior elements, (v) facet

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dislocations reduced through closed methods with a MRI showing cervical disc herniation with significant compression on the spinal cord, and (vi) unilateral facet dislocations with failed closed reduction and disc herniation with significant compression on the spinal cord [35].

Patients suffering from multilevel degenerative cervical disease mainly demonstrate anterior spinal cord compression due to the formation of osteophytes and ligamentous hyperplasia associated with disc herniation. More rarely, posterior compression, due to the hypertrophy of the ligamentum flavum, can be encountered. These patients develop 'pincers'symptoms, due to anterior cord compression and should be treated through an anterior approach. Additionally, Diangelo et al support that anterior approach is also favorable for patients with ossified anterior longitudinal ligament [28]. Although anterior procedures are often applied for cervical spinal cord injury, several studies report that postoperative complications are more likely to happen with anterior approaches [21, 24-26].

**Posterior Approaches**

According to Anderson et al, a posterior approach is preferred for facet dislocations and injuries of the posterior ligamentous system. For unilateral dislocations, optimal approach could be either posterior or anterior; however closed reduction via cranial traction should be performed prior to surgery. On the other hand, for bilateral dislocations, a posterior approach is recommended for the effective treatment of residual instability [16].David et al support that in the upper cervical spine, the posterior approach is recommended for: (i) type II/III odontoid fractures, (ii) atlantoaxial instability, (iii) atlantoaxial rotatory displacement, and (iv) type II/III Jefferson unstable fractures. In the subaxial cervical spine, posterior approaches are indicated when: (i) there is significant injury to posterior elements, (ii) reduction, either closed or through anterior approach, is not feasible, and (iii) there is no anterior spinal cord compression (no disc herniation) [4]. Based on Liu et al, posterior approaches, including laminectomy and spinal fusion, have been applied to posteriorly decompress spinal cord, in the absence of anterior compression. Since posteriorly, the space of spinal canal is narrow, lesions of the cervical spine may induce compression at the tethering point of the nerve root. The latter has been recommended as main reason for segmental motor paresis (C5 nerve root palsy), influencing long-term postoperative outcomes. However, physiological curvature of the cervical spine cannot be restored using only a posterior approach. Loss of physiological curvature and emerging kyphosis prior to the operation are relative contraindications to the posterior approach [22].

**Combination of Anterior and Posterior Approaches**

Wang et al suggest that a combination of anterior and posterior procedure is performed, when injuries are highly unstable, and lesions affect both anterior and posterior columns. The "360 degrees" procedure is also indicated for Chance-like fractures [10]. Axiang et al insist on the combination of anterior and posterior approach for patients with subaxial cervical spinal cord injuries that cannot be reduced through closed or open anterior techniques, in the presence of disc herniation requiring decompression [9].

Pui et al reported that despite the numerous benefits of cervical surgery for treating SCI, several complications are likely to arise. For anterior approaches, the prolonged and forceful retractions should be avoided to prevent injury to the esophagus, recurrent laryngeal nerve and carotid arteries. For posterior approaches, protective foraminotomy minimizes the risk of postoperative C5 nerve root palsy. Preservation of posterior muscles and their attachments is essential to avoid postoperative neck pain and kyphosis [1].

Careful preoperative assessment of the bony and vascular structures should be performed, especially when internal fixation is chosen. Despite surgical approach, spinal cord monitoring should be mandatory in all cases of cervical spine surgery. Hee et al stated that with thorough preoperative assessment and intraoperative monitoring, cervical spine surgery demonstrates acceptable complication rates [23].

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In the study of Sasso et al, the authors analyzed several parameters that could influence recovery following cervical spine surgery. ***(i) Age***: the younger patients are more likely to demonstrate a fast recovery; however, it is quite rare for younger people to require neck surgery**.** *(ii)* ***Overall health***: preexisting comorbidities or unhealthy lifestyle demonstrate a negative influence on recovery time; the healthier the patient at the time of SCI, the shorter the recovery. Parameters such as smoking, obesity and drinking impact negatively on wound healing. (iii) ***Lifestyle:*** those who lead an active life and engage in regular healthy physical activity tend to recover quickly. Those who have very demanding, physical jobs, however, tend to recover much more slowly. If the patient is highly active, it will usually take longer to get back to that level of activity as well [24].

The most important goal is to realize the idea of independent mobilization for both complete and incomplete quadriplegic patients during the chronic period. Ambulation can be social, domestic and aimed at exercise. Individuals with a spinal cord injury, depending on the level and type of lesion, may have many complex needs and face wide-ranging, long-term restrictions in their ability to live independently, drive or use public transport, return to work or education, participate in leisure and social activities. Vaccaro et al stated that to ensure successful long-term management, coordinated community rehabilitation services and long-term support is required to know the long-term and on-going needs of individuals with a spinal cord injury [26].

***Conflict of Interest***

*The authors declared no conflicts of interest.*

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CASE REPORT

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# Normal variants of the glenoid superior and anterosuperior labrum; case presentation and review of the current literature

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## ABSTRACT

A 22-year-old male professional basketball player underwent shoulder arthroscopy for assessment and treatment of a symptomatic type II SLAP lesion. During the course of arthroscopic evaluation, a cord-like middle glenohumeral ligament was identified in conjunction with absence of the antero-superior labrum (Buford complex). The detached biceps tendon anchor was subsequently repaired by means of diathermy debridement and suture anchors fixation. The Buford complex was readily identified and ignored. The patient had an excellent result in terms of pain control and shoulder function during follow-up and was eventually discharged from clinic after 12 weeks. Normal variants of the superior and antero-superior labrum are increasingly identified during shoulder arthroscopy and do not necessitate repair since they are not regarded as independent contributors to shoulder instability.

**KEY WORDS: Sublabral recess, sublabral foramen, Buford complex**

**Introduction**

The role of various anatomic structures in maintaining shoulder stability is well defined. Normal variants, however, are increasingly recognized especially since the advent of shoulder arthroscopy. The most common anatomic variations include a separation of the biceps tendon anchor from the superior labrum named as sub*labral recess*, the presence of a *sublabral foramen*, which is characterized by detachment of the anterosuperior quadrant of the labrum from the underlying glenoid and the *Buford complex* which combines the presence of a large sublabral foramen with a thickened cord-like middle glenohumeral ligament (MGHL). Identification of such variants is of paramount importance, since they can be easily mistaken for pathologic lesions and thus lead to unnecessary overtreatment with likely adverse results.

**Case report**

A 22-year-old male professional basketball player was referred to our service for evaluation of de-

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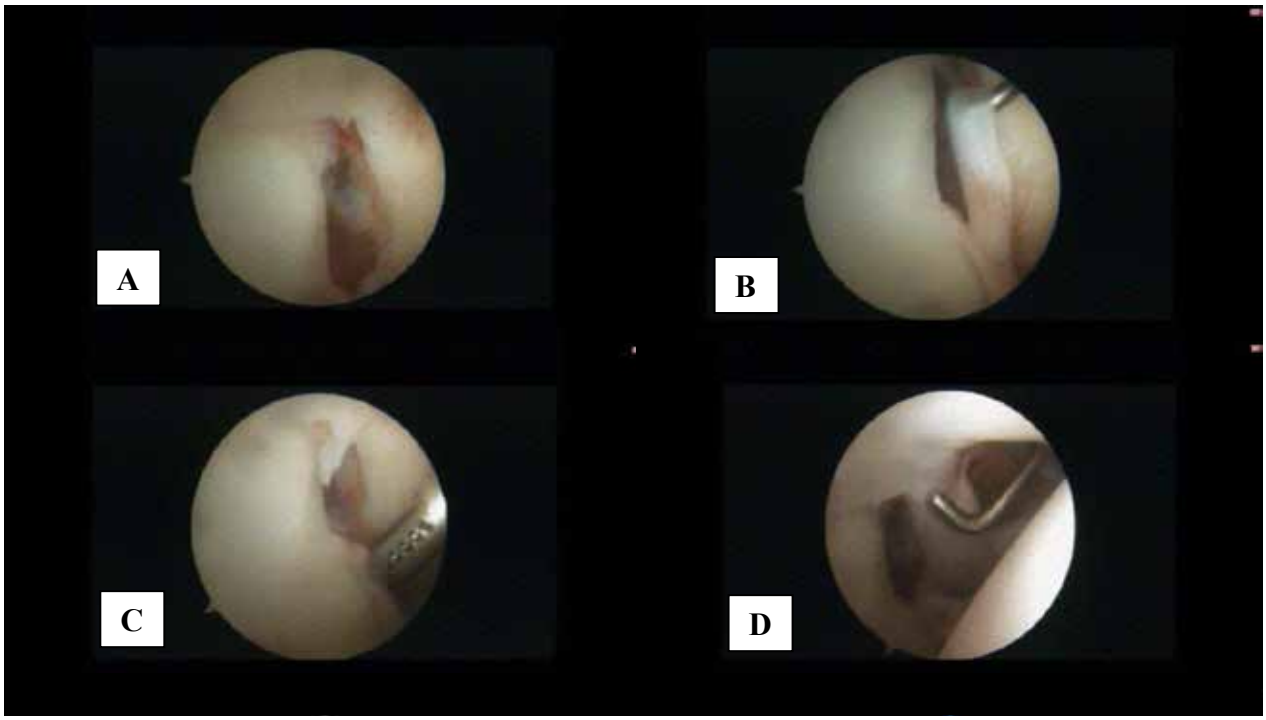


***Figure 1.*** *Intraoperative arthroscopic findings. A sublabral foramen is depicted in picture A. Pictures B and D reveal the presence of a thickened cord-like MGHL, which is stouter superiorly and gradually fans out inferiorly.*

bilitating pain affecting his right shoulder, following a sport-related injury during basketball. His past medical history was free of any systemic disease. Clinical assessment suggested the presence of a SLAP tear, which was further investigated by means of an MR arthrogram. Following confirmation of the labral injury, the patient was listed for shoulder arthroscopy.

*Shoulder arthroscopy*

The patient was placed in beach chair position and the right shoulder was routinely sterilized and draped. Standard posterior viewing and anterior working portals were created. Diagnostic arthroscopy revealed the presence of a type II SLAP lesion, namely fraying and detachment of the biceps tendon anchor from the superior glenoid. Peel back test was positive with the labrum sliding medially over the glenoid when the arm was placed in 90 degrees of abduction and external rotation. Absence of the labrum at the anterosuperior quadrant of the glenoid was noted in conjunction with the presence of a thick cord-like MGHL which was extending from the base of the biceps tendon anchor, crossing the subscapularis tendon at a 45 degrees angle, towards the humerus. (**Figure 1**) This was readily identified as Buford complex and therefore ignored as is the prevailing practice. Attention was turned back to the biceps tendon anchor which was debrided by means of arthroscopic diathermy and subsequently repaired with two suture anchors. Stability of the biceps tendon anchor was evaluated following the repair and deemed satisfactory.

The patient was followed up for a total period of twelve weeks in the outpatients' clinic before discharge. Constant-Murley score at final follow-up was 96/100 suggesting an excellent outcome.

## Discussion

*The role of labrum and its ligaments to glenohumeral stability*

The glenohumeral joint is often analogized to a golf ball sitting on a tee, to highlight the relatively limited contact area between the shallow glenoid and the much larger humeral head. These unique anatomic features provide the shoulder with an excel-

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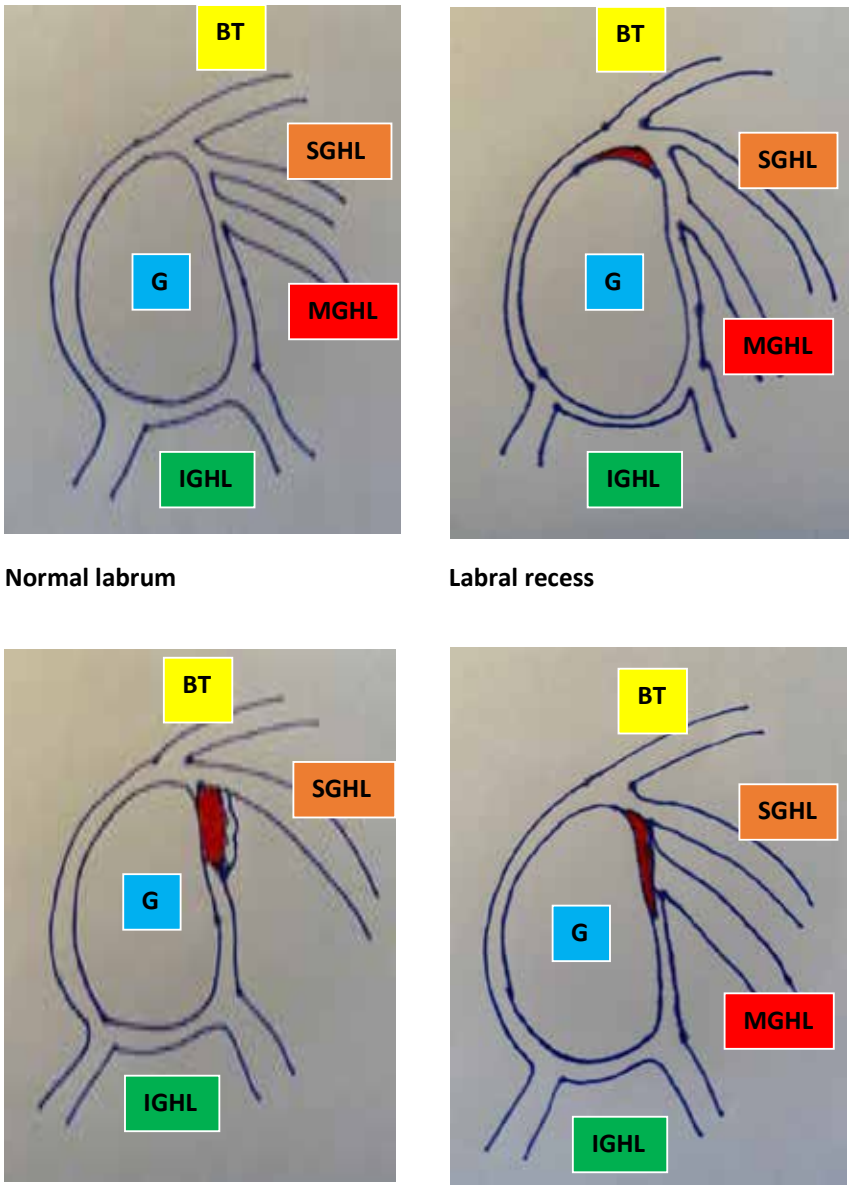


***Figure 2.*** *Schematic description of the antero-superior labrum normal variants. (Drawings by I.K.Triantafyllopoulos)*

*Abbreviations*

**G:** Glenoid and the surrounding labrum

**BT:** Biceps Tendon

**SGHL:** Superior Glenohumeral Ligament

**MGHL:** Medial Glenohumeral Ligament

**IGHL:** Inferior Glenohumeral Ligament (anterior and posterior branch)

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**TABLE 1. Definition of the antero-superior labrum normal variants**

| Sublabral recess | Sublabral foramen | Buford complex |
|---|---|---|
| • A separation of the Biceps Tendon anchor<br>• Located at the site of attachment of the biceps tendon<br>• It may coexist with a sublabral foramen<br>• Can be confused with SLAP lesion. | • A separation of the labrum from the underlying glenoid<br>• Located anterosuperiorly and can extend down to but not below the 3 o'clock position, which divides the anterior labrum into superior and inferior halves<br>• It may coexist with a sublabral recess | • It is the absence of the anterior superior labrum in conjunction with a thickened cord-like middle glenohumeral ligament<br>• Can be confused with a sublabral foramen or pathologic labral detachment |

lent range of movement, allowing for a wide array of actions ranging from activities of daily living to high-intensity sports.[1] To preserve the balance between function and stability, a number of anatomic structures, including the labrum and the glenohumeral ligaments, act in concert. (**Figure 2) The fibrocartilaginous labrum**, which is firmly attached to the glenoid in its lower half, increases the concavity of the glenoid socket and acts as an attachment for the capsule and the glenohumeral ligaments. However, its superior half is more variable and loosely attached to the glenoid, occasionally giving rise to anatomic variants.[2] The labrum also deepens the glenoid by 9mm and 5mm in the vertical and horizontal planes respectively, accounting for more than 50% of the total glenoid depth.[3] **The superior glenohumeral ligament (SGHL)** originates from the supraglenoid tubercle and anterosuperior labrum running just anterior to the long head of the biceps tendon (LHBT) and parallel to the coraco-humeral ligament (CHL) within the rotator interval. It inserts superior to the lesser tuberosity of the humerus and acts to limit inferior translation and external rotation when the arm is adducted.[2] Further studies have provided evidence that it limits posterior translation of the humeral head when the arm is in forward flexion, adduction and internal rotation.[4] **The middle glenohumeral ligament (MGHL)** originates from the supraglenoid tubercle and anterosuperior labrum in close relation to the SGHL. It is the most variable in appearance and size and runs down obliquely towards the humerus, inserting just anterior to the lesser tuberosity. The MGHL prevents excessive inferior translation of the humeral head when the arm is adducted and posterior-anterior translation of the humeral head when the arm is abducted between 60 and 90 degrees.[5] Lastly, **the inferior glenohumeral ligament (IGHL)** originates from the lower half of the labrum and glenoid neck and inserts just inferior to the MGHL attachment on the humerus. It has further been anatomically divided into 3 distinct components, namely the anterior band, the axillary pouch and the posterior band. The IGHL prevents posterior translation of the humeral head when the arm is internally rotated and inversely anterior translation of the humeral head when the arm is externally rotated. During abduction of the arm, it functions as a net to prevent inferior translation of the humeral head.[6]

*The normal variants of the superior and anterosuperior labrum*

As stated above, the superior half of the labrum is more loosely attached to the glenoid and occasionally a detachment in the anterior superior quadrant can be seen. Thus, normal variants of the anterosuperior labrum must be recognized during arthroscopy. (**Table 1**)

There is an intimate relationship between the superior labrum and the biceps tendon anchor. The attachment of the superior labrum to the glenoid at the site of the biceps tendon insertion may show considerable variation. A **superior sublabral recess** is located at the 12 o'clock position and it is classified into three types. [7] (**Figure 3**) In type I attachment, the labral-bicipital complex attaches firmly to the glenoid rim, so that an arthroscopic probe cannot be inserted between the deep side of the labrum and the glenoid. In type II attachment, a small sulcus is present between the labrum and the glenoid rim. In type III attachment, a deep sulcus is present between the labrum and the glenoid rim, allowing a probe to be inserted between the labrum and the glenoid cartilage. A superior sublabral recess may

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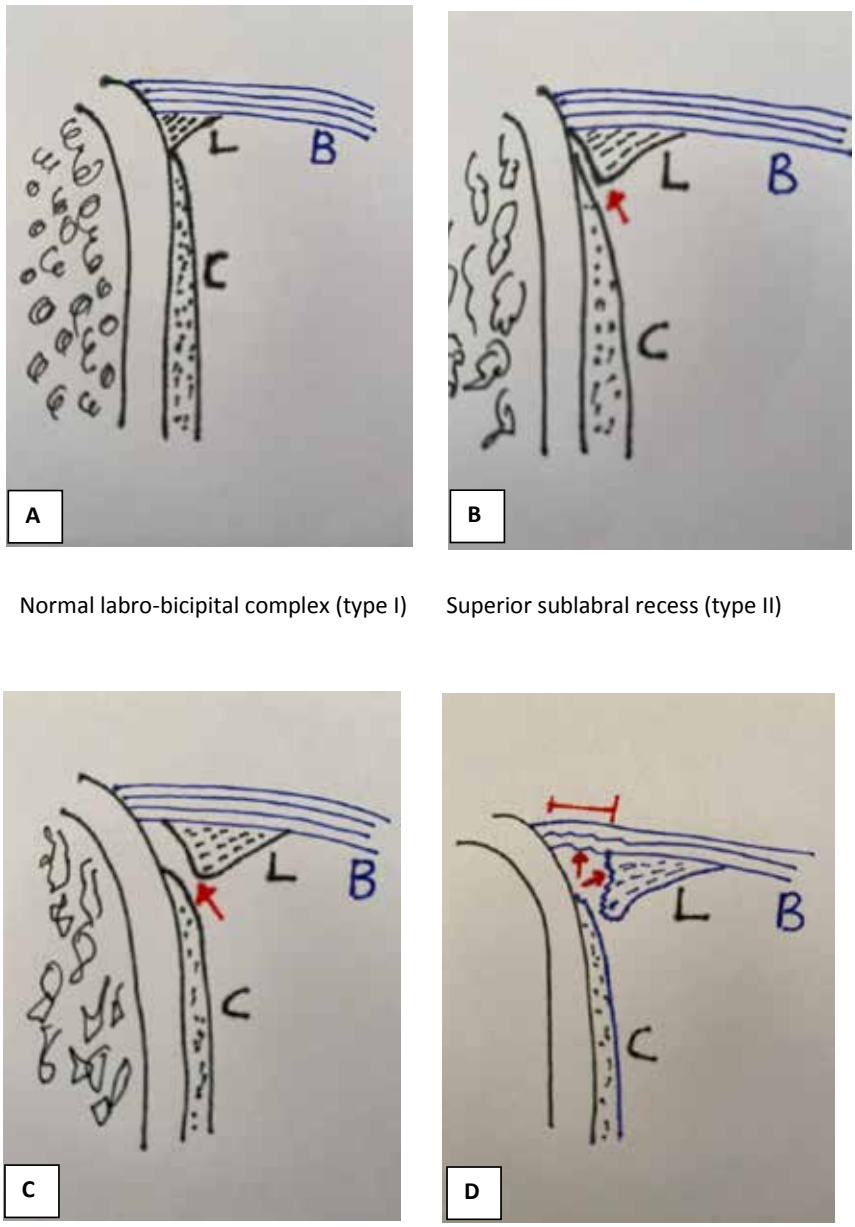


Normal labro-bicipital complex (type I)

Superior sublabral recess (type II)

Superior sublabral recess (type III)

SLAP lesion arthroscopic findings

*Abbreviations*

L : Labrum

C: Cartilage

B: Biceps tendon

***Figure 3.*** *Superior sublabral recess. Drawings representing a coronal section through the labral-bicipital complex illustrate type I (picture A), type II (picture B), and type III (picture C) labral attachments. In type I, the labrum (L) is tightly attached to the glenoid, whereas in types II and III, a recess is present between the labrum and glenoid (red arrow). In picture D, a real SLAP lesion is represented as fraying, tear or detachment of the labral-bicipital complex from the superior glenoid (red arrows) (Drawings by I.K.Triantafyllopoulos)*

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be continuous with a sublabral foramen. Differentiation on imaging studies between a type III attachment and a type II SLAP lesion may be extremely difficult. However, the surgeon must be aware of such normal variations in order to avoid a false overtreatment.

**The sublabral foramen** can vary in size from a few millimeters to the whole antero-superior quadrant. (**Figure 2**) A number of studies suggest that it is an age related phenomenon, being more prevalent in the elderly.[8,9] Park et al,[10] noted a 7% prevalence in patients aged 19-24 years old while Yeh et al, [11] reported an incidence of 40% in individuals between the ages of 61 and 96 years old. Sublabral foramens are not associated with glenohumeral instability and as such, the prevailing practice is to ignore them during shoulder arthroscopy.[12]

**The Buford complex** is a well-defined variant consisting of a large sublabral foramen and a thickened, cordlike MGHL. (**Figure 2**) Its prevalence ranges between 1.3% and 6.5% in studies.[13,14] On MRI, the Buford complex can be easily misdiagnosed as an avulsion of the anterior labrum. However, the absence of labral fraying and the smooth edges of the MGHL make it readily recognizable during arthroscopy.[15] The presence of Buford complex alone does not necessitate repair,[1] though there is some evidence in literature to suggest a higher incidence in patients with SLAP tears,[16] as was the case in our patient. More recently, a novel arthroscopic repair technique was described by Crockett et al, [17] for patients with type II SLAP lesions in conjunction with the presence of Buford complex. The authors suggest fixing the stout superior half of the cordlike MGHL to the anterosuperior glenoid, while leaving the inferior part of the ligament free so as not to impair external rotation. In our opinion, this option could be useful in cases of tenuous SLAP lesion repairs due to poor tissue quality. It should not be regarded, though, as a first-line technique due to the risk it carries for development of shoulder stiffness.

Conclusively, normal variants of the superior and antero-superior labrum are increasingly identified during shoulder arthroscopy and do not necessitate repair since they are not regarded as independent contributors to shoulder instability.

***Conflict of interest statement***

*The authors declare that there is no conflict of interest regarding the publication of this article.*

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CASE REPORT

# The Piriformis Syndrome. A sciatic nerve entrapment misdiagnosed as lumbar radiculopathy. A case report and literature review

E.K.Frangakis M.D.

## ABSTRACT

The term Piriformis Syndrome describes an extrapelvic pressure of the whole or part of the Sciatic Nerve, at the level of the Piriformis muscle caused by various conditions and characterized Clinically by symptoms of sciatica. As early as 1928 Yeoman described extra pelvic entrapment of the sciatic nerve by the piriformis muscle as a cause of sciatica. After Mixter and Barr in 1934 described nerve root compression by disc prolapse as a cause of sciatica, this diagnosis dominated the Clinical thinking for nearly three decades and what had been previously described was nearly forgotten. The development of imaging techniques revealed other intraspinal compressing elements. On the other hand, cases of negative root exploration for Sciatica focused attention to extrapelvic sciatic nerve pathology. This report concerns the case of a patient, who after a negative root exploration for severe sciatica proved to have an extrapelvic cause for this problem at the level of the piriformis muscle due mainly to anatomic variation of the sciatic nerve in relation to the piriformis muscle.

**KEY WORDS: Sciatica, Sciatic nerve, Piriformis Muscle**

**Case report**

A sixty-four-year lady suffered from a severe sciatica in the S1 distribution of the left leg i.e. pain in the left buttock radiating to the posterior aspect of the thigh and calf and numbness of the plantar surface of the foot, with mild low back pain. These symptoms started one and a half year earlier after a fall on the buttocks and remained ever since being aggravated in sitting position.

After six months her doctor diagnosed PID and referred her to a specialist who treated her with epidural steroid injection and physiotherapy without any improvement. The patient was referred to us with the diagnosis of Lumbar radiculopathy.

On physical examination, the lumbar spine was painless with free motion. The Lasegue test was positive at 60d there was mild atrophy of the left calf and absence of left Achilles tendon reflex. She could not stand on the toes of left foot. There was diminished sensation on the area of peroneal

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nerve. There was intense tenderness in the left sciatic notch. In EMG there are no recordings of the muscles innervated by the gluteal nerves.

Plain x rays revealed a mild stenosis of L5-S1 level. CTscan was negative for disc prolapsed but disclosed a narrowing of left iv foramina of L5. EMG and nerve conduction studies done elsewhere six months earlier disclosed lesion of the S1 nerve root (polyphasic recording in the gastrocnemius muscle and absence of H reflex). There were no recordings of the muscles innervated by the gluteal nerves. On the basis of the above findings the diagnosis of lateral spinal stenosis was made and the patient was operated on. Exploration of the left S1 nerve root by fenestration and foraminotomy revealed no abnormality. The nerve root was completely free and mobile. Two months later there was no improvement of the symptoms. There was again exquisite tenderness in the major sciatic notch. However, the clinical test described by Friberg and Vinke[14] and by Pace and Nagle[31] i.e., resisted external rotation of the hip from a position of internal rotation was negative. Repeat and more detailed electromyographic and nerve conduction study showed polyphasic potentials of the muscles innervated by the inferior gluteal and peroneal nerves (gluteus max and gastrocnemius) with sparing of the tibial and superior gluteal nerves. Nerve conduction studies of the sciatic nerves demonstrated prolongation of the F response, and absence of the H reflex. These findings were consistent with those of extapelvic entrapment of sciatic nerve at the level of the Piriformis muscle. Therefore, we had to explore this area and approach the sciatic nerve and its relation to the piriformis muscle. Leaving the pelvis through the greater sciatic foramen the sciatic nerve, usually passes under the piriformis muscle. (Fig.1)

But, in this case we found the sciatic nerve being divided well proximal to this muscle with the Tibial component passing below and the common Peronial above it. The peroneal branch, lying on the surface of the piriformis muscle was adhered to it by perineural fibrosis. By meticulous removal of perineural fibrous tissue the nerve was released from the muscle surface. The piriformis muscle was detached from its insertion to the trochanter and reflected medially leaving the peroneal branch of sciatic nerve to run free parallel to the tibial branch.

Clinical recovery was almost complete within three months.

**Discussion**

The piriformis syndrome may be due to various conditions, of which the relationship of the sciatic nerve to the piriformis muscle have a prominent role. This relationship is not constant. In most of the cases, the sciatic nerve leaving the pelvis through the greater sciatic foramen, usually passes under the piriformis muscle. (Fig.1) The muscle however may split in two parts and the nerve too, may have entirely separate tibial and common peroneal components. Therefore, several schemes of relationship between the two parts of the sciatic nerve and the piriformis muscle may occur. (Fig.2)

In a study of 1500 extremities Anson and Maddock[2] described the various schemes of relation of sciatic nerve to the piriformis muscle according to their occurrence (Fig.3). In case similar to one we report here, i.e., one of the branches of the divided sciatic nerve (the common peroneal) passed superficial to piriformis muscle and the Tibial behind (deep) to it, occurred only in 0,86%. In reported cases of P.S. available to us, we found no similar relationship of sciatic nerve to piriformis muscle.

The common peroneal nerve is vulnerable to trauma such as fall on the buttocks, which may give rise to a traumatic inflammatory process with epineural fibrosis and adhesions. The traumatic factor has been often reported in cases of Piriformis Syndrome.[24,31,38]

Another causative factor of P.S. reported in a number of cases is the persistence of sciatic artery[1] which is a fetal vessel, being the principal blood supply to the lower extremity in human embryo. Persistence of this artery in the adult is rare, leaving the pelvis in close proximity with the sciatic nerve. It is prone to vascular anomalies such as aneurism or sclerosis, which may cause pressure to sciatic nerve. [18,23,29]

Pseudoaneurysm of the inferior gluteal artery may cause pressure to the sciatic nerve. Isolated cases of enlarged piriformis muscle due to trauma or to pyomyositis have been reported as compress-

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***Figure 1.*** *The Sciatic nerve undivided passes under the piriformis muscle. This relationship of the nerve to the piriformis muscle is the most usual (88%, in 1500 Extremities found by Anson and Maddock). From the book "Surgical Anatomy by Anson and Maddock" W. B. Saunders. Co.1938*

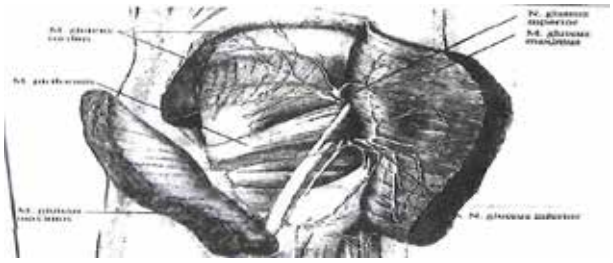

***Figure 2.*** *Adapted from Fig 1. The Sciatic nerve have been divided proximal to Piriformis muscle. The Tibial branch passing behind the muscle and the Peroneal above lying on the surface of it. (Our reported case)*

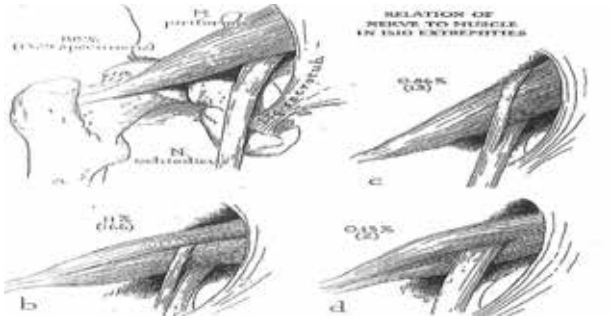

***Figure 3.*** *The percentage incidence of various relation of sciatic nerve to the piriformis muscle in 1500 extremities. By Anson and Maddock In the Book Surgical Anatomy 3d ed. Saunders Co London 1953, adapted from Beaton and Anson, J. Bone & Joint. Surg.20:686-688,1938*

ing factors to sciatic nerve.

The symptoms of sciatica may suggest a lumbar radiculopathy. Saal et, at reported that of 4000 patients referred for suspected for lumbar radiculopathy, 36 were found to have peripheral nerve entrapment. Of these 49% had backpain problems. The similarity of clinical symptoms of P.S. to lumbar root entrapment, may drive to erroneous nerve root exploration (as it happened in our case), especially if there are concomitant spinal pathology buttocks, sciatic notch or pain in sitting position and some cases pain during sexual intercourse in younger women, suggest the diagnosis of compression of the sciatic nerve. The most specific clinical test described by Friberg and Vinke, and by Pace and Nagle is not always positive because the peroneal branch of sciatic nerve passing superficial to piriformis muscle is not compressed by the maneuver. Rectal examination is useful in cases of enlarged or inflamed piriformis. Neurophysiological studies are essential in the confirmation of diagnosis but keeping in mind the entrapment of sciatic nerve at the level of piriformis. In a such cases, the superior gluteal nerve, arising proximal to piriformis muscle is free, therefore the gluteous medius, minimous and the tensor fascae latae show no abnormal potentials. On the other hand, muscles innervated by the inferior gluteal nerve (Glut. Maximus) which arise distal to piriformis muscle may show abnormal findings. Nerve conduction studies of the sciatic nerve demonstrate either delay or abrogation of F waves and H reflexes. Computerized Tomography and MRI are helpful in diagnosis only in cases of enlargement of the piriformis muscle, either from tumor or inflammation. Some cases have been reported to have been successfully treated by local corticosteroid injections or by physiotherapy. However, in a great number of cases conservative treatment fails to relieve symptoms and the recommended treatment is surgical by section of the tendon of piriformis and in some cases such as the reported here, neurolysis of the affected branch of the sciatic nerve.

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# ACTA

# YOUNG SCIENTISTS' PAGES

# The effect of botulinum toxin on gait analysis of paraplegic patients with lower limb spasticity

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## ABSTRACT

Often, people who have suffered spinal cord injury or stroke present spasticity in the lower extremities, due to uncontrolled muscle spasms, walking is completely prevented. Thus, to treat spasticity and regain walking, existing treatments include medications with substances that act on the central nervous system, such as baclofen, and substances whose infusion causes muscle denervation, such as botulinum toxin. The purpose of this study is to analyze the effect of botulinum toxin on lower extremity spasticity in paraplegic patients, and its contribution, when injected into selected muscle areas, to reduce focal hyperactivity. Research is also made, to determine the role of botulinum toxin in rehabilitation programs, when combined with other means, to improve quality of life in patients with spinal cord injury. For this review, research was made in Pubmed and Medline databases. The use of botulinum toxin issafe and effective, to reduce spasticity after spinal cord injury and other upper motor neuron damage. As for the improvements offered by botulinum toxin on walking,in patients with spinal cord injury, the results are indirect and related to the level of injury damage.In database, there are some articles with small sample of patients or case reports, so further research is needed to establish botulinum toxin's ability to regain gait,on population that has suffered from spinal cord injury.

**KEY WORDS: Botulinum Toxin, Spasticity, Spinal Cord Injury**

**Introduction**

Botulinum toxin improves walking ability in patients with lower limb spasticity following spinal cord injury [1]. Inhalation with botulinum toxin appears to be an effective additional therapy in the management of paraplegic spasticity, as spasticity is one of the most common complications following spinal cord injury [2,3]. However, the sample in most studies examining the effect of botulinum toxin on population who suffer a spinal cord injury and its contribution to gait analysis consists of a small number.

**Botulinum Toxin – BT**

Botulinum toxin belongs to a class of proteins with toxic action [4]. Produced by anaerobic bacteria *(Clostridium botulinum)*, its chemical formula is as follows: $C_{6760}H_{10447}N_{1743}O_{2010}S_{32}$. There are 8 different types of toxin; however only one, type A, is often applied in the field of medicine mainly for hyperactivity syndromes. The toxin acts in a bimodular way. On one hand, it suspends the secretion of acetylcholine during neuromuscular contraction resulting in muscular chemical denervation while on the other hand it affects the neurosis

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of several glands, through acetylcholine action on the parasympathetic nervous system [5]. Therefore, it is also used for the treatment of hyperhidrosis and salivation. It causes focal, dose-dependent and reversible muscle denervation that lasts from 12 to 16 weeks, while the degradation of the toxin and its pathological factors begins after a 4-week period.

**Botulinum Toxin in Motor disorders**

Botulinum toxin mainly affects neuromuscular synapses, preventing the release of acetylcholine. As a result, the toxin is capable of controlling spasticity, an abnormal increase in muscle contraction often caused by damage to central motor pathways that control voluntary movement. Treatment with botulinum toxin has shown to reduce spasticity due to spinal cord and brain injury, multiple sclerosis, cerebral palsy, stroke, and other neurodegenerative pathologies [6]. Botulinum toxin is considered as a milestone in the treatment of mobility disorders, such as dystonia, myoclonus, tremor, and is the mainstay of treatment for certain mobility disorders in neurological diseases. The toxin exerts its action through balancing the abnormal equilibrium between agonists and muscle competitors, highly affected by SCI's increase in muscle tone and spasticity [7]. Spastic muscle overactivity may be encountered in one or more limbs and is then referred as "focal". In focal spasticity, the intramuscular chemical attenuation caused by botulinum neurotoxin is an important therapeutic technique that has been shown to be effective and safe when administered under certain conditions (dosage, intramuscular injection, specialized physicians) [8]. Richardson et al reported that selective use of botulinum toxin to weaken muscles can reduce resistance to passive movement around a distant joint, thus improving passive range of motion and focal spasticity [9].

The purpose of this review is to evaluate the role of botulinum toxin in paraplegic patients with lower extremity spasticity and investigate its contribution to reducing pain and recovering and facilitating gait ability, thus affecting patients' quality of life.

It also discusses the application of botulinum toxin in rehabilitation programs and its proper combination with other medications and treatments in a multi-factor approach to treating people with lower limb spasticity.

The authors performed a comprehensive search of the published medical literature, using the following electronic databases Medline and Pubmed. An extensive search was conducted, from which 100 articles were found. Following the removal of duplicate articles, articles that had limited access and articles that were not entirely relevant to the subject being investigated, the number used to compile the paper was limited to 59. (Table 1)

**Discussion**

**Botulinum Toxin in Spinal Cord Injury – BT in SCI**

Bravo-Esteban Eet al, in a descriptive study of 66 people with spinal cord injury, reported lower limb hypertension and spasticity, during subacute and chronic phase, that affected their daily activities [10]. Losing voluntary bending and hypertension of extensors, seemed to contribute strongly to the loss of gait activity. Botulinum toxin appears to be an effective treatment for focal spasticity and disabilityrestriction in people with spinal cord injury [11]. According to the diagrams of 28 adults who received toxin injection, 56% reported improvement in movement and 71% better placement, while in total, upper limb function improved at 78%, hygiene at 66.6% and pain decreased at 83,3%. Botulinum toxin is effective in focal spasticity and is also recommended as a good additional therapy for oral medication to spasticity in people with spinal cord injury and generalized spasticity, according to a study with 90 patients with incomplete spinal cord injuries treated with BT for the first time. Therapy lasted for at least 1 year, and patients showed improvement in pain levels by 38.9% and improved muscle tone. ASIA D injuries showed the greatest improvement as far as muscle tone was concerned [3]. Subjective and objective improvement in spasticity was recorded following selective injections of botulinum toxin, in a patient with incomplete damage to the twelfth thoracic vertebra accompanied with strong and painful spasms in lower limbs, who was unwilling to receive intrathecal baclofen treatment, at two years follow-up [12].

**Gait Analysis in Spinal Cord Injuries**

Kinematics in gait analysis, via video, is a sensitive tool for quantifying gait abnormalities, while spasticity and injury level determine the pattern of gait anomaly following spinal cord injury [13]. In a study of 27 people with spinal cord injury who had retained the ability to walk (Frankel D), a statistically significant difference was found between people with thoracic injuries demonstrating a decrease in rhythm, frontal and angular knee speed, and those who suffered from injuries to the lumbar spine, showing reduced stride length and velocity in the ankle joint. People with neck injuries did not have a statistically significant difference in gait analysis.

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Patrick JH suggests that the prognosis for gait depends on factors such as loss of muscle strength, degree of spasticity, type of deformity in lower limbs joints and the availability of treatment [14]. Incomplete spinal cord injuries, especially ASIA D injuries, often lead to walking retraining efforts, which can be performed after proper understanding and assessment of kinematics and forces exerted on the hip, knee and ankle. In addition, the analysis of muscle synergies during cycling can provide a detailed quantitative assessment of functional motor impairments caused by abnormal activation of agonist and antagonist muscles following incomplete spinal cord injury, as cycling shares similar synergistic control with that observed in walking [15].

**Assisted Gait in Spinal Cord Injury**

Robotic devices are making a significant progress, as an innovative and effective treatment for people with spinal cord injury. Among the promising results recorded using robotic gait are reduction in pain perception and spasticity, increase of proprioception, sensitivity to temperature, vibration, pressure, reflexive behavior, gait speed, step length, distance traveled and body placement [16]. Robot walking is well accepted by people with spinal cord injuries and has shown positive results in reducing pain and spasticity. More specifically, in a study with 21 individuals performing a walking session with a powered exoskeleton robotic machine, results demonstrated high scores on positive senses and low scores on unpleasant sensations [17]. Exercising with robotic assistance, in patients following spinal cord injury, seems to have a positive effect on restoring functional gait and improving motor ability, thus allowing patients to maintain a healthy lifestyle and increase their level of physical activity. A review analysis, on 502 participants, reported significant improvements in walking distance, foot strength and functional mobility level from robot-trained groups compared to conventionally-trained groups, in the acute phase, and significantly greater improvement in walking speed, in the chronic phase, for the robot-assisted group [18]. A pilot study describes the use of a voluntary driven exoskeleton system as a new tool for rehabilitation in chronic spinal cord injury and supports that exercising in an electric treadmill using a hybrid assisted exoskeletal limb improved gait, leading to the conclusion that hybrid assisted exoskeletal limb facilitate walking ability [19]. In a study of 8 subjects, improvement in walking time, distance and speed were found with the use of the hybrid exoskeleton. Additionally, improvement was demonstrated in functional abilities, without the use of the exoskeleton, while total muscle strength was increased. Among many exoskeletons created to support walking in people with spinal cord injury, a novel system is required that would detect onset and cessation of gait via electroencephalographic signals, with the aim to control extracorporeal lower limb, thus assisting walking ability of paraplegic patients [20].

**Botulinum Toxin on Gait Analysis**

The spastic activity of the rectus femoris and the abnormal movement of the knee, impede the activity of walking and the ability to stand upright, in people with SCI. These factors can be reversed after a motor nerve block of the rectus femoris [21]. Injection of botulinum toxin into the spastic rectus, inhemiplegic patients, may improve muscle kinematics during walking but does not reach normal values in maximum muscle length [22]. However, a study reports significant increase in muscle length as well as muscle lengthening speed, following the injection of botulinum toxin into ten patients with knee stiffness and rectus femoris spasticity. The toxin also improved muscle tone, spasm rate and joint mobility. Although statistical significance for these parameters was not encountered, gait rate was improved [1]. According to Cioncoloni D. et al, significant improvement in gait performance can be achieved in chronic patients with lower extremity spasticity following injection of botulinum toxin into several muscles, especially the hip adductors [23]. Botulinum toxin seems to be effective and safe for focal spasticity of the lower extremities in paraplegic adult patients following cervical or thoracic spinal cord injury or patients with multiple sclerosis. Patients who have been administered toxin into the hip adductors, knee flexors and ankle flexors have experienced a reduction or resolution of pain [24].

**Botulinum Toxin for Neuropathic Pain**

In addition to botulinum toxin use in muscles with hyperactivity to reduce spasticity, there are evidence showing the toxin's contribution to neuropathic pain treatment. Botulinum toxin can be applied effectively in disorders based on both muscular (dystonia, spasticity) and non-muscular pain (neuropathic pain). However, no significant difference on pain relief was detected, thus implying the presence of independent mechanisms of toxin-induced pain relief [25]. Moreover, the effects of botulinum toxin on neuropathic pain associated with spinal cord injury, post-stroke pain,

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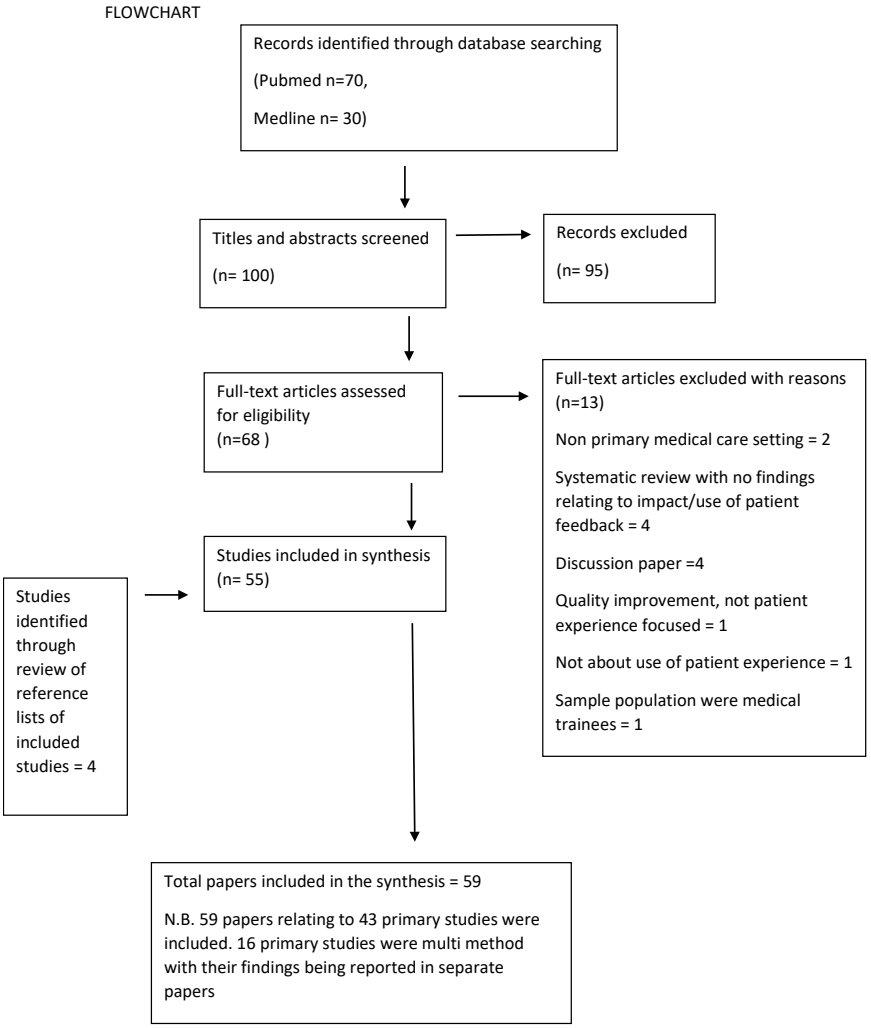
**Table 1**




and multiple sclerosis have been shown to be beneficial [26]. According to Jung Hyun Park and Hue Jung Park, the mechanism by which botulinum toxin acts on neuropathic pain involves inhibiting the release of inflammatory mediators and peripheral neurotransmitters from the sensory nerves. Thus, botulinum toxin injections are useful in managing a variety of disorders such as in treating post-herpetic neuralgia, diabetic neuropathy, trigeminal neuralgia and intractable neuropathic pain such as post-stroke pain and spinal cord injury [27].

**Combined Therapies**

Spasticity occurs as a symptom of upper motor neuron damage in patients with central nervous system pathology resulting in significant pain and limited mobility, leading to reduced quality of life and difficulty in maintaining personal care. Therefore, available treatment options for spasticity include oral medications, with centrally acting agents such as baclofen, clonidine, tizanidine, and anticonvulsants such as benzodiazepines, gabapentin and peripherally actingdantrolene. As far as interventional procedures are concerned, botulinum toxin, phenol or alcohol injections and intrathecal baclofen pump may be applied, together with surgical treatments such as selective dorsal rhizotomy and neurectomy [28]. Since oral medications can cause side effects in the central nervous system, a multidisciplinary ap-

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proach combined with medication and physiotherapy to treat spasticity should be considered. Vogt T. and Urban P. suggested that combining intrathecal baclofen and botulinum toxin may improve clinical benefits and reduce side effects [29]. Spasticity following spinal cord injury should be evaluated regularly, and treatment strategy should depend on the state of functional insufficiency. Active exercise, physical therapy and oral medication are the simplest and most affordable options, although the use of tablets may be accompanied by severe side effects. International guidelines recommend a combination of botulinum toxin, physiotherapy injections and intrathecal baclofen pump in cases of peripheral spasticity as well as and orthopedic surgery or neurosurgery in selected patients with ineffective spasticity [30]. In their study, Yan X. et al. testing the efficacy and safety of botulinum toxin in spinal cord injuries, showed that the group receiving baclofen tablets was significantly improved compared to the group treated with botulinum toxin injections, while the botulinum toxin also showed steady improvement. Taking into consideration the addiction caused by the continued use of baclofen, botulinum toxin is being suggested as an effective treatment for spasticity following spinal cord injury [31]. However, instead of comparing botulinum toxin with baclofen, many studies speak of their combination, as the use of botulinum toxin can be an important adjunct in increasing the therapeutic effect of intrathecal baclofen pump, thus facilitating the use of gait orthoses and improving performance of rehabilitation programs. In a case study of a patient treated with intrathecal baclofen pump, unable to wear orthoses due painful muscle spasms, the situation resolved when bilateral injections of botulinum toxin were administered into the flexor digitorum brevis muscles [32]. Since there has been a significant reduction in patients with focal spasticity who received botulinum toxin, it is suggested that combination of botulinum toxin injections with proper orthoses may provide better results for SCI patients following rehabilitation programs [33]. Based on literature guidelines (level 1b), botulinum toxin injections reduce patients' lower extremity spasticity compared to physiotherapy alone, and when additional treatment is applied through a lower extremity cast, the results seem to improve [34]. Alongside, there is suggestion of combinate electroacupuncture and botulinum toxin injections to treat muscle spasticity following spinal cord injury, claiming that a safe and complete treatment can be achieved by reducing pain and improving quality of life faster [35].

**Conclusion**

Literature data support that botulinum toxin causes a decrease in muscle tone [9]. This is particularly useful for spasticity management of SCI and other upper motor neuron diseases, where there is an abnormal increase in muscle tone. More specifically, its infusion is ideal in cases where focal spasticity is detected, since it allows a better control of lower limb movements and improved walking ability. Paraplegic patients with lower limb spasticity, when injected with botulinum toxin into appropriate muscle groups, will be able to perform rehabilitation programs, maintain their functional ability and keep up their physical status. In addition, several studies report that botulinum toxin demonstrates an analgesic action; however, the exact mechanism has not been documented. The fact that the use of botulinum toxin decreases pain sensation expands its use to treat pain in clinical practice. Literature data reports additional advantages of botulinum toxin application. The healing of pressure ulcers through muscle spasm control assists medical stuff to provide better trauma care and higher patients' compliance for the rehabilitation programs. Still, botulinum toxin, in most of the available resources, has not been shown to directly improve the gait of paraplegic patients, but apparently acts indirectly, by reducing muscle spasms and regulating spasticity at certain points. In conclusion, optimum results following botulinum toxin administration are more likely to be observed in comprehensive rehabilitation programs, when combined with other medical treatments and assisted by orthoses, casts and exoskeleton systems. However, further evidence is needed to establish treatment protocols that will accurately determine the infusion criteria, frequency and dose of toxin, area of injection, appropriate rehabilitation programs and the application of orthoses to assist patients suffering from spinal cord injuries [18,22,36].

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# The effect of depression in hospitalization and rehabilitation of patients with spinal cord injury

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## ABSTRACT

Spinal cord injury (SCI) is a rare condition, however its consequences might be devastating, since it affects patients' physical function as well as psychological well-being. Therefore, it is not surprising for patients with SCI to develop mental health problems, such as depression and/or anxiety. Depressive symptoms include agitation, restlessness, fatigue, changes in appetite, helplessness, loss of interest as well as problems in sleeping. The presence of depression has been connected with extended length of hospitalization and development of secondary medical complications, as well as reduced quality of life (QOL) and self-efficacy. The purpose of this review is to investigate the existing literature to identify the effect of depression on hospitalization and rehabilitation in patients with SCI. From the 31 studies included in this paper, it is obvious that SCI patients with depression have longer periods of hospitalization and/or rehabilitation as well as worse functional outcomes. Moreover, it was shown that SCI individuals with depressive symptoms frequently develop other secondary medical complications which subsequently affect the length of stay and the rehabilitation outcomes. Acknowledging these facts can improve diagnosis and intervention, which may also improve the patient's recovery outcome.

**KEY WORDS: SCI, depression, hospitalization, rehabilitation**

**Introduction**

Spinal cord injury (SCI) is a devastating injury that can lead to severe secondary health problems [1]. According to a WHO report SCI can lead to major injury as well as disability [2]. The incidence of SCI in developed countries varies from 10.4 to 83 per million people per year [3]. More specifically, the incidence rates that have been reported in the USA range from 28 to 55 per million people [4]. From those, about 10,000 represent new cases of SCI patients. Published reports showed that SCI incidence in the rest of the world varies, and it seems that the rates are lower than those observed in the United States. Analytically, the incidence rates varied 25 to 59 per million people per year with an average of 40 cases per million people. However, it was noted that the incident rate progressively increased in several countries, such as Norway, where from 6.2 per million it was increased to 26.3 per million people over the last 50 years [5].

Spinal cord injury influences both patients' physical function and psychological condition. Many studies have demonstrated that patients post SCI manifest low subjective well-being, participation in life and quality of life (QOL) [6-8]. As a result, it is quite common for patients with SCI to present a number of mental health problems,

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such as depression and/or anxiety [9]. One of the most studied psychological factors among patients with SCI is depression [10]. It represents a frequent secondary condition following spinal cord injury [7]. It has been associated with psychological problems caused by injury, such as perceived low quality of life and increased stress. Severe depression is the most common psychological condition associated with spinal cord injury and is estimated to be experienced by 11% to 37% of patients, depending on the method used for the diagnosis, which is significantly higher compared to the depression rates reported to other medical conditions [11,12]. In a recent study conducted in Greece, it was estimated that 18.2% of the SCI patients included had depression, which is a relatively low percentage [13].

The symptoms of depression vary from agitation and restlessness to fatigue, change in appetite and helplessness. Some patients have also reported loss of interest as well as problems in sleeping [14].

Moreover, it is not uncommon for SCI patients with depression to also develop other comorbid psychiatric illnesses that can increase the visits to the healthcare facilities and also lead to extended hospitalization and worse rehabilitation outcome [7]. The presence of depression can affect severely patient's daily activities and therefore is associated quality of life (QoL) [15]. High levels of depression are reported to lead to poor QoL, which subsequently can result in premature mortality for the individual [16].

The presence of depression is associated with increased periods of hospitalization and secondary medical conditions, as well as reduced social reintegration, quality of life, and self-care efforts [9]. The development of depression also seems to affect, among other things, the way a person copes with any medical complications [17]. Many factors have been connected to depression and its symptoms such as such as age, gender and socioeconomic status [10, 11]. Additionally, it has been demonstrated that quadriplegic SCI patients have significantly higher prevalence depression rates, which can be explained by the fact that these patients show limited physical ability and greater dependence on others [11].

There were many studies indicating that almost all SCI patients will develop depression at some point in their life [18]. However, later studies have shown that this is not always the truth [15,18,19]. At the same time, there are many factors that can affect the development of depression in these patients. These include pain, medication, isolation, medical complications, and post-traumatic stress disorder [9,20-22]. Depression can, however, affect the recovery process of the patient due to negative expectations, social withdrawal and reduced energy. Hence, depression can affect the patient's stay at the hospital and their rehabilitation.

The aim of this paper is to review the existing literature in order to specify the effect of depression on hospitalization and hence on rehabilitation in patients with spinal cord injuries. This knowledge can improve significantly diagnosis and intervention, which may also improve the patient's recovery outcome.

A literature review was conducted in a scientific publication resource; the MEDLINE (PubMed) (https://www.ncbi.nlm.nih.gov/pubmed). Temporal criteria were applied in order to access the literature of the last 37 years (from 1983 to 2020). In the research were included only articles published in English language. The keywords applied regarded spinal cord injury, depression, hospitalization and rehabilitation. The search of the databases returned 8554 articles. Publications that did not match the research criteria were excluded from the study. The final number of articles included was 31.

**Discussion**

The association between spinal cord injury and depression has been studied largely. The purpose of this study is to investigate the existing literature regarding the effect that depression has on the hospitalization as well as the rehabilitation of SCI patients.

The number of relevant studies revealed was 31 in total. In more detail, 17 studies were investigating the effect of depression on the hospitalization and 14 on the rehabilitation process.

There are many factors affecting the length of stay (LOS) in patients with SCI, such as demographic agents, secondary health complications due to spinal cord injury as well as hospital related agents [23-25]. Regarding the role of depression in LOS for SCI patients, we discovered 4 studies on this subject. Specifically, Malec and Niemeyer focused their research in finding a correlation between depression and length of stay among 28 patients with spinal cord injury. They concluded that depressed SCI patients tend

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to require longer length of stay in comparison to non-depressed [26]. Similar results were also reported by Elliot and Frank, who have associated depressive symptoms with extended length of stay as well as higher costs [10]. Another study investigating the psychological symptoms during rehabilitation, demonstrated that depression significantly prolonged hospitalization for SCI patients compared to patients with no or other psychological conditions [27]. However, the results of a retrospective survey showed no difference on the length of stay between SCI patients with depression and those without any psychological imbalance [28].

A negative connection between levels of depression and rehabilitation results for SCI patients has been described by several authors. An early study conducted by Lawson, showed that the SCI patients with lower depression levels had also better results during rehabilitation [29]. The author concluded that depression was detrimental to the patient's rehabilitation process. In addition, another study revealed that the presence of depressive symptoms is associated with the functional outcome, although this fact is not always reflected on the relevant scores [30]. In a study that was conducted in Saudi Arabia, researchers investigated the possible predictors for functional outcome for patients with traumatic SCI [23]. Their results showed that patients with depression and/or anxiety were more prone to worse outcomes. The results of a similar study in a rehabilitation center in Singapore, also validated that depression leaded to poorer functional outcomes in SCI patients [31]. A longitudinal study conducted by Kennedy and Rogers, showed that depression was negatively associated with worse functional independence [32]. A recent qualitative study showed the importance of good mood to better self-management and therefore adjustment of patients with traumatic SCI, leading to better functional capability [33]. The results from other similar studies also strengthen the point of view that depression affects the patient's self-management which by extension results in difficulties during hospitalization and rehabilitation [34-37]. Other studies have also concluded that SCI patients with depressive symptoms develop a number of difficulties during their rehabilitation process, thus they cannot obtain the best functional outcome [38,39]. Specifically, it was reported that SCI patients with high levels of depression might manifest problems in the attendance of therapies, in the exercise of effective problem-solving and interpersonal skills as well as in the adherence of medical treatments.

As far as functional capability is concerned other studies, however, report contradictory results. Specifically, depressive symptoms have also been investigated in 140 SCI patients that live in the community by Fuhrer et al. The researchers manifested that there was not a statistically significant connection between depression and functional outcomes for these patients [40]. Similarly, another study that included 36 patients with spinal cord injury showed that the prevalence of depression was much higher in these patients 6 months after the injury [41]. Moreover, it was demonstrated that patients with worse functional outcomes showed lower depression levels than other SCI patients.

It is not uncommon for SCI patients to develop health complications such as pressure ulcers (PUs), urinary tract infections (UTIs), respiratory tract infections, chronic pain etc. [42,43]. There are many studies that suggest that depression among SCI patients can lead to health complications which subsequently prolong the length of stay in the healthcare facility and lead to poor functional capability. Herrick et al., in their study, showed that depression was one of the determinants that led SCI patients to manifest health complications [44]. These findings are in accordance with the results obtained by an earlier study [26]. An empirical study has similarly found that SCI patients with high depression levels are at greater risk to develop several health complications during rehabilitation [45]. Furthermore, a study that investigated the relationship between mental health problems and medical complications in 466 SCI patients manifested that individual with depression (21%) were more prone to develop a variety of medical complications such as pressure ulcers, urinary tract infections and pain [46]. Other studies also, have shown that depression in SCI patients can lead to health deterioration and pain [19,47-50]. Moreover, the results of another study evaluating depression levels and quality of life for SCI patients showed that depression was strongly linked to pain as well as patient's health status [51]. A cross-sectional study analyzing factors affecting the development of severe neurogenic bowel dysfunction in SCI patients showed that SCI patients with depression were more prone to have this condition in comparison to SCI

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patients who did not have depression [52]. Anderson et al., conducted an interview survey including SCI adults injured during childhood. They concluded that although depression was not statically associated with demographic factors, it was linked to a series of medical complications [11]. Moreover, pressure ulcers have also been identified as a strong predictor of depression among patients with spinal cord injuries; however, a study conducted by Gelis et al., provided little evidence that depression can work as a potential risk factor for pressure ulcers [53,54].

Depression is quite frequent, although not always necessary, for patients with SCI, affecting both the hospitalization and the rehabilitation process of these patients with various ways. In this review we examined the literature for the effect of depression on hospitalization and rehabilitation of patients with SCI. In more detail, after our search we found few studies investigating the role of depression on length of stay of SCI patients in healthcare facilities [10,26-28]. All these studies, with the exception of the study conducted by Arango-Lasprilla et al., concluded that depression was an important factor that prolonged significantly the LOS of SCI patients. However, the results of other studies that investigated how depression affects LOS, have shown that patients with depressive symptoms have significantly longer LOS in comparison to patients without depression [55-57]. We must highlight, moreover, that although recent literature is full of studies that examine the factors that affect LOS for individuals with SCI, depression or other psychological determinants are rarely included. Therefore, it is difficult to come to safe conclusions. It is important that more studies to be conducted on this subject.

Many SCI patients can develop depression during the rehabilitation process. It has been declared by many researches that self-efficacy plays a fundamental role to rehabilitation since it is considered a major component of this process, which can subsequently lead to better health outcomes [33-58]. Therefore, SCI patients that present low self-efficacy and self-management are more prone to develop depressive symptoms. There are many studies that support that there is a direct connection between depression and worse functional outcomes for these patients. Specifically, the majority of studies that were included in this review suggest that SCI patients with depression had significantly poorer functional capabilities in comparison to SCI patients that did not develop depression. Two studies did not agree with the above-mentioned results. In fact, in the study conducted by Fuhrer et al., this can be mainly explained by the fact that the number of patients that were included was small and therefore their results cannot be representative [40]. In the other study that showed contradictory results, apart from the fact that the number of patients included was small, an additional limitation was that the survey was conducted with patients that were recently injured (only 6 months after injury), and thus they hoped to have better outcomes in the near future [41].

Although there were many early studies that acknowledged the role of secondary health complications, such as UTIs and PUs, to the development of depression in patients with SCI, there are not many studies that investigated whether the development of depression was due to these complications or the other way around [44,53]. Regarding this topic, all studies included in our review, showed significant results that reinforced the point of view that depression can lead to the development of secondary health complications. In the majority, these medical complications not only interrupt the individual's activities but also keep them in isolation while they increase the clinical severity of their already burdened health status. In addition to that, during the last decade there is a growing interest for studies investigating the role of depression on chronically ill patients, such as diabetes [59-61]. The studies concerning the association of depression and health complications, try to create a conceptual model to explain the way that depression could lead to the development of short-term health complications [62]. However, more studies are required to thoroughly understand and describe the responsible mechanism.

Empirical research showed that depression is not a universal phenomenon or a necessary precursor of adaptation to SCI [9-12,45]. Indeed, these studies suggest that about one-third of patients with SCI experience depressive symptoms, and that the presence of depression can be used as a predictor of poor adjustment to the injury. Also, another study suggested that depression levels increase gradually 48 weeks after the injury [26]. This fact can explain the higher depression levels that are observed in newly injured SCI patients, which gradually decline. Moreover, these surveys make progress towards the functional diagnosis of post-SCI depression as well as the use

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of credible criteria for diagnosis, since the detection of depression in SCI patients is connected with several methodological issues that make the interpretation difficult [66]. In addition, the significant correlations that have been reported between depression and medical complications by these studies, suggest that depressive symptoms can be used as a tool to detect patients with preventable health complications from those admitted for routine examinations or for other reasons.

Since depression has such an effect on hospitalization as well as rehabilitation of SCI patients, many researchers suggest the administration of antidepressant medication, especially for patients that have severe symptoms [63]. However, it was demonstrated that the usage of antidepressant medications by SCI patients not only extended significantly the length of stay but also led to worse functional outcomes [64]. One possible explanation for this may be that the use of antidepressants may interfere with the recovery of the nervous system that occurs during rehabilitation, especially when this takes place relatively early after the injury. Another explanation might be that the patient may have some untreated symptoms that limit the effectiveness of rehabilitation, and this fact subsequently leads to the administration of antidepressants.

In a prospective study that investigated the association between several health factors and the mortality risk of SCI patients, it was shown that depression was one major health predictor among surgeries, infections as well as fractures [67]. Therefore, it is of the utmost importance both for the rehabilitation and for the general health of the individuals with SCI to early detect and treat depression to obtain optimal results [65]. Also, it is suggested by the majority of the studies included that SCI depression targeted interventions should aim at factors as self-management and self-efficacy to improve depressive symptoms in these patients. Hence, these interventions can also improve other outcomes such as medical complications and QOL of the individual with SCI.

It has been reported by several studies that during the rehabilitation process of SCI patients it is of great importance to minimize patients' psychological distress, which can also help to develop better self-management behavior [26]. Furthermore, it was demonstrated that some SCI patients, during the first three months post injury, were more prone to develop depressive symptoms that disrupt their daily activities [68].

In conclusion, this review manifested that depression affects significantly both hospitalization and rehabilitation of patients with spinal cord injury. In more detail, the studies that met our inclusion criteria showed that depression played an important role on prolonging LOS of SCI individuals in health-care facilities, which by result increased costs both for patients and the health-care system. Moreover, it was demonstrated a strong connection between depression and secondary health complications, mainly urinary tract infections and pulcer ulcers, which also decrease patient's quality of life. At last, depression was found to be associated with poorer functional outcomes for patients with SCI. Therefore, it is necessary that health professional should seriously considered these aspects that depression has on individuals with spinal cord injuries to have appropriate treatment as well as better functional capabilities. Simultaneously, early detection and treatment of depressive symptoms can lead to reduced costs both for the patients and the health system of each country.

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# Factors that prolong hospitalization of patients with spinal cord injury

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## ABSTRACT

Spinal cord injury (SCI) is a severe condition which can cause damage to the sensation as well as to the motor function of the individual. Many factors have been reported to affect the length of stay (LOS) of the SCI patient in the hospital or the rehabilitation center. These factors vary among different countries, and therefore the LOS also varies. The purpose of this review is to investigate the existing literature to detect factors which may prolong hospitalization of patients with SCI. Identifying these parameters can help minimize the length of hospital stay as well as the costs and also complete rehabilitation within a required period of time. The 40 studies that were included manifested that demographic factors such as age, gender and marital status did not seem to contribute to extended hospitalization whereas both severity and etiology of injury and secondary medical complications were significantly associated with longer LOS. Moreover, prolonged length of stay of SCI patients has been associated with hospital determinants, e.g. the institutional facility and the insurance status of the patient. However, since the studies that investigate the role of hospital factors on LOS are few, more studies are required on this subject in the future.

**KEY WORDS: SCI, hospitalization, rehabilitation, length of stay**

**Introduction**

Spinal cord injury (SCI) is a devastating condition that can cause damage or loss of sensation and motor function, as well as dysfunction of multiple organs [1]. It can also lead to functional, psychological and socioeconomic disorder [2]. The annual incidence of SCI in various countries varies. More specifically, the incidence rates of SCI in the developed countries range from 13,1 to 163,4 [3-4] per million people, with similar rates in developing countries (13,0 to 220,0 [5-6] per million people). In Greece the incidence rates are 33.6 per million people [7]. Also, the causes of these injuries vary, with some of the most common being motor vehicle accidents, falls, sports-related injuries, violence related injuries and occupational injuries [8].

There are many factors affecting the length of stay in patients with SCI, which varies among different countries due to medical issues and/or the country's health care system. It has been reported that the median number of hospitalization of SCI patients in Australia is 133 days, in United States 20-74 days, in Italy 91-143 days, in the Netherlands 154 days, in Spain 198-222 days, in Denmark 149-285 days and in Israel 239 days [9-11]. It is understood that a prolonged hospital stay for patients with SCI can impose great burden both to the individual and the health-care system [12]. It was estimated that the direct cost of a patient with spinal cord injury was $85 565 288.00 [13]. Therefore, it is important to identify and understand the factors that affect long of stay in hospital for these patients.

According to the literature, the determinants that may prolong hospitalization for spinal cord injury patients are classified as either personal or factors mainly related to the hospital [14, 15]. The personal factors include age, severity

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of injury, degree of disability on admission, marital status, other demographic factors as wells as the development of secondary medical complications mainly urinary tract infections, respiratory infections, and pressure sores [16], whereas hospital factors comprise the type of the institution (public or private), the availability of beds and staffing levels [17].

Most of the patients with spinal cord injuries receive rehabilitation after their discharge from the hospital, to address the impact of their injuries, since rehabilitation aims to help patients' restore range of activities and active participation in all aspects of human life, maximize independence and prevent further complications. Rehabilitation can also enhance patients' emotional adaptation as well as promote reintegration into the community [18]. Early rehabilitation of SCI in an organized multidisciplinary care system has been shown to be beneficial, as it offers lower mortality, reduced pressure ulcers, slightly greater chances of neurological recovery and shorter length of stay which therefore results to lower hospital costs [19].

The aim of this study is to review the existing literature to detect factors which may prolong hospitalization of patients with spinal cord injuries. Identifying these parameters can help minimize the length of hospital stay and also complete rehabilitation within required period of time.

For this purpose a literature review was conducted in a scientific publication resource, the MEDLINE (PubMed) (https://www.ncbi.nlm.nih.gov/pubmed). Temporal criteria were applied in order to access the literature of the last 30 years (from 1987 to 2020). In the research were included only articles published in English language. The keywords applied regarded spinal cord injury, prolonged hospitalization, and length of stay. The search of the databases returned 6315 articles. Publications that did not match the research criteria were excluded from the study. The final number of articles were 40.

**Discussion**

According to Post et al., the term length of stay (LOS) is determined as the time between the first admission and the final discharge from the hospital or other health care facility [20].

Our search revealed 40 papers that were relevant with this topic.

Of these included studies, 34 investigated the personal factors that affect LOS of patients with spinal cord injuries while 6 studies analyzed the connection between hospital factors and LOS in these patients.

As far as personal factors are concerned, the main determinants according to the included studies are age, gender, and marital status of the subject, as well as the presence of medical complications, the severity and the etiology of the injury [15].

There are many studies that have demonstrated that the patient's age plays an important role in the length of stay following SCI. In more detail, a study that included 284 patients with SCI, showed that older patients tented to have shorted LOS in comparison to younger patients [21]. However, in this study older SCI patients also had more complications and therefore worse outcome in comparison to younger patient group of the survey. Moreover, in a study conducted by Roth et al., the results were similar with the above mentioned [22]. A recent study that investigated several predictors of 529 patients with SCI, demonstrated that age, among others, was a significant factor [23]. The authors showed that younger patients (≤ 45 years old) had longer LOS. These results were also confirmed by another study on patients with traumatic spinal cord injuries [24].

However, the results of other studies were contradictory. A large scale study showed that no significant differences were found between LOS and age, however rehabilitation time were greater for older patients [25]. De Vivo et al., conducted a large scale study investigating SCI patients over a period of 13 years [26]. The authors concluded that age was not a risk factor that prolonged hospitalization. There are additional studies, also verifying these results [10, 11, 27-31].

Another demographic characteristic that may affect hospitalization is gender. An early study conducted in SCI patients in Saudi Arabia showed that male patients with SCI were more prone to have longer LOS in comparison to female patients [28]. Contrariwise, Ronen et al., concluded that male SCI patients did not have statistically greater LOS when compared to female patients [11]. Similarly, an earlier multi-center study examining the correlation of gender and rehabilitation LOS demonstrated no statistically significant association between gender and LOS in patients with spinal cord injury [32]. Also, Milicevic et al., in their study reported that gender was not associated with longer LOS of SCI patients [23]. A similar study that took place in Ankara, Turkey reported that gender was not a significant predictor for prolonged hospitalization [29]. Despite the above, there have been studies that concluded that demographic factors such as age and gender are not statistically significant deter-

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minants of LOS in these patients [10, 30].

Marital status is also another demographic factor that has been investigated as a possible predictor of prolonged stay in SCI patients. Specifically, Go, DeVivo and Richards reported that more than 50% of SCI patients in their study were single at the time of the injury, while 30% were married [33]. A later longitudinal prospective study demonstrated that no statistical significance between the marital status of patients and LOS was detected [34]. However, we must emphasize that most of the patients included in this study were married. Norton, in his study, reported that 45% of SCI patients in Australia were either married or in a serious relationship [9].

There are also studies that underline the importance of the severity of the injury in LOS. Specifically, Pompei et al., found a great correlation between the severity of injury and LOS, in patients with spinal cord injury [35]. Many studies also confirmed these results. A study that investigated the role of complications in 191 patients with SCI showed that the more severe the injury of the spinal cord and the vertebral column, the greater the LOS [30]. Similarly, in a study that investigated whether hemoglobin and albumin could be used as predictors of LOS in spinal cord injured patients, it was shown that patients with more severe injuries also had longer LOS [36]. Additionally, a study that included 1367 patients with spinal cord injuries demonstrated that the severity of the injury was statistically associated with higher LOS [11]. Al-Jadid et al., (2010) conducted a retrospective study in Saudi Arabia that verified the above mentioned results [28]. In a similar study conducted in Turkey, the researchers showed that patients with tetraplegia had longer length of stay in comparison to paraplegic patients [29]. Another study also confirmed the above mentioned results [37]. Moreover, Norton, states that severity of injury can be used as a predictor of prolonged hospitalization for SCI patients [9]. Also, another study concluded that SCI patients with complete injuries were more prone to prolonged stay in health facilities in comparison to those with incomplete injuries [38]. The results of a retrospective study that took place in Serbia were in accordance with the results of the other studies presented here [23]. However, a study conducted in patients with spinal cord injury in Korea revealed no correlation between the severity of the injury and LOS. Therefore, the researchers concluded that other factors, mainly socio-psychological, prolonged hospitalization in theses SCI patients [10].

The etiology of injury is another factor that may affect hospitalization length in patients with spinal cord injury. Ronen et al., concluded that SCI etiology was correlated with LOS [11]. The authors showed that patients with traumatic SCI presented a statistically significant greater LOS in comparison to patients with non-traumatic SCI. A multicenter retrospective study that included 859 SCI patients also demonstrated that patients with traumatic spinal cord injuries had longer LOS than non-traumatic ones [39]. Other studies also confirmed these results [40, 41]. Also, Al-Jadid et al., manifested that non-traumatic SCI patients had much shorter LOS than traumatic SCI patients regardless the age [28]. Similar results were reported from a Turkish study [29]. The findings of another study that compared LOS of patients with traumatic and non-traumatic spinal cord injuries support the fact that the first have longer length of stay than the second ones [42]. Jang et al., demonstrated that patients with traumatic SCI stayed longer in health facilities [10]. Specifically, they reported that SCI traumatic patients, due to motor accidents, had longer LOS compared with SCI patients due to other causes. Yet, there is a study that reports that although patients with traumatic SCI have more severe lesions and therefore more problems and complications, no statistical significance was revealed between etiology and LOS [43].

Additionally, it is quite common for patients with spinal cord injury to present medical complications during or after the acute phase of injury [44]. According to the literature, the most frequent complications include pressure sores and infections such as urinary and respiratory tract complications [45, 46].

It has been estimated that 17% to 33% of patients with SCI will develop pressure ulcers [47]. A study conducted on SCI veterans showed that the majority of the patients would develop pressure sores during the first year of the injury, no matter the treatment that was used [47]. Also, the same study reported that a predictor for the development of pressure ulcers was the longer sitting time at discharge, showing the importance of early mobilization in these patients. An earlier retrospective study that included 176 SCI veteran patients, also confirmed the above mentioned results as it demonstrated that 35% of these patients had a recurrent pressure sore [48]. Moreover, Milicevic et al., also confirmed that SCI patients that developed pressure ulcers had a significant longer LOS [23]. A study conducted in Italy showed that pressure ulcers were the major complication in patients with SCI and therefore a factor for longer hospitalization [24]. Similarly, other studies also demonstrated similar results [39,49,50]. In a study investigating the prevalence of

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pressure ulcers in SCI patients in the United Kingdom, the authors demonstrated that this secondary complication was a strong predictor of longer hospitalization. Moreover, in the same study it was shown that when a patient developed a pressure sore, then his stay at the hospital was prolonged by 55 days [51]. A retrospective five year survey showed that LOS for SCI patients with pressure ulcers was longer than those that did not have this specific complication [52]. A much earlier study also demonstrated that LOS of SCI patients with pelvic pressure ulcers was significantly greater compared to patients with non pelvic pressure ulcers or no pressure ulcers at all [53].

Urinary tract infections (UTI) occur often in patients with spinal cord injuries, prolonging their length of stay [54]. It has been estimated that more 60% of SCI patients will develop a urinary tract infection at some point [55]. A prospective follow-up study that included 128 patients with spinal cord injury showed that these patients were at greater risk of developing UTI, leading to prolonged hospitalization [56]. Another study, reported that the use of catheterization for a period of time greater than five years can cause injuries at the urethra and therefore, in some cases, UTI [57]. Moreover, it has been established that UTI can also develop in SCI patients that are under catheterization [58]. A retrospective study have shown that patients developing UTI stay longer in the hospital and/or rehabilitation center in comparison to patients that do not show any secondary complication [23]. Chu et al., in a nationwide study conducted in Taiwan, reported similar results [49]. Also, a later conducted study in Tianjin, China with 631 SCI patients demonstrated that patients with urinary tract infections had significant longer LOS [50]. In addition to the above, a study that investigated the role of complications and the costs in patients with spinal cord injury demonstrated as well that patients with UTIs had longer LOS [30].

Another complication that occurs often in patients with spinal cord injury concerns the respiratory tract [59, 60]. It has been estimated that the prevalence rates concerning this complication in SCI patients are between 36% to 83% [61]. It can prolong the length of stay either at the hospital or at the rehabilitation center. As it has been described, the development of respiratory complications has been linked with the severity of the injury [62]. In a study that investigated the incidence of respiratory problems in 46 SCI patients, it was shown that pneumonia (63%) was the most common complication [63]. Moreover, the same study showed that, depending on the type of injury, the patients develop different complication of the respiratory tract. A multicenter study that also investigated the incidence of respiratory complications in SCI patients showed that the most common complication was atelectasia followed by ventilatory failure, pleural effusion, and pneumothorax or hemothorax [64]. A later study that examined the lifetime risks for three diseases outcomes, including spinal cord injuries, demonstrated a direct correlation between tetraplegia and respiratory infections, showing that these patients were more prone in developing complications in the respiratory tract [65]. Also, a retrospective study conducted from 1993-1997 showed that SCI patients that developed respiratory complications had longer LOS [66]. The scientists concluded that the respiratory complications were a more important factor of LOS in comparison to severity of injury. Moreover, Post et al., in their study, concluded that pulmonary infections are an important predictor of prolonged stay for SCI patients [20]. Tator et al. showed that respiratory complications increase not only patients' LOS but also the overall cost of stay [8]. Yet, another survey studying the factors affecting LOS in SCI patients in China showed that patients with respiratory complications and infections did not have longer LOS [50].

The hospital determinants that affect LOS of SCI patients include hospital facilities as well as the type of the institution (private or public) [17]. The results regarding the facilities of the hospital are contradictory. Specifically, there are studies reporting that LOS in larger hospitals, with more beds and facilities is longer [67] while others support the exact opposite, meaning shorter LOS for these patients [14].

Moreover, another study regarding the impact of public or private insurance showed that the LOS of patients in public hospitals were longer comparing to private ones [68]. A study conducted in China investigated the factors that affected LOS in 631 SCI patients, including not only demographic and personal determinants, but also hospital determinants as well [50]. The researchers showed that when hospital factors were examined, the location of the hospital was a statistical significant predictor of LOS. More specifically, it was demonstrated that hospitalization in a suburban hospital increases LOS. A recent study aiming to specify factors that determined LOS in patients with spinal cord injury, demonstrated that the healthcare system organization and processes affected LOS of these patients, regardless of patients' demographics [69].

In some cases, it has also been reported that prolonged

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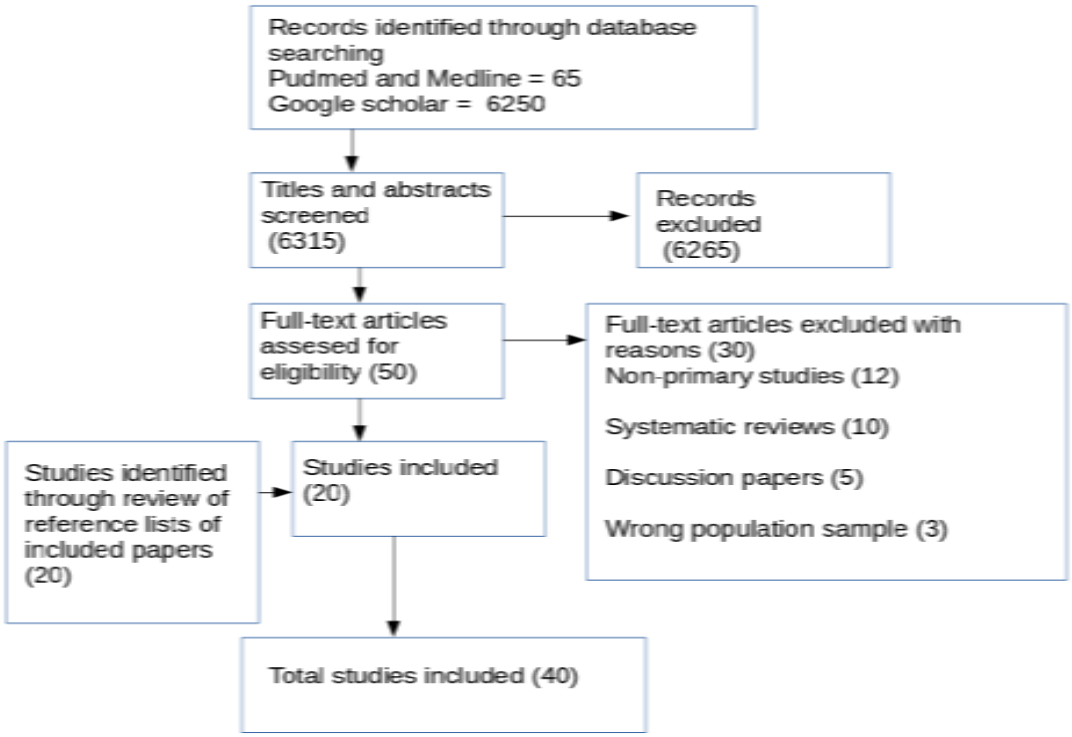


***Table 1**: Flowchart*

hospitalization was due to medical doctors' workload [70]. Nevertheless, literature data is insufficient to support such conclusion.

In our review, we investigated the factors that may prolong the length of stay of SCI patients in health care facilities, such as hospitals and rehabilitation centers. According to the literature, these factors are categorized either as personal factors (age, gender, marital status, secondary complications etc.) or hospital factors (hospital facilities, private or public health care facilities, the health care system of each country etc.).

As far as the age of the patient is concerned the results were contradictory since there were studies that demonstrated that age was a significant factor that determined LOS [21-23] and others that concluded that age did not affect the length of stay of these patients [8, 10, 11, 25-29, 31]. It has been reported that the majority of individuals that are affected by spinal cord injuries belong to younger age groups [71]. This can be explained by the fact that younger individuals are more active, therefore they have greater risk for injuries, including spinal cord injuries. However, age did not seem to cause prolonged hospitalization in the majority of the studies included, meaning that age is not considered a strong predictor of prolonged stay in SCI patients.

Also, gender was another factor that was investigated as a possible determinant of prolonged hospitalization. Similarly, with age our research for gender revealed contradictory results as well. Yet the majority of the studies concluded that gender did not affect LOS [10, 11, 23, 29, 30, 32]. It has been reported that SCI incidence is four times more frequent in males than in females [72]. This was also the case for the most of studies included in this review. This high incidence can be due to the fact that men, in majority, are more physically active and more engaged in outdoor activities therefore they have greater risk for a spinal cord injury in comparison to females. Although, most of the studies presented a higher male proportion than female, the statistical analysis did not reveal an association between gender and LOS in SCI patients.

Only few studies investigated the role of marital status in prolonged hospitalization of SCI patients [9,33,34]. Although 45% of patients with spinal cord injury are married or in serious relationship, no statistically significant connection was found between these two factors.

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Socioeconomic factors also have been identified as a possible factor that affects hospitalization. Another prospective study investigated the role of income, education and occupation in the LOS, showing that patients with lower incomes have longer LOS [73]. A similar study conducted in Jordan showed that socioeconomic factors can affect the length of hospitalization of patients with SCI [14]. In more detail, in this study patients with high socioeconomic status were more prone to have shorter LOS when compared to patients from lower socioeconomic levels. Still, since the studies that investigated these factors are few, more quality studies are needed in order to come to safer conclusions.

The severity of the injury was also investigated in many studies included in our review. All of the included studies underlined the fact that as the severity of the injury increased so did the length of stay of the patients. It was demonstrated that patients with tetraplegia had longer LOS than patients with paraplegia. This can be explained by the fact that quadriplegic patients have more severe injuries and therefore can have more complications than paraplegic patients. Additionally, it has been reported that although injury severity is significantly linked to extended LOS, there are also other factors that present much stronger associations [74]. In more details, physiologic status, and body region injured play also an important role to LOS. Only one study showed no correlation between severity and LOS of SCI patients [10]. This can be due to the relatively small number of patients included in that study.

Several authors have assessed the etiology of SCI and its role in LOS. All studies demonstrated that traumatic SCI patients have significantly greater LOS compared to non-traumatic patients. However, there was one study concluding that, despite the higher severity of lesions of traumatic SCI patients, no statistical significance was revealed [43]. The drawback of this survey was that they included a small sample of SCI patients (67 patients).

Furthermore, another study that aimed to determine the role of surgical complications, showed that secondary complications lead to longer length of stay [75]. Specifically, the development of pressure ulcers is quite common in patients with SCI. Many researchers have studied the role that these complications play to LOS following spinal cord injuries. All studies came to the conclusion that pressure ulcers were strong predictors of prolonged hospitalization. A review that investigated pressure ulcers in SCI patients in developed countries manifested that SCI-associated pressure ulcers are frequent and can increase the healthcare costs [76,77]. Furthermore, they are associated with rehabilitation problems, which might lead to a worse functional outcome [47].

Another significant factor of morbidity and mortality that is often seen in SCI is respiratory infections [59]. According to the level of the lesion, SCI patients may demonstrate inadequate breathing and/or coughing capacity, thus becoming more prone to respiratory infections [78,79]. The studies included in this review demonstrated that respiratory complications can lead to increased stay at the health centre [80].

Urinary tract infections (UTIs) are predominant secondary complications in patients with SCI and represent one of the main reasons for seeking medical advice [12, 81]. They are mainly due to the frequent use of a catheter, due to bladder dysfunctions [81]. All studies examining the impact of UTIs in LOS demonstrated an important association between those two factors. In more details, it was shown that patients that developed a UTI had stayed significantly longer in the health facility in comparison to SCI patients that did not develop UTI.

According to O'Keefe et al., clinical factors alone represent only 27% of the variation in extended LOS [82]. Prolonged length of stay of SCI patients has been associated with hospital determinants. A study conducted in Turkey, investigated the length of stay in university hospitals [83]. The factors that determined prolonged LOS in this study were the institutional facility as well as the insurance status of the patient. Also, other researchers in a similar study conducted in Jordan, showed that the insurance status of the patient was a strong predictor of LOS [14]. Specifically, patients with insurance had significant longer LOS. Another cross sectional survey that studied hospital stay of the Dutch health care system concluded that inappropriate hospital stay was linked to the lack of health care facilities as well as the lack of appropriate discharge facilities [84].

A retrospective review that examined the factors affecting hospital discharge of SCI patients showed that four factors were significantly related [85]. These factors were the age of the patient, the preinjury living conditions, the insurance status as well as the private funding for specialized assisting equipments. Therefore, it is advised that these factors should be taken into account before discharging an individual with SCI in the community. Another retrospective study investigating the role of non-clinical factors to LOS of patients

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with traumatic injuries demonstrated that insurance status and discharge location were strongly associated with LOS. [74]. In more detail, patients with Medicaid had significantly longer LOS in comparison to patients with commercial insurance. Moreover, patients that were discharged to a nursing home or a rehabilitation facility had longer LOS in comparison to patients that were discharged to other location. These results were also confirmed by other smaller studies [86-88].

Many other hospital factors have been proposed as possible predictors of prolonged LOS including infections acquired at the health care facility, unsuitable clinical facilities, inappropriate stuff training and absence of health care centers [14]. However, in our research we did not find any studies that investigated the aforementioned factors for SCI patients. More studies should be oriented towards this direction in the future.

In conclusion, our review showed that patients' determinants such as severity and etiology of the injury, as well as secondary medical complications can lead to prolonged hospitalization of SCI patients. Additionally, hospital determinants can also affect LOS and result to extended stay in the health facility. Therefore, all these factors should be taken seriously into account by all health professionals to reduce LOS and consequently provide a better functional outcome after rehabilitation. At the same time, the reduction of LOS, apart from achieving improved rehabilitation outcomes, may also assist to the significant reduction of private and health-care system expenses.

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# The use of occupational therapy in the rehabilitation of patients with spinal cord injuries

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## ABSTRACT

**Introduction:** Occupational therapy addresses physical and psychomotor disorders through specially selected activities in order to help individuals achieve the maximum level of functionality and independence in all aspects of their lives. The role of the occupational therapy in the rehabilitation of patients with spinal cord injuries (SCI) is complex. Its main goal is to compose and intertwine all the skills so that the SCI patient is able to have an independent, happy and productive life. The purpose of this study is to review the role of occupational therapy in the rehabilitation of SCI patients.

**Material and methods:** In the PUBMED database the following search was done with the following keywords: "occupational therapy", "spinal cord injuries". The search results showed 413 papers. After checking titles, abstracts and accessibility to full texts, 297 articles were rejected. Of the 116 publications evaluated, 35 were rejected for various reasons. So there are 81 studies left for this literature review.

**Results:** Occupational therapy has been proven to have a significant role in the rehabilitation of SCI patients as it facilitates motor retraining, basic functional movements, home alterations, gait training, wheelchair use, personal independence, entertainment and return to work to SCI patients. Occupational therapy is an important parameter of SCI patients rehabilitation, as it helps them to regain the skills they possessed before his injury, to be re-trained in the roles of daily life and to learn ways to repair shortcomings. Moreover, it helps SCI patients to fulfilldaily activities, such as clothing, nutrition and personal hygiene, and to improve memory, attention, perception and concentration. Ongoing research gives us hope for further improvement in the care and treatment of SCI, but even when new developments are used in practice on a daily basis, the neurological rehabilitation team is fundamental to tackling these patients, so that they can have a productive life.

**KEY WORDS: Occupational therapy, Rehabilitation, Spinal cord injuries**

## Introduction

Spinal cord injuries (SCI) are caused by a variety of reasons, including trauma. Regardless of their pathogenesis, these lesions lead to significant impairment of motor and sensory function[1]. Patients with a complete SCI are less likely to recover (less than 5%). If 72 hours after the injury, there is still complete paralysis, the chance of recovery is virtually zero. At the beginning of the 20th century, mortality one year following SCI, in patients with complete damage, reached 100%. The improvement in prognosis has since been large-

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ly due to the introduction of antibiotics to treat pneumonia and urinary tract infections. The prognosis is much better for incomplete SCI.If some sensory ability is maintained, the patient is more than 50% more likely to walk. Eventually, 90% of patients with incomplete SCI return to their homes and regain their independence[2].

Traumatic SCI is one of the most serious injuries and, given prolonged survival, rehabilitation is essential. The main objectives of the rehabilitation are the prevention of secondary complications, the optimization of bodily function and the reintegration into the community. Rehabilitation of SCI is most effective when an interdisciplinary, group approach is applied [3-5]. Physiotherapists usually deal with lower limb function and mobility difficulties. Occupational therapists deal with upper limb dysfunction and difficulties in daily life activities. Rehabilitation nurses deal with bowel and bladder dysfunctions and the treatment of bed sores. Psychologists deal with the issues of behavior and emotion that occur in the recently injured patient and with possible cognitive impairments.The rehabilitation team operates under the guidance of a spine-physician. Although each member of the rehabilitation team has his or her own field of employment, they all work together, collectively and in a team spirit, to address emerging problems[6].

The reason for the intervention of occupational therapy is to help SCI patients who have not acquired the required skills at all, or who have lost them or they are no longer sufficient. The main goal of occupational therapy programs is to compose and intertwine all the skills so that the SCI patient is able to have an independent, happy and productive life[7]. The role of the occupational therapy is complex. The occupational therapist, understanding the importance of projects and activities in people's daily lives, works with SCI patients of all ages who have dysfunctions and / or disabilities, restrictions on the execution of projects and activities of their daily lives, and / or difficulties in equal social participation [8,9].The purpose of this study is to review the role of occupational therapy in the rehabilitation of SCI patients.

**Material and methods**

In the PUBMED database, a search was conducted with the following keywords: "occupational therapy", "spinal cord injuries".

The search results showed 413 papers. After checking titles, abstracts and accessibility to full texts, 297 articles were rejected. Of the 116 publications evaluated, 35 were rejected for various reasons. Thus, there are 81 studies left for this literature review.

**Results**

Occupational therapy is one of the major pillars of rehabilitation, focusing on improving activities of daily living performance and fine motor activities [10-14]. Its benefits on the functional independence of SCI patients have been proven by many high-quality studies [6,15-25]. The greatest amount of time of occupational therapy is spent on interventions for improvement of muscle power, walking and hand rim wheelchair propulsion [26,27]. The timing of occupational therapy is important, as decreasing the time from SCI to initiation of occupational therapy, may improve final outcome [28]. Its contribution to the management of pressure injuries is significant [29]. The results of occupational therapy seem to depend on age of SCI patients, as older patients may experience a different clinical pathway in comparison to younger patients. Older people teen to spend less time in occupational therapy and have higher rates of rehospitalization [30]. However, little is known about the exact timing, nature, therapeutic dose, cost-effectiveness and efficacy of occupational therapy following acute and subacute SCI [31].

*Initial Motor Retraining*

Once the spine has been stabilized and general conditions allow, patients are allowed to sit in bed before sitting in the wheelchair. A brace is usually needed for 2-3 weeks, to avoid intense bending until spinal muscles are strengthened. Patients with cervical lesions use a collar holding the neck in the anatomical position. Initial motor retraining includes static sensation retraining and muscular retraining [32].

The patient with complete SCI has not only lost the sense of touch, pain, temperature and motor strength of the torso and limbs, but also the sense of posture and kinesthesia below the level of the lesion. The retraining of static sensation is achieved by balancing exercises in the sitting position and in the wheelchair [33]. They are mainly performed with the patient sitting on a bench (or wheelchair) in front of a mirror. A pillow is placed under the buttocks as a precaution against excessive pressure. The thighs and legs are well supported so that a right angle is formed in the hips, knees and ankles. The occupational therapist supports the patient from behind with his hands, constantly providing instructions and en-

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couragement. Gradually the patient proceeds to exercises in a self-supporting sitting position, as well as to exercises of the upper limb unilaterally and then bilaterally.It is important for patients with complete lesions to strengthen latissimus dorsi, upper limb muscles, shoulder muscles and abdominal muscles [34,35]. Occupational therapists possess a special role in the selection and management of SCI patients with tendon transfers [36,37].

***Basic Functional Movements***

Immobilization in bed for weeks will cause some degree of trunk stiffness. In order for the patient to learn the activities of daily life, adequate mobility is necessary. For this reason, the mobilization of the trunk in all directions and the stretching of the tight muscle groups are part of the early recovery. The use of the head and shoulder girdle is essential in many functional activities, especially in quadriplegics [38]. In order for the patient to feel confident, the activities must be done on a wide bench. Lifting the buttocks with a push from the hands is the basis of most activities of daily living. Particular attention should be paid to the practice of the following movements, which form the basis for functional activities such as clothing, bed rotation and transport: movement of paralyzed limbs, moving to the sitting and supine position, rolling in the prone position and turning to the side [4]. In the movement of paralyzed limbs, the quadriplegic patient needs to be able to move the lower extremities along the bench, cross one ankle over the other, cross the ankle at the knee and bend the lower extremity in the sitting position. The balance can be maintained when moving the lower limbs by tilting the trunk forward. This position leaves the hands free to lift, push or pull the lower limb. The pelvis should be straight and the patient tilted slightly to one side and forward to keep the center of gravity above the static lower limb. Rolling is achieved by bending the head and shoulders to place the upper limbs to one side and then placing them on the opposite side after a short quick movement. The direction of the upper extremities is transmitted to the lower extremities and the lower half of the body is also rotated [39].

***Home alterations***

The two major problems of patient resettlement are ensuring a proper home and work. The majority of quadriplegic patients return home, often with full support from social services and the family.The home may need modifications or extensions, or it may be completely unsuitable, in which case the only solution is to relocate the patient [40,41].The need for home adjustment varies greatly, depending on the patient's level of damage, age and gender [8]. The most common conversions are those in the bathroom, which are usually small, and in the kitchen. Access to the toilet and bathtub is essential for patients who can be transported independently. In order to cook without unnecessary risk, some adjustments are needed in the cupboards, the electric stove and the height of the kitchen surfaces.Free access to the house from the outside is essential and those who are able to drive will need a parking space wide enough to accommodate the wheelchair next to the car for independent transport.Some patients will need little, if any, special equipment at home, while others will need a lot [40,42].

***Gait training***

Patients with lesions from C5 to C8 use a standing frame or stand upright inside the parallel bars. Unsupervised standing position in the parallel bars promotes static sensation retraining, even for patients with low cervical lesions, because the patient employs all the innervated muscles of the upper limbs and trunk to maintain balance. It is therefore an excellent exercise, even for those who will not be able to walk. Robotic-assisted gait training is an innovative and effective method for the rehabilitation of SCI individuals [43,44].

***Wheelchair Use***

The right choice of wheelchair allows patients to expand their environment and increase community accessibility [45]. For quadriplegic patients, hand-driven wheelchairs are suitable, either the standard light wheelchair or the sports wheelchair. The standard lightweight wheelchair is manufactured by most companies as a variant of the standard models. It weighs about 2/3 of the standard model. Some patients who put the wheelchair in the car all the time prefer this type. The sports wheelchair is a very lightweight wheelchair, weighing less than 12.5 kg and is designed for intense use in sports activities with wheelchairs. Its frame is disassembled and stored in a special box [46]. Proper placement of the patient in the wheelchair is important, so as not to create bedsores and deformations, and the patient to gain maximum stability for independent activity [47]. Protective pads and cushions are important for the prevention of pressure injuries [48-50]. Small tilt angles are suitable for postural control [51]. The posture should be as symmetrical as pos-

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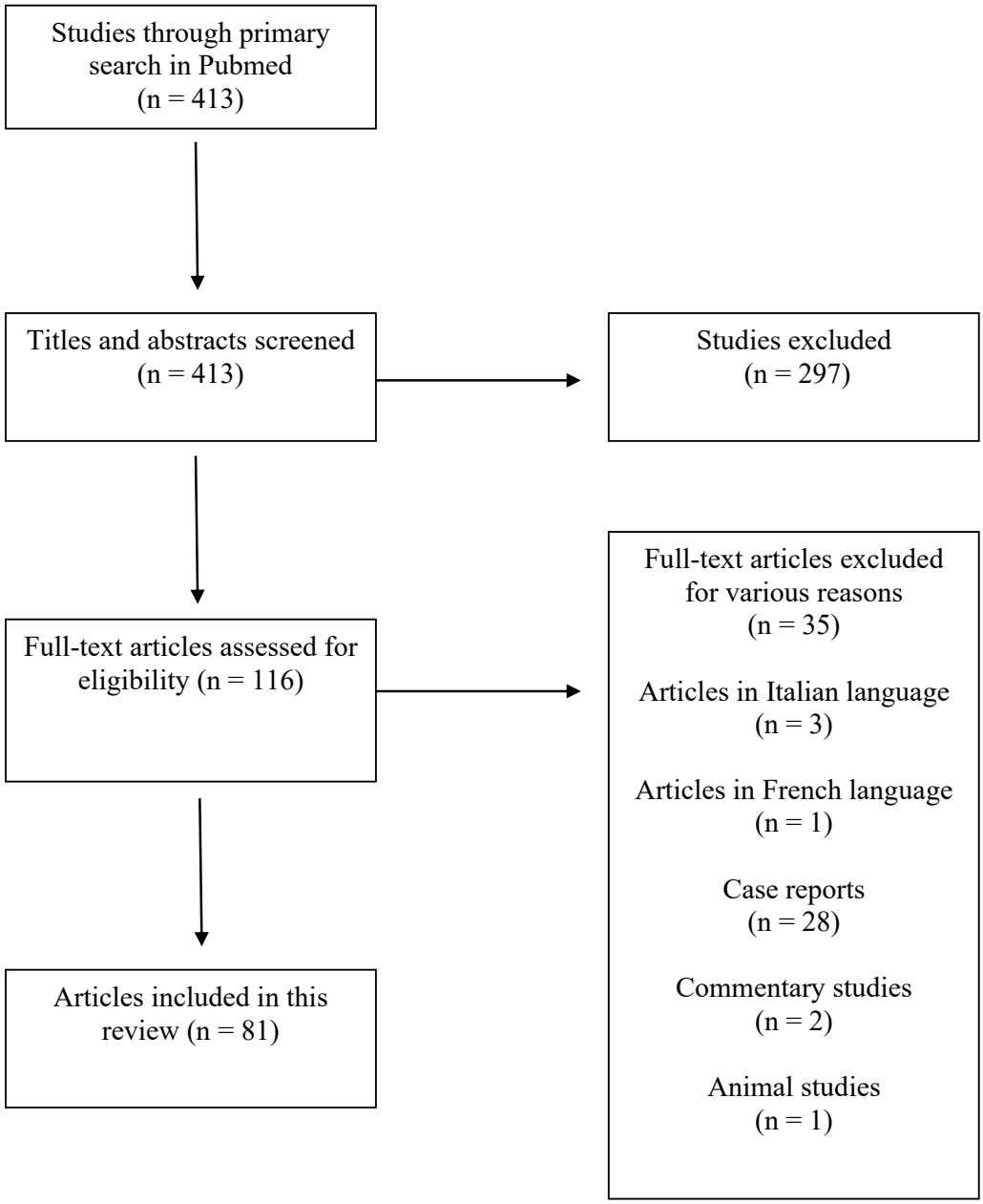
**Table 1. Flowchart**




sible and the weight should be equally distributed through the ischial tuberosities, buttocks and thighs [52-54].

The basic movements in the wheelchair in which the quadriplegic patient should be trained are: use of brakes, subtraction of an armrest, obtaining objects from the floor, extent to the feet and lift the buttocks forward in the wheelchair. The initial maneuvers in which the quadriplegic patient should be trained are: advancement in ground level, use of the wheelchair on sloping ground, turning thewheelchair.In case of advanced maneuvers, the patient should be trained in advancing the wheelchair over a 5-cm step. Instead of the wheelchair, occupational therapists may train SCI patients to use mobility scooters [32,55].

Falls have a major psychological impact for SCI patients [56]. Proper training of wheelchair use has been shown to reduce fall incidence and improve quality of life of SCI patients

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[57,58]. Moreover, it increases the comfort and the satisfaction of SCI patients [59,60].

***Personal independence***

For feeding, SCI patients begin using a strap to hold the fork or spoon, extending and relaxing the wrist. After some practice, the strap is removed and the fork is held in place by balancing it on the thumb and against the palm of the hand or over the little finger [61]. A plate protector can help a lot. For drinking, a cup or mug with a large handle is held in place by hooking the thumb through the handle and extending the wrist. A glass without a handle can be lifted by sliding the fingers and thumb around the glass with the wrist extensors loose, and then the wrist extension will provide the necessary grip. Coated mugs are preferred during training. The most skilled patients will then use regular mugs [62].

For teeth cleaning, the toothbrush is used inside the strap or tied between the fingers. In order for the patient to unscrew the cap from the tube, he holds it with his teeth and rotates the tube with both hands. Teeth can be used to push toothpaste out. The patient can be supplied with special tubes by companies that specialize in the production of products for people with disabilities [62,63]. For hair brushing, most patients find it easier to use a large brush with a long handle.To allow the patient to shave on their own, a soft leather case can be sewn around the razor and a strap can be attached around the dorsal surface of the hand. Many patients learn to handle the razor without this case. The patient moves the razor in place between the fingers and palm of the right hand, with the razor's head projecting between the thumb and forefinger. He then places the left hand around the right, to strengthen the handle [64].

During the period of absence of reflexes, the bladder can be emptied in various ways, such as catheterization of the ureter (intermittent or permanent). As the absence of spinal reflexes subsides, which can last from days to several weeks, two main types of bladder condition develop, the overactive (spastic) bladder and the underactive (flaccid) bladder. Both types of bladder can be emptied, as long as their function is understood; there is gradual training and avoidance of active bladder infection. Bladder training absorbs much of the patient's time, which can be discouraged. But persistence is necessary, because the bladder will gradually be trained. The same training is done for both sexes, but it is absolutely necessary for women as there is no satisfactory catheter on the market. Incontinence diapers are the only protection in case of leaks between discharges or catheterizations. When bladder training is ineffective, the patient learns self-catheterization with anintermittent, but not always regular schedule [64]. For bowel care, the correct training program begins as soon as the patient is on a complete diet. The goal is to transfer the contents of the intestine to the rectum at the same time each day or every other day and remove them with reflex defecation when the patient is prepared. The evacuation takes place either on the bed or in the toilet. For most patients, this procedure is done with aid [64,65].

Computers can be used for work and entertainment. Most patients use a small rod with a plastic edge, attached to anextension splint in the 1st or 2nd finger. Wherever possible, both fingers are used [62,63]. Electronic aids include assistive technology interventions that may facilitate daily activities and improve quality of life [66-68]. Robotic therapy and virtual reality, issued by occupational therapists, has been suggested as a useful tool for upper limb training and improvement of daily living of SCI patients [22, 69-71].

Occupational therapists initiate clothing training as soon as the spine is stabilized. SCI patients need to regain some balance in the sitting position before attempting to get dressed and it is common for them to start by dressing their upper limbs in the wheelchair. Each patient, after learning the basic methods, will find a personal way that will best suit his requirements and daily routine.All clothes must be comfortable. Pants must be at least one number larger than normal to fit the urine collector and not cause injury. The zippers on the side are convenient if the patient has a urine collector. A skirt that folds over and elastic shorts that open at the front is a good choice for women patients who find it difficult to remove their clothes in the toilet. SCI patients usually need shoes that are ½ - 1 number larger than before paralysis, to prevent bedsores and to have space for swelling and spasticity. The inner seams should be smooth and the shoes should stay in place when the legs are raised and should be chosen according to the patient's needs. Since the thumb is used as a hook, in many cases loops or open rings are attached to the movable part of the zipper. The bras should be elastic and free of balloons due to the risk of compression [64,72].

For use of telephone, a telephone device can be modified to allow SCI patients to operate the device without assistance. A special handle can be placed on the handset so that it can catch it and use a typing splint when it wants to make a phone call [62,63]. To facilitate writing, there are several

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small devices for using pencil and pen. It is easy to make small splints that support the thumb and finger [73]. Some quadriplegic patients give up these devices over time and tie the pencil through their fingers or hold it with one hand and put the other on top to strengthen the handle.

***Driving***

SCI patients with injury below C6level are able to drive a car with full independence in transport and in placing the wheelchair inside the car. Getting in the car is done independently, with or without the use of an auxiliary board. Driving requires certain modifications.The transmission should be automatic.A fork or ball on the steering wheel mayreplace the deficit in the catch. The brake and accelerator should be handled with the upper limb [74]. The ability of SCI patients to drive depends on the level of the lesion and the toilet transfer ability [75].

***Sports***

Exercise in clinical practice has made a significant contribution to the rehabilitation of SCI patients. It helps to restore the patient's strength, balance, synchronization and endurance. It stimulates the activity of the mind and promotes self-confidence and interaction [76]. Adapted sports are beneficial for SCI patients as they improve functionality, oxygen uptake, agility, motor skills and quality of life. Moreover, they reduce risk of complications and hospitalizations [77].

Swimming, archery and table tennis have a special value in recovery. Swimming increases muscle strength, improves synchronization, reduces spasticity and contractions, while mobilization in the water is often the only experience of independent body movement for quadriplegic patients, thus promoting the development of independence and personal expression. It also offers an additional opportunity to socialize with the community [78]. The Halliwick method of water independence training suggests that the swimmer must first adapt to the water and then learn to change his position in the water so that he can move on his own in positions where he can breathe [79].

Archery has been shown to be an ideal sport for SCI patients, both for medical and recreational purposes. Special equipment is required for the quadriplegic patient to shoot with an arc. A hook is used to release the arrow without bending or stretching the fingers. A small hook is attached to the edge of a metal splint, which is attached to the palmar surface of the middle finger and extends to the wrist of the hand that stretches the string. The archer performs a slight prolapse of the forearm to release the string [80].The therapeutic value of table tennis includes improvement of hand-eye synchronization, and wheelchair agility. For quadriplegic patients, an adjustable racket has been developed, in which the angle of the racket surface changes with respect to the handle. The racket is firmly attached to the hand using an elastic glove [81]. Hand-cycle training has proven to be beneficial for SCI patients, as it improves physical capacity [38,82].

***Entertainment***

Entertainment activities require special attention. The accessibility of these activities is a primary goal. Therefore, the occupational therapist should facilitate the adaptation of the activities to the skills of the SCI patient, especially when there is no possibility of work. Entertainment activities take place either inside or outside the home. At home, leisure activities include reading, watching TV, playing games, listening to music and crafts. Outside the home, there are plenty of activities such as meetings, conferences and visits to cultural venues such as theater, cinema, museums, libraries and art galleries[8]. Listening to and creation of music has been proven to be quite beneficial for SCI patients as it promotes self-esteem, emotional expression and encourages their reintegration into the community [83].

***Occupational employment***

Occupational employment is highly meaningful to SCI patients [84]. Return to work is not possible unless the duties of the job correspond to the functional capacity of the SCI patient and the possibility of regulating issues such as accessibility, the organization of the workplace, the organization of daily care and the possibility of freedom of movement [85]. In the opposite circumstances, it is necessary to change the situation, which is achieved by the change of job within the same work environment or retraining. This can happen either in a specialized rehabilitation center or in the form of a seminar on workplace training. In any case, patient motivation is a key factor in the success of such programs [8,86,87].SCI patients without higher education or lack viable employment to return to after SCI seem to be vulnerable in return to work [88].

***Sexual Health***

SCI has heavy impact on sexual health of patients, causing temporary or permanent sexual dysfunction. An occupa-

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tional therapist may serve as a sexual health clinician, who can assess and manage sexual problems of SCI patients [89].

***Complementary therapy***

It has been shown that complementary therapies provided by occupational therapists (yoga, Pilates, tai chi, aromatherapy and relaxation techniques) are beneficial for SCI patients in terms of pain reduction [90].

SCI remains a devastating damage to the nervous system. Modern treatments have not been shown to be particularly effective in preventing or reversing SCI. In addition, every effort should be made to maintain the remaining operation and prevent complications. The treatment of these patients has improved significantly with the development of special centers. The emphasis in this treatment is on restoring and adapting to disability as well as preventing secondary disabilities. SCI patients are initially completely dependent on their surroundings and need special care in order to become independent members of the community again.

The involvement and contribution of the occupational therapy is a fascinating challenge. Occupational therapy is an important parameter of a SCI patient's rehabilitation, as it helps him to regain the skills he possessed before his injury, to be re-trained in the roles of his daily life, to learn ways to repair his shortcomings, and ways to ergonomically adjust home or professional space. The goal of occupational therapy is to enable SCI patients to engage in daily activities, such as clothing, nutrition and personal hygiene, and to improve memory, attention, perception, concentration. Ongoing research gives us hope for further improvement in the care and treatment of SCI, but even when new developments are used in practice on a daily basis, the neurological rehabilitation team is fundamental to tackling these patients. It is important that efforts continue to be made to integrate people with disabilities into society so that they can lead a full and productive life.

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# Spinal Stenosis Pain: Primary Management
# Spinal Stenosis: Primary Management

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## ABSTRACT

As spinal stenosis affects a large number of patients compromising their quality of life, pain management is of vital importance. The purpose of this study is to review the methods of pain management in patients with spinal stenosis, in hospital, in doctor's office and at home.

A thorough search was performed at the online PUBMED database using the following keywords: "conservative treatment" OR "non-surgical treatment" OR "conservative management" OR "non-surgical management" AND "pain" AND "spinal stenosis". The search results showed 253 posts. After checking titles and summaries, 131 articles were rejected as not relevant with pain management in spinal stenosis. Of the 122 publications that remained and were evaluated, 29 were rejected for specific reasons. Thus there were 93 studies left for the current review.

Pain management of patients with spinal stenosis is initially conservative, especially if the symptoms are simply numbness and pain. Conservative treatment includes analgesic drugs, physical therapy, steroid injections and acupuncture. However, there is little high quality evidence for the evaluation of non-operative treatment of pain due to spinal stenosis. When conservative management is inefficient, operative treatment displays satisfactory results.

**KEY WORDS: spinal stenosis, pain, primary management**

**Introduction**

Spinal stenosis is defined as a condition in which there is a narrowing of the spinal canal, with subsequent pressure on the spinal cord or spinal nerves. It may be congenital or acquired. The acquired type of spinal stenosis is usually degenerative, and therefore occurs mostly in middle-aged or older people (over 50 years of age) (1).

In addition to the spinal canal, stenosis may involve lateral foramina. It is more common in the lumbar spine, less in the cervical spine and very rarely in the thoracic, where the range of the spinal canal is smaller and the allowable spinal and disc movements are much less. Spinal stenosis can impair nerve roots and cause damage to the distribution of the root being pressed. In more severe cases, in the cervical spine, it can cause cervical myelopathy and in the lumbar spine it can cause cauda equina syndrome. (2).

The most common symptom of lumbar spinal stenosis is neurogenic claudication, which is defined as "pain from intermittent compression and/or ischemia of a single or multiple nerve roots within an intervertebral foramen or the central spinal canal" (3). Back pain can range from simple discomfort to very severe pain. The pain is always aggravated by standing and walking, while it is reduced with the patient sitting or bending forward. This is due to the fact

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that, during extension of the lumbar spine, the spinal canal narrows, while in the sitting or forward bending positions, the canal is widened and the patient is relieved. Numbness and tingling in the legs are often reported, and some patients complain of leg cramps during sleep at night (4).

As spinal stenosis affects a large number of patients, compromising their quality of life, pain management is of vital importance. The goal of this study is to review the methods of pain management in patients with spinal stenosis, at hospital, at the doctor's office and at home.

A thorough search was performed at the online PUBMED database with the following keywords: "conservative treatment" OR "non-surgical treatment" OR "conservative management" OR "non-surgical management" AND "pain" AND "spinal stenosis".

**Discussion**

The search results revealed 253 posts. After checking titles and summaries, 131 articles were rejected as non-relevant with in spinal stenosis' pain management. Of the 122 publications that remained and were evaluated, 29 were rejected for specific reasons, leaving 93 studies for the current review (Table 1).

The initial approach of any patient with spinal stenosis should be conservative, in order to improve its clinical symptoms, especially pain. Conservative treatment may include the use of brace, physiotherapy, exercises, steroid injections, anti-inflammatory and analgesic drugs (5-9). It should be noted that the goal of conservative treatment is to relieve pain, improve claudication and overall quality of life of the patient, but it is impossible to widen the spinal canal with conservative measures (10,11). A large percentage of patients with spinal stenosis have a satisfactory response to conservative treatment and no surgery is required. The effectiveness of conservative treatment is checked within 3-6 months; if there is no improvement in the patient's quality of life, then he should resort to surgery (12-15). Conservative treatment may be more beneficial for young patients in comparison to elderly patients, where surgical management may have superior results (16).

**Conservative treatment**

***Analgesic drugs:*** a variety of per os and topical analgesic drugs are available to treat pain of spinal stenosis, including opioids and non-opioids, and adjuvant analgesics. These drugs include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids that can be administered at home or at hospital.

Paracetamol, although less effective for acute pain than NSAIDs, is a reasonable first choice treatment because of its favorable safety and cost profile. It has analgesic but not anti-inflammatory properties (17). In combination with opioid analgesics, paracetamol can be administered for severe pain. NSAIDs are among the most commonly used drugs for musculoskeletal pain due to their established efficacy, as anti-inflammatory and analgesic agents. Their effectiveness has been documented in numerous acute and chronic conditions of musculoskeletal pain including spinal stenosis (18-20). NSAIDs are generally preferred over opioids due to their established efficacy and limited potential for abuse. However, they have a number of side effects (cardiovascular, nephrotoxic, gastrointestinal) and the risk of complications is dose-dependent. For this reason, increasing the dose of an NSAID should be done with caution and alternative therapies should be used if the effectiveness does not increase (20). Paracetamol and NSAIDs are generally effective for mild to moderate musculoskeletal pain and their activity is enhanced when given in combination (21).

Opioids are used in cases where paracetamol and NSAIDs cannot achieve adequate pain control (22). Opioids are usually kept as a second-line treatment for musculoskeletal pain that does not respond to paracetamol and NSAIDs. Despite the effectiveness of morphine and its opioid analogues in the acute regulation of pain, these drugs generally have poor efficacy in the regulation of chronic pain. This can be attributed, in part, to patients' tendency to develop tolerance to these drugs and the impact of side effects (constipation, nausea, indigestion, headaches, euphoria, confusion, drowsiness, lethargy, urinary retention) associated with opioid administration. However, these risks are often overestimated, and opioids are often the only option for severe pain and may be a good option for specific groups of patients, such as the elderly. They can also be an alternative when long-term NSAID treatment is not recommended (23). For spinal stenosis, prolonged opioid use has been correlated with female sex, obesity and prior opioid use (24). In these patients, opioids may be used perioperatively at lumbar decompression and spinal fusion surgery (25, 26).

Muscle relaxants have been shown to be effective in patients with pain-associated muscle spasm, but the magnitude of the effect could not be measured. A systematic review found strong evidence that some muscle relaxants are superior to placebo in treating acute low back pain, but

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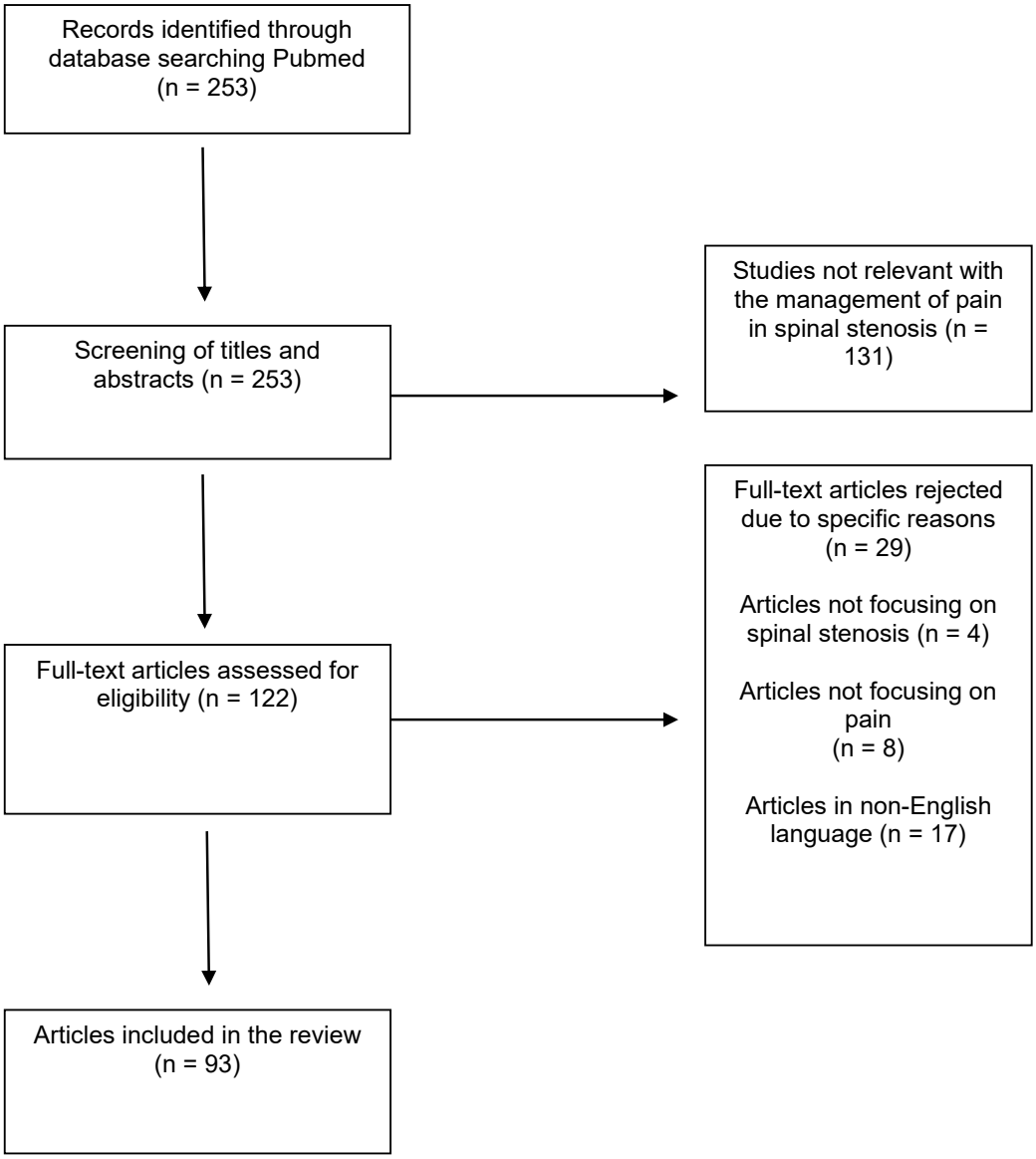
**Table 1.** Flowchart of the study




there is little evidence of their efficacy in treating chronic low back pain (27). Alternatively, for chronic musculoskeletal pain, tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors may be used. These drugs increase the levels of serotonin, norepinephrine, and / or dopamine in the central nervous system. It is believed that the increased concentrations of these neurotransmitters lead to the downward regulation of pain transmission (28). Gabapentin has been observed to improve pain intensity, but causes mild to moderate drowsiness and/or dizziness (29). Pregabalin has been administered in the treatment of neuropathic pain in patients with lumbar spinal stenosis where NSAIDs show no benefit (30). One study has shown that calcitonin is superior to paracetamol in relieving pain in patients with lumbar spinal stenosis (31).

***Physical therapy***: physical therapy is a standard treatment of neurogenic claudication; however, current data has not established its role. It is commonly recommended for patients with mild or moderate lumbar spinal stenosis. Physical therapy has three goals: (i) strengthen the muscles around the

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spine, (ii) maintain their flexibility, and (iii) improve patient's balance. Classical physiotherapy may offer a temporary remission of the symptoms, but they may return soon (32-37). It has been found that physical therapy may postpone spinal surgery at least for one year (38). According to a multi-center, randomized study in United States, physical therapy was associated with improvement in quality of life and a reduced rate of progression to surgery, within one year. However, the level of pain was not affected (39). In a systematic review published in 2016, it was demonstrated that exercise is effective in pain reduction and decreases anger, depression, and mood disturbance providing physiological stability (40). There are studies reporting that physical therapy is potentially as efficient as surgery (41,42). The role of exercise is especially important in people with spinal stenosis and can significantly improve patients' clinical symptoms (43,44). However, the short-term efficacy of exercise is not yet established as it is based on low quality data. Exercise should include strengthening of the deep supporting muscles of the lumbar spine and pelvis, treadmill or stationary cycling, lordosis reduction exercises, chest stretching, balance exercises, flexibility training and posture control (45-48). Flexion-distraction exercises of the lumbar spine are effective for pain relief among patients with lumbar spinal stenosis (49, 50). The best combination of these exercises and their frequency, duration, and appropriate setting is unclear (51,52). Evidence has shown that supervised physical therapy is more effective than a home-based exercise program (53-55).

***Steroid injections:*** an important step of the conservative treatment is spinal steroid injections. They are applied right next to the irritated nerves, to control the inflammation, under computed tomography guide (56). Steroid injections appear to provide a good short-term relief for a maximum of 6 months, but their long-term use is questionable (57-59). Spinal infusions have shown promising results, especially, in combination with physical therapy. Their duration, however, ranges between two weeks and six months (60).

Epidural steroid injections are a relatively safe and less invasive alternative to surgical intervention. When compared to NSAIDs, caudal epidural injections containing steroids and local anesthetics provide faster pain relief in patients with spinal stenosis. They are a preferable and low cost choice for the management of subacute/chronic low back and radicular pain, if applied by experienced specialists (61-66). Additionally, the use of local anesthetic, may provide superior pain relief (67). Transforaminal epidural steroid injections are being used widely for controlling radicular pain induced by lumbar foraminal spinal stenosis; however they demonstrate short-term efficacy (68,69). Lumbar interlaminar epidural injections are more efficient than caudal epidural injections in lumbar central spinal stenosis (70). Nevertheless, there are little data that support the efficacy of epidural injections in pain relief in patients with spinal stenosis (71). A systematic review by Liu *et al* observed that epidural injections offered minimal pain relief in patients with lumbar spinal stenosis (72). Friedly *et al* observed that epidural spinal injections of glucocorticoids in combination with lidocaine had minimal or short-term benefit in comparison with epidural injection of lidocaine alone (73). The combination of epidural steroid injections with physical therapy is not superior to epidural injections alone (74). The addition of calcitonin to epidural steroid and local anesthetic injections may reduce pain intensity and analgesics consumption in degenerative lumbar spinal stenosis (75). In terms of adverse events, there is evidence that steroid injections may cause cortisol suppression (76).

***Neuromodulation:*** spinal cord stimulation is an invasive technique that involves epidural implantation of the electrodes, either percutaneously or through direct skin incision requiring a laminectomy. Electrodes must be placed at the exact spinal level, to cover the area of the reported pain (77). Spinal cord stimulation has been shown to be effective against leg pain in patients with lumbar spinal stenosis with a reported analgesic efficacy of 65% (78). The main proposed mechanisms are: (i) the suppression/regulation of abnormal activity of neurons at the posterior horn of the spinal cord, (ii) the normalization of neurons excitability and (iii) the postsynaptic suppression (78).

***Bracing:*** braces and belts used for spinal stenosis aim to reduce lumbar lordosis, thus reducing the width of the spinal canal (79,80). Semi-rigid lumbosacral bracing and lumbosacral corsets have been found to potentially reduce pain (5,81). The proposed mechanism is that an anterior pelvic tilt may reduce the lumbar lordosis and therefore, the associated increase of the volume of lumbar spinal canal may result in improved blood flow to the spinal nerves. Moreover, lumbar braces reduce movement of the lumbar spine and provide additional mechanical support during walking, resulting in improved sense of stability and balance, walking confidence and pain decrease (79).

***Acupuncture:*** it involves the placement of very fine needles on the body and face. Typically 10 to 20 needles are applied. Once the needle is inserted, the patient feels absolutely

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no pain. A session usually lasts from 20 to 30 minutes. The needles are placed not only near the points of pain but also in other parts of the body that are associated with the overall improvement of health (82). For chronic low back pain, acupuncture is more effective for pain relief than no treatment at all, demonstrating short-term functional improvement (83). It has been shown that acupuncture has a significant short-term effect on pain and quality of life in patients with lumbar spinal stenosis (84-87). Oka et al have observed that as far as pain relief is concerned, acupuncture may be superior to physical therapy (88). According to a meta-analysis by Kim et al, pain intensity, functional outcome and quality of life related to lumbar spine stenosis, showed significantly favourable improvement in patients subjected to acupuncture compared with the control group, lasting for up to 6 months post-treatment (89). In patients who do not respond to conventional acupuncture, spinal nerve electroacupuncture may be an effective treatment (90, 91).

**Failure of Conservative treatment**

When conservative treatment is not effective and patients' quality of life is negatively affected, then surgical management is necessary. Predictive factors for surgical management are: (i) cauda equine symptoms, (ii) degenerative scoliosis or spondylolisthesis, and (iii) long disease duration with untolerable pain (92). Surgery is superior to continued conservative treatment. Delaying surgery for a period of conservative management does not affect surgical outcome (93). Moreover, it has been proved that the cost-effect of conservative management versus surgical treatment, for spinal stenosis, is unfavorable (94, 95).

The goal of surgical treatment is the decompression of the spinal canal without compromising spinal stability and the prevention of further structural deterioration. There are many different surgical options for indirect lateral and central lumbar stenosis, including open, minimally invasive and endoscopic procedures. The purpose is the decompression of the compromised neural structures and the provision of pain relief. The gold standard is open posterior decompressive laminectomy, with or without spinal fusion, depending on the disease characteristics and surgeon preference (96).

Minimal invasive lumbar decompression (MILD) has been used for central stenosis direct decompression. Under fluoroscopic guidance, a cannula is inserted through a 6-gauge portal and tissue and bone sculptors are used to perform a minimal laminotomy and resection of the ligamentum flavum so that the affected dural sac or nerve roots are decompressed (57). The method has shown significant improvement in pain intensity and functional outcomes in comparison to control groups (97).

Percutaneous lumbar decompression is effective and safe especially in elderly patients with lumbar spinal stenosis (98). Minimally invasive discectomy may achieve decompression through nucleotomy and indirectly relieves pressure on the exiting nerve root, while minimally invasive transforaminal endoscopic decompression procedures may achieve spinal decompression through either a direct or an indirect approach (99). Radiofrequency ablation technique is a simple and safe alternative method to relieve pain of lumbar stenosis, especially in the elderly. It may reduce the soft tissue component of the stenosis and enlarges epidural space (100).

**Conclusions**

Pain management of patients with spinal stenosis is initially conservative, especially if the symptoms of spinal stenosis are simply numbness and pain. Conservative treatment includes analgesic drugs, physical therapy, steroid injections and acupuncture. However, there is little high quality evidence for the evaluation of non-operative treatment of pain due to spinal stenosis (101). When conservative management is inefficient, operative treatment demonstrates satisfactory results.

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# Neuropathic pain assessment scales in spinal cord injuries: a review of recent data

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## ABSTRACT

Pain due to central or peripheral nervous system lesions, following spinal cord injuries is a widely known pathology, referred to as neuropathic pain.Many inventories have been developed for the evaluation of neuropathic pain, such as the inventory of neuropathic pain symptoms (NPSI) and the short form McGill pain questionnaire 2 (SF-MPQ-2). Neuropathic pain assessment tools represent a significant progress in clinical and in neuropathic pain research and are practical guides for the evaluation of neuropathic pain in patients, especially in primary care settings, providing clinical information for distinguishing neuropathic pain from non-neuropathic pain. Some tools evaluate qualitatively neuropathic pain (mostly used in clinical settings), while others use quantitative parameters (mostly used in research). In this literature review, different neuropathic pain assessment tools are reviewed as well as the usefulness of verbal pain description items, in the classification of pain following spinal cord injuries. Moreover, their predictive validity is considered. According to literature, verbal pain description inventories are not sufficiently specific for the diagnosis and classification of spinal cord injuries pain. Researchers suggest the implementation of multiple variables inventories for pain classification and for the evaluation of their validity either as clinical or research tools.

**KEY WORDS: neuropathic pain, verbal descriptor, spinal cord injury, pain scale, assessment tool**

**Introduction**.

Pain is defined as an unpleasant physical sensation or emotional experience associated with an actual or possible tissue damage. Pain evoked by injuries to the central or peripheral nervous system, known as neuropathic pain, has been studied for centuries. The study of neuropathic pain (NP) on animal models resulted in a better understanding possible mechanisms of NP and in the development of effective treatments [1]. The identification of NP by primary care healthcare professionals has become a field of growing interest and importance. Thus, several clinical evaluation tools have been developed for either clinical or research purposes. Most inventories were developed to distinguish NP from non-neuropathic pain (non-NP) and are based on qualitative parameters, while others quantitative tools were developed for the classification of the severity of NP, the monitoring of the effectiveness of the treatment and are used in research [1]. There are many similarities between the various NP evaluation inventories, with some important differences though. In 1997, the neuropathic pain scale (NPS) was published. A number of publications followed on other NP evaluation tools, developed almost simultaneously in various European countries and the USA. Most of these NP tools

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were developed according to symptoms characterizing multiple types of NP. A remarkable exception is NPS, developed in patients with post-herpetic neuralgia (PHN).The unique content of one assessment tool can give additional validity to one test against another when applied to a specific NP patient who exhibits these unique features [2].

The aim of this study is to critically review the latest scientific literature in order to expose the available data regarding the NP assessment tools and their characteristics. Moreover, it is reviewed the validity of the implementation of verbal descriptions for the differentiation between the types of NP evoked by a spinal cord injury.

A literature review was conducted in a scientific publication resource; the MEDLINE (PubMed) (https://www.ncbi.nlm.nih.gov/pubmed).Temporal criteria were applied in order to access the literature of the last fifteen years (from 01/01/2005 to 01/01/2020). In the search were included only articles published in English language. The keywords applied regarded the injury (spinal cord injury), the type of pain (neuropathic pain) and the assessment tools (e.g. scale, inventory, tool, verbal descriptor).

The Boolean search string applied is: "spinal cord injury AND neuropathic pain AND assessment" and "neuropathic pain AND verbal descriptor".

The search of the databases returned 190 articles and publications that did not match the research criteria were excluded during the reading of abstracts. Articles focusing on the treatment or other types of pain were excluded. The literature was screened and reviewed and the final number of articles was 17. The final articles were reviewed and the data were analyzed through narrative (Table 1).

**Discussion**

Although the scientific community has reached a consensus about the frequency of pain following a spinal cord injury, the definition and classification of this pain is still confusing. This has resulted in an increasing number of different classification systems in literature (up to 29 different classifications until 2002). These classifications are based on various descriptive parameters, resulting in different estimates for the different types of pain following spinal cord injury. Different classification systems, also lead to differences in pain prevalence in the general population. For example, the prevalence of visceral pain is estimated to range from 5-34%, while the prevalence of neuropathic pain due to spinal cord injury is estimated about 14-40% [2]. The overall prevalence of pain, following a spinal cord injury, is estimated about 25-96%, while for severe pain the prevalence is about 30-51%. A main problem, leading to a difference in prevalence is the lack of definition and classification system for the pain following a spinal cord injury, making comparisons between studies arduous [3]. Misclassification due to nomenclature problems and the different definitions used for the same pathology, is a further problem reflected in literature.

The definition of neuropathic pain, following a spinal cord injury reached a consensus in 2011. The International Classification of Chronic Spinal Cord Injury (ISCIP) was adopted by many of the world's leading professional associations on spinal cord injuries and pain. The validity and reliability of this classification was tested [4].Pain characteristics are classified in three grades; Tier 1 (pain type) consists of nociceptive, neuropathic, other and unknown pain, Tier 2 (pain subtype) consists of a further classification according to the location of the pain (e.g. in neuropathic pain, the symptom is further classified according to the level of the spinal cord injury), Tier 3 (source of pain or pathology) consists of a more specific classification according to the site of injury [5]. In this classification, the neuropathic pain caused by spinal cord injuries is described in relation to the neurological rather than the skeletal level of injury. As this may differ between the two sides of the body, the lowest level in the spine with normal sensation or motor function is used[5].

In individuals with pain following a spinal cord injury, it is recommended also the evaluation of the anatomical site, where the pain is perceived, the severity of the pain, the recurrence of pain and the triggering and protective factors. The International Classification of Chronic Spinal Cord Injury (ISCIP) proposes a standard list of pain points, as well as coding schemes for other features. Numbness, defined by the IASP as an unpleasant, abnormal, spontaneous, or causing sensitivity, should be classified only if accompanied by a painful sensation [6].

Several tools have been developed for the qualitative evaluation of neuropathic pain. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) was developed in 2001 and was the first tool for the differential diagnosis of NP from non-NP. It combines items regarding the patient's symptoms and physical examination and requires a trained physician. However, a modified version of the tool has been also suggested, the S-LANSS that can be self-administered by the patient [7]. A score>12 (max. total score24) is indicative of NP with 82% sensitivity and 80% specificity [8].LANSS is relatively simple tool, validated in many languages, with a higher specificity and sensitivity compared to other tools. However, it cannot assess quantitatively the severity of NP [9].

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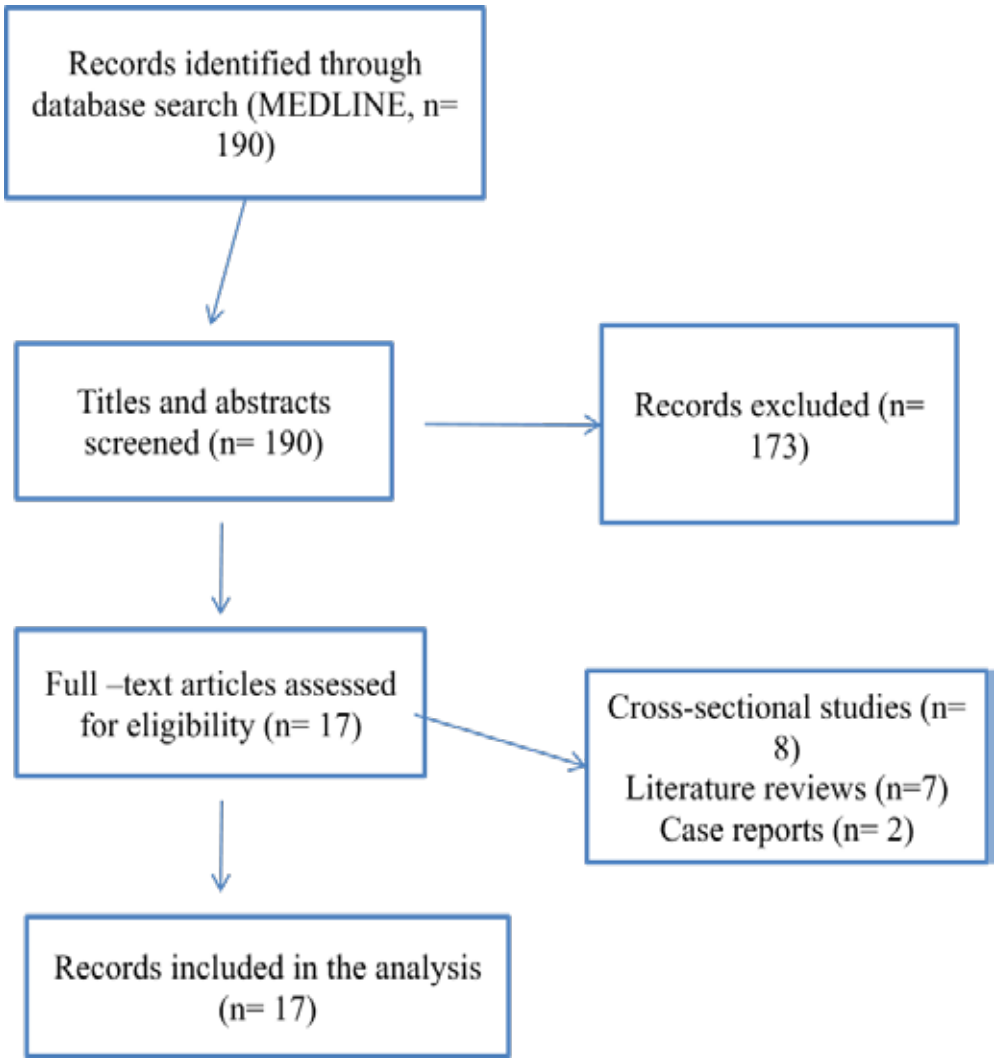
**Table 1. Flow-chart**




The neuropathic pain questionnaire (NPQ) is a self-administered questionnaire of 12 questions about the quality of symptoms (e.g. burning, sensitivity to the touch, numbness, tingling, compression, feeling cold), the aggravating factors and the effect of emotions (discomfort, shock) on pain sensation. The sensitivity and specificity of the questionnaire is 66.6% and 71.4% respectively [8]. NPQ is useful for the differentiation of NP from non-NP and it may be particularly useful for primary care physicians. Moreover, it is the only tool taking into consideration information regarding the impact of weather conditions on the individual's pain, and the psychological impact of NPS [8].

The Neuropathic Pain Diagnostic Questionnaire (DN4) is a four-items questionnaire having a 82.9% specificity and a 89.9% sensitivity for NP screening. It is a quantitative evaluation tool, which has been also used for the evaluation of NP therapy results[8,10].Pain DETECT is a seven-items self-administered questionnaire evaluating the quality of symptoms such as burning, tingling /stinging, numbness and sensitivity to light pressure. The analysis of patients' pain description was included in the development of this tool. The tool has an 85% sensitivity and an 80% specificity [11]. Another self-administered tool for the qualitative evaluation of NP is the ID Pain. This is a quick and easy, six-item questionnaire, that has a73% sensitivity and a 69% specificity. This tool evaluates also the distribution of pain

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[8]. The Standardized Evaluation of Pain (StEP) is a twelve-item questionnaire that has been developed for the diagnosis of NP related to lower back pain due to a peripheral nerve compression. This tool has a high sensitivity and specificity of about 95-97% respectively. However, this test can be administered only by trained personnel [12].

Several tools have been developed for the evaluation of NP in research settings. These are the neuropathic pain scale (NPS) and the modified Pain Quality Assessment Scale (PQAS), which are research tools for the evaluation of the response of treatment in patients with NP, rather than for use in daily practice [3].The Neuropathic Pain Symptom Inventory (NPSI) has been developed for the evaluation of the various symptoms of NP and for the identification of the different subtypes of NP, even those types that are characterized by psychological components. It is a tool that has not been developed for the differentiation of NP from non-NP and it is used in research settings [13]. Another evaluation tool that has been developed for the assessment of NP and the response to therapy, but has a low diagnostic value in the differentiation of NP from non-NP, is the latest version of the Short Form McGill Pain Questionnaire-2 (SF-MPQ-2) [14].

Neuropathic pain assessment tools are an important aid in practice and research and are suitable for providing significant information to diagnose NP or differentiate it from other types of pain. Quality tools are simple and accurate enough to use in clinical practice, and those that have quantitative parameters are important research tools, especially for developing new phenotypic profiles of patients with neuropathic pain based on their symptoms. The use of verbal descriptors in characterizing the individual's pain such as "numbness" or "burning" or "tingling" is common and these labels can be used in the development of NP phenotypes [15].Verbal descriptors are used by most inventories to categorize NP following a spinal cord injury. Unfortunately, the validity of the verbal descriptions for the differentiation between the types of pain that follow the spinal cord injury has not yet been determined. The combination of both quantitative methods and qualitative inventories based on verbal descriptors is recommended, since more information is obtained regarding the individual's pain and a better therapeutic plan can be structured [8]. Moreover, it is emphasized the usefulness of verbal descriptors in NP management for the development of individualized therapeutic plans and the individual's follow up [16]. The experience from a study on cancer patients in Norway, using verbal descriptors for the characterization of the quality of pain, showed that verbal descriptors are a valuable tool in pain definition and management, even though they cannot be used as a single tool for the understanding of the mechanism of the symptom [17].

The development of NP assessment tools has changed the clinical practice of pain diagnosis and management. Advances in the field of research have also been accomplished. These tools provide important information for the diagnosis of NP and the location of the injury. NP tools have different characteristics and some of them have been developed for specific populations, such as the Standardized Evaluation of Pain (StEP) tool that has been developed for the diagnosis of NP related to lower back pain due to a peripheral nerve compression. Tools based on quality parameters are simple and sufficiently accurate to use in clinical practice, and those that have quantitative characteristics are preferred for research purposes. The review of current literature reflects the vast availability of these tools and the thorough study of their characteristics, their validity, specificity and sensitivity in pain diagnosis. The researchers point out the need for further study in the use of verbal descriptors in pain assessment tools and suggest that future studies will provide additional information on the efficacy of these features in both research and clinical practice.

***Conflict of interest disclosure***

*The authors declared no conflicts of interest.*

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# Painful Intervertebral Disc: Cell Therapies

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## ABSTRACT

Intervertebral disc-related low back pain is a common helath issue, responsible for disability for numerous patients world-wide. Disc degeneration is a process with an almost universal development at advancing age and is connected not only with low back pain, but also with disc herniation and neurological deficits. Conservative treatment for discogenic low back pain is mainly symptomatic, often has short effect and/or is inadequate for a subgroup of patients. Surgical treatment is does not address the biology of disc degeneration, is connected with morbidity and may hasten adjacent level disc degeneration. Among the biological treatments being investigated, aiming to hault or even reverse the degeneration process, cell therapy has attracted rising interest recently, including the administration of both autologous and allogenic stem cells and chondrocytes. In this study, it is attempted to review the recent literature concerning application of cell treatment to patients suffering from discogenic low-back pain and highlight certain promising results, as well as future obstacles for further clinical trials and possible clinical application of cell therapy. Twelve clinical trials and case reports have been included, all published since 2006.

**KEY WORDS: Low Back Pain, Intervertebral Disc Degeneration, Cell- and Tissue-Based Therapy, Stem Cells, Chondrocytes**

**Introduction**

Low back pain is an important health issue worldwide. It is a common cause of visit to the doctor, affects a measurable portion of the population and is often connected with disability. Its direct and indirect annual cost at the US economy is estimated up to 500 billion[1]. The degeneration of the intervertebral discs is a common cause of low back pain and disability. Disc degeneration, although in many cases asymptomatic, is associated with sciatica and disc herniation or prolapse. It alters disc height and the mechanics of the spinal column, possibly adversely affecting the behavior of other spinal structures such as muscles and ligaments. In the long term, it can lead to spinal stenosis, a major cause of pain and disability in the elderly [2]. Its incidence is rising exponentially with current demographic changes and an increased aged population [3,4].

The intervertebral discs lying between the vertebral bodies, are the main joints of the spinal column and occupy one-third of its total height [5]. Their major role is mechanical, as they constantly transmit loads arising from body weight and muscle activity through the spinal column. They provide flexibility, allowing bending, flexion, and torsion. They are approximately 7 to 10 mm thick and 4 cm in diameter (anterior–posterior plane) in the lumbar region of the spine. The intervertebral discs are complex structures that consisting of a thick outer ring of fibrous cartilage (the annulus fibrosus),

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and a gelatinous core (the nucleous pulposus). The fibrous ring is made up of a series of 15 to 25 concentric lamellae of alternating oblique collagen fibres, lying parallel within each lamella. The central nucleus pulposus contains collagen fibers, organized randomly and elastin fibers (sometimes up to 150 mm in length), arranged radially, and embedded in a highly hydrated aggrecan-containing gel. Between the disc and the vertebrae (cranially and caudially) lies a thin horizontal (usually under 1mm) layer of hyaline cartilage, the cartilaginous endplate [5].

The intervertebral disc is a highly hydrated structure, especially the nucleus pulposus, as in a healthy state, over 80% of its weight is water. The IVD contains a rich collagen network, formed mostly of type I and type II collagen fibrils,-making up approximately 70% and 20% of the dry weight of the annulus and nucleus, respectively. It provides tensile strength to the disc and anchors the tissue to the bone. Aggrecan, the major proteoglycan of the disc, is responsible for maintaining tissue hydration through the osmotic pressure provided by its constituent chondroitin and keratan sulfate chains. The proteoglycan and water content of the nucleus (around 15% and 80% of the wet weight, respectively) is greater than in the annulus (approximately 5% and 70% of the wet weight, respectively) [5,6]. Notochordal cells are present from the early embryonic formation of the intervertebral disc and undergo a gradual transition towards chondrocyte-like cells during the first decade of life[7]. These mature nuclear chondrocytes produce collagen type I, but reduced amounts of water-attracting proteoglycans and collagen type II.

Disc degeneration in the lumbar spine is almost universal over the age of 50 years[8]. This observation appears related to humans' recent evolution to an upright posture and S-shaped spinal column. However, the aetiology of intervertebral disc degeneration remains obscure and the current consensus is that it is "multi-factorial[7]. The process of degeneration consists of several changes at a cellular, biochemical, structural and biomechanical level. Among them is the increase of acidity, the decrease of the water content of the IVD and the intradiscal hydrostatic pressure. This is connected to the increase of the catabolic activity of the. There is a progressive increase in the expression of inflammatory cytokines like IL-1 and TNFa[9,10,11] , a reduction in the expression of proteoglycans and collagen type II genes and an increase of colagen type I expression with increasing degeneration, resulting in a limited tissue water-binding potential[7]. Loss of intradiscal pressure reduces disc height; increases stress concentrations within the disc; and increases shear forces in the nucleus. Additionally, MMP-3 production is reduced, and tissue inhibitor of metalloproteins-1 (TIMP) production is increased reducing remodelling of the extracellular matrix. In the annulus, loss of intradiscal pressure will reduce tension in annulus fibers and increase in- and out-ward bulging. This bulging can increase shear forces between laminae, leading to delamination of the translamellar bridges, and consecutive risk of tears. In the endplates, the loss of annulus tension and the reduced stress distribution by the nucleus will alter the biomechanical stresses on the endplates which may be the cause of endplate sclerosis, fractures, or Schmorl's nodes[12]. The increased vascular and neural ingrowth seen in degenerate discs and associated with chronic back pain is probably associated with proteoglycan loss, since disc aggrecan has been shown to inhibit neural ingrowth. Changes at a cellular level procede the visible structural changes of disc degeneration, such as loss of disc height, disc bulging and protrusion, sclerosis of the subchondral bone, development of osteophytes. The model of the "degenerative cycle " presented by Vergroesen et al[7], attempts to connect the separate procedures of disc degeneration in the "degenerative cycle", a positive feedback loop involving cells, extracellular matrix, and biomechanics.

The purpose of this study is to review the current literature concerning clinical studies of cell therapies for the degeneration of the intervertebral disc during the last years. A search was conducted for relevant articles in the PubMed and Google Scholar internet databases, and a total of 7841 publications were found (including articles registered on both databases). After a screening of titles and "abstract" texts, 42 articles were chosen for a full text assessment, of which 13 articles refer to a total of 12 clinical studies, dating from 2006 (Table 1). The results of these studies are being presented and discussed further in this study.

## Discussion

### *Current treatment options and the investigation of feasible cell treatment*

Treatment options have been limited to conservative care, steroid injections, prescribed opiates, and surgery. The degenerated IVD surgery rate has shown recognizable growth in the last decades[13]. For herniated or bulging discs, with signs of compressed spinal nerves, (micro) discectomy will be considered. Alternatively, complete IVD replacement will

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be attempted, either by fusion surgery or total disc arthroplasty; however, these surgical procedures are highly controversial. The most common surgical approaches for discogenic back pain are spine fusions, with the clinical success rate ranging from 50% to 70%. Although existing surgical treatments provide better pain relief than

non-surgical interventions, they do not address the biology of disc degeneration, namely high pro-inflammatory cytokine levels or the inherent loss of nucleus pulposus cells[14,15,16,17,18]. Surgery, in most cases, can temporarily address changes from mechanical wear/stress and spinal instability, but there are many cases where the loss of motion from spinal fusion contributes to increased biomechanical stress due to alterations in spine kinematics and onset of degenerative cascade of adjacent segments. Genetic abnormalities are not addressed by surgery, leaving the patient susceptible to continued degenerative changes at other disc levels. In addition, surgical treatment can be applied after there has been a significant progress of the degeneration cascade connected with structural changes in the IVD and quite often, neurological symptoms. One also has to take the morbidity and the cost of a surgical intervention into account. Conservative therapy, on the other hand, is efficient for a short time and, although it may provide pain relief and improvement in disability, it does not slow or alter the degeneration cascade, and a subgroup of the treated patients proceeds to the chronic low back pain state.

As stated by Schol and Sakai[19], there is a "treatment gap" considering the option to treat intermediate low back pain, which cannot be alleviated by conservative treatment, but on the other hand is not characterized as disabling pain, which would make the patient a surgical candidate. Recent focus has been put on the development of novel regenerative therapies aimed at re-establishing a healthy IVD. Such treatments could involve protein, compound, biomaterial injections, and gene therapy, aiming to redirect or support endemic cells. In addition, investigators are exploring tissue engineering strategies to create biological IVD replacements.

There have been several clinical trials studying the transplantation of various cell populations, still leaving open questions regarding the ideal cell population for safe and effective IVD regeneration. The number of viable cells is already low in normal IVD (approximately $5x10^6$ /$cm^3$ in the NP and $9x10^6$ /$cm^3$ in the AF), and their functionality is further decreased during ageing and degeneration. In addition, increased cell senescence has been described in degenerative discs[20].

***Cell populations researched for administration***

For articular cartilage repair, autologous chondrocyte transplantation has advanced to an established procedure within the last two decades. Clinical application of autologous chondrocyte intradiscal transplantation is ongoing and trials are underway aiming to corroborate findings from initial studies[20]. In order to enhance their proliferative capacity and activity in terms of matrix production, cells isolated from disc tissue obtained during surgery can be stimulated by co-culture with autologous mesenchymal stem cells (MSCs). Short term co-culture with bone marrow derived MSCs under direct cell-to-cell contact significantly increased the growth and proteoglycan synthesis of human NP cells, while no indication of chromosome abnormalities and tumourigenesis was found[21]. The procedure appears safe and effective and is currently subject of a clinical study where such activated NP cells are injected in adjacent discs with underlying mild degeneration of patients undergoing fusion surgery. Recently, the feasibility of NP cell cryopreservation has been studied[22]. Results indicated no significant changes in cell proliferation and matrix production in cryopreserved compared to freshly isolated cells, opening the possibility of activating and transplanting the cells independent from the initial surgery and according to the patient's request. Moreover, the option for allogeneic cell transplantation can be considered. Indeed, allogeneic juvenile chondrocytes in combination with a protein-based carrier have been applied to patients with moderate lumbar disc degeneration and showed promising clinical and radiographic outcomes[23]. As an alternative to differentiated disc cells or chondrocytes, injection of MSCs has largely been investigated in animal models of disc degeneration and in certain clinical studies. Bone marrow remains the most common source for MSC harvest, although adipose tissue derived MSCs have shown regenerative potential in the disc as well[24]. In animal models of disc degeneration induced by annular puncture, nucleus aspiration or enzymatic means, implantation of MSCs has resulted in restoration of disc height, disc-like phenotype expression, discogenic extracellular matrix synthesis and improvement in MRI signals[25,26,27]. In vivo studies injecting MSCs in mouse[28], rabbit, and canine discs confirmed MSC differentiation, while also human cells implanted into rat or porcine discs were shown to adopt the chondrogenic or IVD-like phenotype[29-33].

***Challenges for an effective cell therapy: disc microenviron-***

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***ment, possible adverse effects and administration issues***

Cell therapies for disc degeneration,have to face certain challenges to emerge as viable treatment options. The intradiscal environment has characteristics that are not easily demonstrated in other tissues. It is elatively avascular, with low amounts of oxygen and nutrients available for any cell population. Furthermore, low pH and high hydrostatic pressure create a "hostile" environment[20]. Oxygen tension within the disc is significantly reduced towards the center of the nucleus pulposus (NP) and the disc cell metabolism is partly anaerobic, leading to high concentrations of lactic acid and low pH conditions. All those obstacles have to be overcome, to choose an effective cell population for the treatment[34]. The cells chosen (a) have to be able to adapt to the disc microenvironment, (b) should not "antagonize" the native cells for nutrients and oxygen (which could be an important factor to determine treatment dosage) and (c) in the case of not autologous cells a possible immune reaction has to be avoided. Concerning the latter, what leaves room for optimism is that the intradiscal microenvironment can be described as a relatively immunologically privileged environment, which can protect donor cells from a host reaction[23]. In addition, MSCs are immune privileged or immune evasive and inhibit immune responses in a manner not restricted by the HLA system. As a result, non-matched MSC are much better tolerated than other cell types. In fact, there are no reports of rejection in animal experiments and studies of transplanted MSC persistence in the host organism show the same values for autologous and allogeneic cells[35]. In humans, excellent tolerance to allogeneic MSCs has been reported in many clinical trials.

Other obstacles that have to be overcome are those related to the administration of the cells inside the disc. The integrity of the annular ring is of vital importance, and possible injury may provoke disc bulging and consequent hastening of the degeneration cascade. Interestingly, a recent animal study revealed that puncture with a 22G needle did not result in degenerative changes observed in radiography or histology[36]. The choice for an appropriate cell carrier is important as well, (a) to avoid cell leakage outside the disc (taking into account the high intradiscal pressure) and (b) to support the survival and proloferation of the administered cells. A study by Vadala et al, on animal intradiscal MSC injection, demonstrated (a) undesired migration (cell leakage) and (b) display of unwanted differentiation effects (osteophyte formation) at the treated vertebral levels[37]. A number of questions concerning the necessary storage, distribution and parameters concerning the possible cultivation of the cells to be transplanted arise as well. To transfer a feasible cell therapy from the experimental stage to clinical therapy, all those processes need to be clarified, taking into account patient safety and total treatment cost[38,39].

***Clinical studies investigating cell therapies***

In a case report by Yoshikawa et al[40], two cases were presented. Both patients had lumbago, leg pain and numbness. Myelography and magnetic resonance imaging showed lumbar spinal canal stenosis, and radiograph confirmed the vacuum phenomenon with instability. One patient had undergone an L4-L5 spinal fusion fifteen years prior due to left lower leg numbness and low back pain. At about 6 years following surgery, she began to experience low back pain, right lower leg numbness, intervertebral vacuum phenomenon, instability and lumbar spinal stenosis at L2–L3 and L3–L4. The other patient was operated at L4-L5. Marrow fluid was collected from the ilium and MSCs were cultured in an autogenous serum medium. In surgery, fenestration was performed on the stenosed spinal canal and then pieces of collagen sponge containing autologous MSCs were grafted percutaneously to the degenerated intervertebral discs. At the two-year follow-up, radiograph and computed tomography showed improvements in the vacuum phenomenon in both patients. On T2-weighted magnetic resonance imaging, signal intensity of intervertebral discs with cell grafts was high, thus indicating high moisture contents. Roentgenkymography showed improvement of lumbar disc instability. With intervertebral disc regeneration therapy, low back pain and neurologic symptoms improved. No adverse effects were reported.

In a study published by Orozco et al[41], ten patients with persistent low back pain, diagnosed with lumbar disc degeneration with intact annulus fibrosus, were treated with autologous expanded bone marrow MSC injected into the nucleus pulposus area. Clinical evolution was followed for 1 year and included evaluation of back pain, disability, and quality of life. The back pain was assessed via the Visual Analogue Scale, the disability via the Oswestry Disability Index and the quality of life via the short form-36 (SF-36) life quality questionnaire before the injections and at 3, 6 and 12 months after the injections. There was also an assessment of sciatic pain concerning six patients who presented such symptoms before cell transplantation. Magnetic resonance

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imaging measurements of disc height and fluid content were also performed, in T2-weighted sagittal images. There were positive results, as mean scores concerning pain (including sciatic pain), disability and quality of life were all improved. Pain and disability demonstrated statistically significant improvement in the first three months post-treatment with pain approaching 71% of optimal during the first year. The analgesic effect of the intervention was rapid, as most of the improvement in pain (85%) was attained by 3 months. The SF-36 questionnaire revealed, by the end of treatment, a significant improvement of the physical component with no change of the mental component. The treatment appeared to compare favorably with previous trials exploring physical treatments and spinal fusion with or without disc replacement or complemented with expanded disc material. Moreover, although there was no improvement in disc height, the fluid content of the affected disc segments was significantly elevated at 1 year following the intervention. No serious adverse effects or safety issues were reported.

In a study by Centeno et al[42], 33 patients with low back pain and degenerative disc disease presenting with a posterior disc bulge, diagnosed with MRI, underwent percutaneous, intradiscal, single-level injections of autologous cultured mesenchymal stem cells derived from bone marrow (posterior iliac crest), along with autologous platelet lysate. The results were promising after a six-year follow-up period. The improvement at the overall average for the last reported modified single assessment numeric evaluation (SANE) rating was 48.2%, at an average of 40.6 months post-treatment, with 50.4% reporting greater than or equal to 50% improvement. At 3-years post-treatment, 90% (30 out of 33) of patients reported > 0% improvement. In reference to the numeric pain score (NPS), they were found to be statistically significantly improved at 3 months, 4 years, and 5 years for the group of 25 patients who provided a baseline score. Functional Rating Index (FRI) change in scores was significantly different than baseline at 3 months and 5 years post- treatment. In addition to patient-reported outcomes, changes in IVD posterior projection or bulge beyond the vertebral body were also measured. A decrease in posterior disc bulge was detected in 85% of patients at an average of 6 months post-treatment. In determining how much of a decrease in bulge size measurement is clinically significant, patients with at least a ≥ 25% reduction in disc bulge reported significantly lower pain scores at 6 months compared to patients with a < 25% change in bulge size. All 3 of the reported adverse events were pain related and resolved, while one AE was reported, a large herniated nucleus pulposus, occurring months after the injection. This was either related to trauma from the needle procedure, or simply been a progression of the degenerative process.

In the study by Elabd et al[43], 5 patients with painful disc degenerative disease and pain, spasm, or functional disability in the low back, andfailed conservative treatments for at least 3 months, but no longer than 5 years received autologous, hypoxic cultured, bone marrow-derived mesenchymal stem cells. Four to six years after the cell transplant, they were re-examined to evaluate long-term safety and feasibility of this treatment. This follow-up consisted of a physical examination, completion of a quality of life questionnaire, and spine MRI. Four patients received injections in the intervertebral disc at the L5-S1 level and one at the L4-L5 level, and the amount of MSCs injected varied from 15.1 to 56.1 million. All five patients reported improvement of muscle strength, four patients improvement of mobility, while there was an overall improvement at the QoL questionnaire in the range of 10-90%. It is interesting to note that four out of five patients showed an improvement (reduction) of the protrusion size. Additionally all patients displayed maintenance or only mild worsening in disc height after long term follow up, and no adverse effects were reported.

In a randomized controlled trial by Noriega et al[35], 24 patients, diagnosed with Pfirrmann grade II-IV degenerative disc disease, unresponsive to conventional treatments (physical and medical) for at least 6 months and with 1 or 2 affected discs, with the lesion located at L1-L2 (n=1), L2-L3 (1), L3-L4 (3), L4-L5 (18), or L5-S1 (15) were divided into two groups at an allocation ratio of 1:1 (12 patients at each group). One group received MSCs ($25x10^6$ MSC in 2 ml of saline per disc) under local anesthesia and the other (control group) sham infiltration of paravertebral musculature close to the affected disc(s) with 2 ml of 1% mepivacaine. The MSCs were allogenic, received by five healthy donors. There was clinical evaluation and routine analyses, pain evaluation (VAS), Oswestry Disability Index (ODI) and short form-12 (SF-12) life quality questionnaire, at 8 days, and 3, 6, and 12 months after implantation. Quantitative MRI exploration was performed before the treatment and at 6 and 12 months after the injections. No major adverse events occurred. Eleven patients (8 controls /3 cell-treated) required brief treatments with NSAID-type analgesics for minor pains and 2 (1 control/1 cell-treated) required opioids. Both lumbar pain

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and disability were significantly reduced at 3 months after MSC transplantation, and the improvement was maintained at 6 and 12 months. Compared to the basal level of pain and disability, improvement was statistically significant at all time points except at 8 days, which could possibly be due to a placebo effect or the result from the anesthetic infiltration, although there is no indication of this extra-fast early improvement in the group of cell-treated patients. A fast decrease of pain was detected at the 8th day in the control group, but there was not any tendency to further improvement thereafter. The distribution of the cell-treated group is suggestive of a bimodal distribution in the Huskisson plot; a responders subgroup of 5 patients is close to the blue line that represents perfect treatment, whereas the other 7 (non-responders) resemble to controls, with no indication of effectiveness. The SF-12 life quality questionnaire did not reveal significant improvements of either the physical or the mental component scores. The height of the affected discs, as measured at the MRI imaging, had a bigger mean decrease in the controls than in the cell-treated patients, but the difference was not significant. Although the water content of the affected discs improved after treatment with the MSC, no statistical significance was observed. What is notable however is that the evolution of Pfirrmann staging was clearly different in the control and in the experimental group. In controls, there was a deterioration from (mean ± sem; n=20) Pfirrmann stage 3.15 ± 0.15 to stage 3.78 ± 0.16 ($p<0.001$), whereas in the cell-treated patients there was an improvement from stage 3.68 ± 0.13 to 3.18 ± 0.17 ($p<0.01$). The efficacy of allogeneic treatment found in the present trial (0.28) was smaller than the reported for autologous cells, 0.71[41]; yet, direct comparisons are difficult because the previous study by Orozco et al was uncontrolled. It would be most interesting to directly compare autologous with allogeneic cells in different arms of the same trial, in future studies.

At a phase-I clinical study by Kumar et al[44], 10 patients with chronic low back pain due to moderate IVD degeneration (Pfirrmann's grade III–IV at one or two levels based on T2- weighted MRI) and degenerative symptomatic discs confirmed by discography underwent a single intradiscal injection of combined HA derivative and autologous adipose tissue mesenchymal stell cells (AT-MSCs) at a dose of $2 \times 10^7$ cells/disc (n = 5) or $4 \times 10^7$ cells/disc (n = 5). The AT-MSCs were cultured for three weeks after isolation from subcutaneous abdominal adipose tissue, which was harvested via liposuction. Safety and treatment outcomes were evaluated by assessing VAS, ODI, SF-36, and imaging (lumbar spine X-ray imaging and MRI) at regular intervals over 1 year (1 week and 1, 3, 6, 9, and 12 months post transplantation). Based on discographic findings, AT-MSCs combined with HA derivative was implanted into the L4/5 disc in nine patients, whereas one patient received injections into the L4/L5 and L5/S1 disc. Seven of the 10 patients showed significant improvement ≥ 50% in the VAS and ODI at 6 months, whereas final treatment success (reduction ≥ 50% in the VAS and ODI compared with pretreatment VAS and ODI) was found in six subjects at the 12-month follow-up. No case of height loss at the lumbar X-ray or degeneration of the injected IVD was detected at the 12-month follow-up. Furthermore, the Pfirrmann grade of the transplanted disc increased from grade IV to grade III at the 6-month and final follow-ups in one case, who also achieved significant VAS improvement at 6 months. Among the six patients who achieved treatment success at the final follow-up, three cases showed increased water content based on the ADC map one year after the treatment. During the 12-month follow-up period, no adverse effects related to cell transplantation where observed. The treatment success rate was not different between the low-dose ($2 \times 10^7$ cells/disc) and high-dose ($4 \times 10^7$ cells/disc) groups. Out of the four patients classified as treatment failure, one reported significant pain relief for LBP (50% pain relief) at the 12-month follow-up, but the ODI improvement was < 30% and notable increases in Pfirrmann grade and in the ADC value were found at the 6-month follow-up. Two out of the "unsuccesfully treated" patients had other structural etiologies for chronic LBP: spondylolisthesis, spinal stenosis, facet joint arthritis, decreased disc height and disc herniation, while the other one had depressive symptoms, which might have resulted in treatment failure. Thus, careful patient selection is essential for achieving therapeutic success in stem cell therapy for chronic discogenic pain.

In a prospective analysis by Haufe et al[45], 10 patients underwent intradiscal injection of hematopoietic precursor stem cells (HSCs) obtained from pelvic bone marrow in an attempt to rejuvenate the disc. Patients were randomly offered the option of this study, and ten patients with confirmed disc pain via provocative discograms underwent intradiscal HSC injections. In the past, all patients were submitted to an endoscopic discectomy in an attempt to eliminate low back pain. Following intradiscal injection of HSCs, all patients underwent a 2-week course of hyperbaric oxygen therapy. These patients were followed up at 6- and

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12- month intervals to determine their degree of pain relief from this procedure. Of the 10 patients, none achieved any improvement of their discogenic low back pain after 1 year. Although animal studies suggest possible regeneration of disc via HSC injections, living human studies reveal that this effect does not correlate with reduced pain, and thus intradiscal HSC injection appears to be of little value.

In a prospective study by Coric et al[23], the safety and efficacy of allogenic juvenile chondrocytes delivered percutaneously for the treatment of lumbar spondylosis with mechanical low-back pain was evaluated. Fifteen patients were treated with a single delivery of juvenile chondrocytes (2 at L3–4 levels, 1 at L4–5 level, and 12 at L5–S1 levels; 12 levels at Pfirrmann Grade III and 3 levels at Grade IV). Each treatment consisted of a 1- to 2-ml injection (mean injection volume 1.3 ml) of juvenile chondrocytes (~$10^7$ cells/ml) combined with a fibrin carrier. Allogenic juvenile chondrocyte cells were harvested from the articular surface of cadaveric donor tissue and expanded in vitro. Patients were evaluated before the injection and at 1, 3, 6, and 12 months post treatment. The mean ODI, NRS, and SF-36 physical component summary scores all improved significantly from baseline, while the SF-36 mental component improved in a not statistically significant volume. At the 6-month follow-up, 13 patients underwent MRI, as one patient underwent CT imaging and another refused imaging. Ten (77%) of these 13 patients exhibited improvements on MRI. Three of the patients showed improvement in disc contour or height. High-intensity zones (HIZs), consistent with posterior annular tears, were present at baseline in 9 patients. Of these, the HIZ was either absent or improved in 8 patients (89%) at 6 months follow-up. The HIZ was improved in the ninth patient at 3 months, with no further MRI follow-up. Of the 10 patients exhibiting radiological improvement at 6 months, findings continued to improve or were sustained in 8 patients at the 12-month follow-up. In this study, no adverse effects were reported. Three patients (20%) underwent total disc replacement by the 12-month follow-up due to persistent, but not worse than baseline, LBP.

In 2002 a prospective, controlled, randomized, multi-center study[46,47], comparing safety and efficacy of autologous disc chondrocyte transplant (chondrotransplant DISC) plus discectomy (ADCT), with discectomy alone was initiated. Interventional surgery for disc herniation is one of the most widely used and effective treatments for back pain that emerges within the broad scope of disc degeneration. Successful removal of herniated disc tissue offers the individual patient substantial relief for associated pain. However, the reduction of tissue involved in the surgical procedure anatomically compromises the function of the affected disc, and affects load transfer to adjacent discs. The goal of the clinical trial was to evaluate whether ex vivo expansion of autologous disc chondrocytes and subsequent percutaneous transplantation would positively affect the treated disc and potentially stabilize the spine in general. There was an aim to embrace a representative patient group, examining the traumatic, less degenerative disc, but also to include patients with persistent symptoms that had not responded to conservative treatment where an indication for surgical treatment was given. Patients having exclusively one level requiring surgical intervention were eligible for participation in the trial. Out of a total of twenty-eight patients, 12 received cell transplantation following discectomy and 16 were treated by discectomy alone. A single puncture with a minimal caliber cannula was used to achieve precise delivery and avoid significant trauma to the annulus. Chondortransplant DISC has been transplanted approximately 12 weeks following discectomy to assure healing of the annulus. Interim analysis was performed after 2 years; Oswestry (low back pain/disability), Quebec Back-Pain Disability Scale, as well as Prolo and VAS score were used for the evaluation, in 3-, 6-, 12-, and 24-month assessments. Differences in initial presentations between the control group and those receiving autologous cells were observed. Surgery, as expected, substantially reduced the patients' disability and pain. However, the trend in reduction of total sum score continued to decrease in patients whose treatment was supplemented by cell transplantation, while the control group did not sustain continual improvement. Descriptive analyses of the mean total sum score of the QBPD prior to sequestrectomy, prior to ADCT/control, and 3 months after ADCT/control demonstrated a decrease in mean and median sum scores in both groups. Although the mean and median values for both the ADCT and the control group decreased between first and second year, the assessments for the ADCT group were clearly lower. At 2 years follow-, both total sum score and disability index of the OPDQ were plainly lower in the ADCT group compared with the control, showing long-term therapeutic benefit in comparison to discectomy alone. Disc height was assessed by MRI. Comparison of the mean inter-vertebral disc heights and the vertebral heights revealed no differences between the groups. Concerning the hydration level of the IVDs, the

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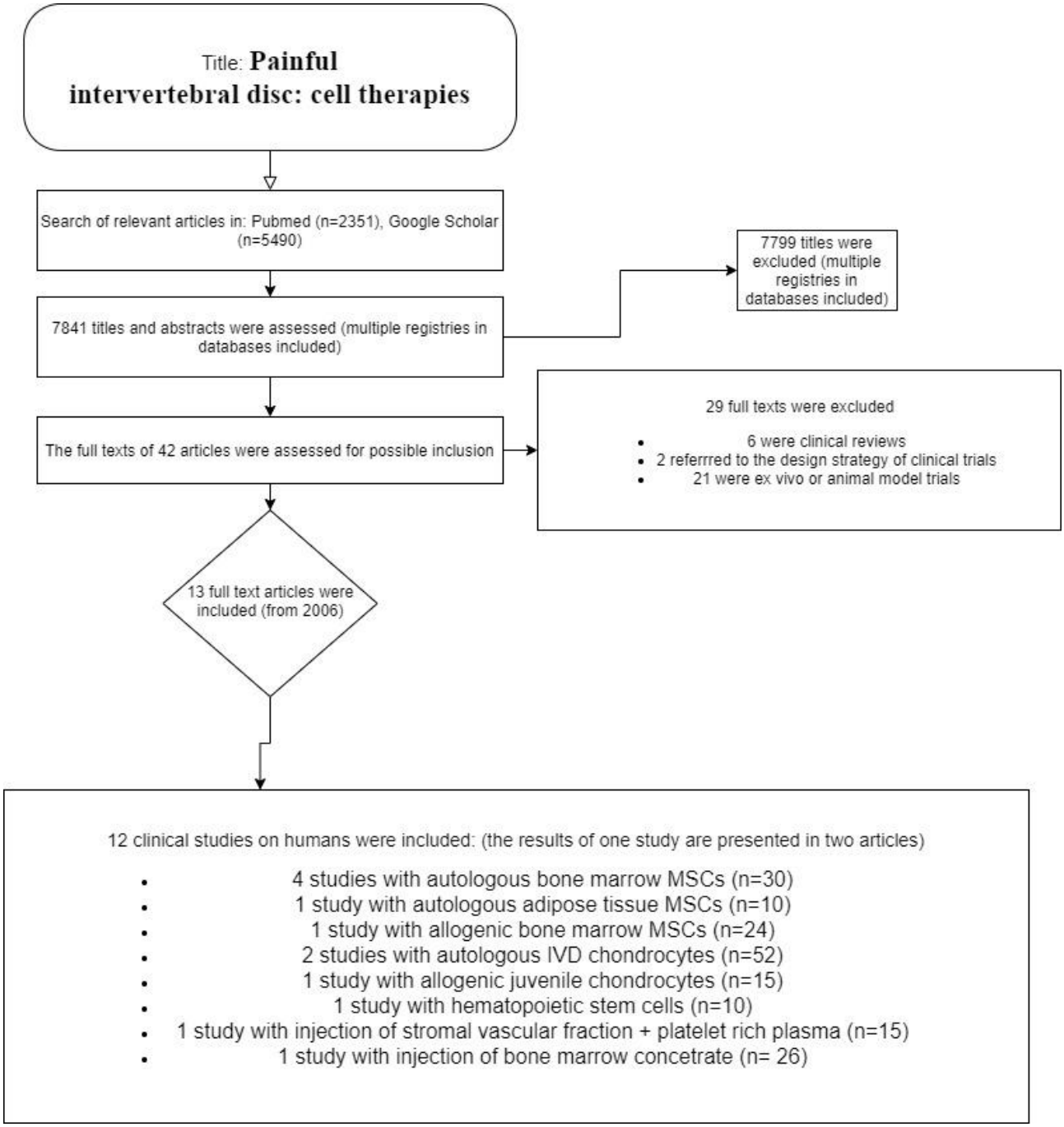
## Table 1-Flowchart



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ADCT treated group showed a substantially higher normalization as a group; 41% normal fluid content compared with only 25% normal content in the control group at the 2-year follow-up. Perhaps most interesting of all the data to emerge from this study comes from inspecting adjacent discs either one, or two segments from the treated intervertebral disc. Fluid levels at both of these segments showed a substantially higher percentage of normal fluid content despite the fact that they were away from the surgical intervention site.

The effects of autologous chondrocyte disk transplantation were also studied at a prospective randomized multicenter phase I/II clinical trial, the safety results of phase I of which were presented by Tshugg et al[48]. The NDisc trial is a multi-center, randomized study with a sequential phase I study within the combined phase I/II trial with close monitoring of tolerability and safety. Twenty-four adult patients with a single-level lumbar herniated disk were randomized and treated with the investigational medicinal product NDisc plus or the carrier material only. The most commonly affected level of disk herniation was at L5/S1 in both groups. NDisc plus is an injectable, in situ polymerizing gel initially consisting of two separate components. Component A is a liquid matrix composed of modified albumin, hyaluronic acid and the cell culture medium containing autologous inter-vertebral disk cells dissolved in cell culture medium supplemented with human serum, chondroitin sulfate, insulin, BMP-2 and ascorbate. Component B is a solution containing bis- thiopolyethylene glycol. NDisc basic is used as control in the NDisc study, in which component A is modified and is a liquid matrix composed of cell culture medium, modified albumin, and hyaluronic acid, the cell suspension is replaced by an aliquot of cell culture medium without additives. Among the inclusion criteria were no previous lumbar spine surgery and no associated lumbar disease such as lumbar spinal stenosis, spondylolisthesis, or fracture. If patients showed an extensive damage of the annulus fibrosus intraoperatively that may subsequently pose a significant greater risk of recurrence or non-containment of the injected material, they were excluded from the trial. Transplantation was performed 90 days after sequestrectomy. In case of a degenerated intervertebral disc adjacent to the treated level, the same procedure was conducted additionally at the adjacent disk. Twenty of the 24 patients were treated, 12 patients with the IMP NDisc plus and eight patients with the control preparation NDisc basic. There were two cases, where adverse effects were assessed by the investigator as related to the medical intervention or to either of the study treatment. One patient of the NDisc basic group experienced spinal pain 21 days post implant (non serious adverse effect) assessed as related to both surgery and study treatment. One patient of the NDisc plus experienced an intevertebral disk protrusion assessed also as related to both surgery and study treatment. The patient underwent further surgery. Laboratory values such as interleukine-6 (IL-6) and C-reactive protein (CRP) as safety parameters were evaluated. These values in both treatment groups increased temporarily after 36 h of sequestrectomy and turned to normal thereafter. CRP did not change after implantation, whereas IL-6 showed minor changes with a peak at 42 h post implantation. There were no statistically significant differences in the results between the two groups. In the MRI, extradiscal fluid collection (EDFC) was observed in three patients (n = 2/12 in the NDplus group vs. n = 1/8 in the NDbasic group) after the implantation, but did not have any space-occupying effect. One of these patients demonstrated a recurrent disk herniation, which later also required surgery (7 months postoperative). Routine treatment (elective sequestrectomy) in the target patient population was considered to be associated with AEs such as recurrent disk herniation or ongoing or recurrent low back pain or sciatica in up to 25 % of patients within 2 years. Symptomatic reherniations occur in approximately 10% of patients with the highest risk within the first 6 months. Overall, the rates of radiological and clinical reherniations as well as of adverse effects are comparable with those expected in the early time course after elective disk surgery. No indications of harmful material extrusion or immunological consequences due to the treatment were observed.

In a study published by Comella et al[49] in 2017, the intradiscal injection of a mixture of stromal vascular fraction and platelet rich plasma was examined. A stromal vascular fraction (SVF) can easily be isolated from fat tissue in approximately 30–90 min in a clinic setting using a mini-lipoaspirate technique. The SVF contains a mixture of cells including ADSCs and growth factors and has been depleted of the adipocyte (fat cell) population. Platelet rich plasma is a mixture of growth factors and fibrin obtained from autologous peripheral blood. By combining PRP with SVF, there may be an increased number of growth factors and proteins which could translate to improved patient outcomes. Fifteen patients underwent a local tumescent liposuction procedure to remove approximately 60 ml of fat tissue. The fat was sep-

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arated to isolate the SVF and the cells were delivered into the disc nucleus of patients with degenerative disc disease. The patients were diagnosed with degenerative disease of one, two or three lumbar discs and experienced predominant back pain after conservative treatment (physical and medical) for over 6 months. The annular ring had to be capable of holding the cell implantation as demonstrated by MRI image. Each injection included approximately 1cc of SVF/PRP suspension. If more than one disc was symptomatic, the SVF was divided and prepared with approximately 1cc of PRP. Clinical evaluations were scheduled at baseline, 2 and 6 months. The subjects were monitored for adverse events, range of motion, visual analog scale (VAS), present pain intensity (PPI), Oswestry Disability Index (ODI), Beck Depression Inventory (BDI), Dallas Pain Questionnaire and Short Form (SF)-12. Safety events were followed for 12 months. The patients demonstrated statistically significant improvements in several parameters including flexion, pain ratings, VAS, PPI, and short form questionnaires. Although ODI and BDI did not show statistically significant changes due to the low number of subjects in the trial, the data was trending positive. In addition, the majority of patients reported improvements in their Dallas Pain Questionnaire scores. Adverse effects other than soreness in the abdomen after the mini-liposuction procedure or soreness in the back after injections (which all resolved within 7-10 days) were not reported.

Another option concerning a potential cell treatment for disc degeneration could be the intradiscal injection of autologous bone marrow aspirate. In a prospective, open-label, non-randomized, single-arm study of Pettine et al[8], 26 patients received this treatment and had a three-year follow-up. All were surgical candidates seeking a consult from the author, had chronic low back pain persistent to conservative treatment and disc degeneration with an MRI confirmed modified Pfirrman grade of 4-7. They were injected with 2 ml autologous BMC into the nucleus pulposus of treated lumbar discs. Thirteen patients underwent an intradiscal injection of autologous BMC at a single symptomatic lumbar disc and 13 subjects had two adjacent symptomatic disc levels injected. A sample aliquot of BMC was characterized by flow cytometry and CFU-F (colony forming units-fibroblast, synonymous to bone marrow-derived MSCs) assay to determine progenitor cell content. There was an improvement of both the pain and the disability of the treated patients from the first post-treatment evaluation (3 months) and the improved VAS and ODI scores remained relatively stable during the 3-year follow-up period for the patients who did not undergo surgery during this period (20 out of 26 patients). There was a 71% improvement in ODI and 70% improvement in VAS in this BMC injection group after two-years and a slight decrease was observed in ODI and VAS scores from two to three years post procedure. Cellular analysis suggests patients with greater concentrations of progenitor cells (both CFU-F and CD34+/lineage– cell types) in their BMC experienced faster and greater pain reduction. MRI imaging showed eight out of 20 patients with imaging had at least one grade increase on the modified Pfirrmann grading scale for disc degeneration at one year. No patients presented worse MRI scores after one year. Patients with higher MSC concentrations, measured as CFU-F/ml, tended to have better outcomes than those with lower concentrations. Other than progression to surgery (six patients in total), there were no serious adverse events related to the study. The morbidity and cost of this percutaneous procedure are substantially less than a surgical option and the clinical results appear to be similar or superior to surgery for chronic discogenic low back pain.

The results of most of the clinical trials reviewed here are promising. Apart from the study evaluating the use of hematopoietic precursor stem cells by Haufe et al[45], all studies evaluating pain and disability showed positive results. In addition, the improvement in pain and disability scores was mostly not lost during the follow-up period, as was shown by the studies with a follow-up period of three to six years [8,42,43]. Although this tendency for long-term positive results has to be confirmed by studies with longer follow up-periods, it certainly leaves room for optimism. Radiological and MRI findings were promising as well. A common positive result was the fact, that the fluid content of the treated discs was higher a year post-treatment. In addition, treated discs tended to keep a steady height at the follow-up imaging. Although not as common, probably even more promising was the fact that in certain studies an improvement at the Pfirrman (or modified Pfirrman) score for disc degeneration was observed. The results of Noriega et al[35] and Pettine et al[8], are most notable. Furthermore, Centeno[42] and Elabd[43] et al both found that the majority of patients had a smaller posterior disc protrusion and disc bulge, respectively. Those findings indicate that the degeneration process of the disc may not only be slowed, but possibly reversed by cell treatment. Moreover, there were no

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serious adverse effects connected to the cell therapy reported (with the possible exception of one patient in the study by Centeno et al[42]) nor did cell therapy show to worsen the possibility of adverse effects when combined with surgery[46,47]. The combination of surgical and cell treatment is a possible therapy option that requires further investigation. These findings show that cell therapy can be a relatively safe treatment option. Further investigation with a prospective, randomized, blinded, placebo-controlled study design is necessary.

There are, however, issues that need to be addressed to safely apply cell therapy from clinical trials to "everyday" treatment. Firstly, the choice between cell populations, as well as between autologous and allogenic cell transplants requires further investigation, as clinical trials are still limited both in number and patient populations. Secondly, the appropriate therapeutic dosage and the cell carrier have to be defined, such as development of carriers that may imbue additional potential and scaffolds that enhance placement. While the study by Pettine et al[8] indicated a connection between viable cell population transplanted and clinical results, only one study[44] examined different dosage schemes without any statistically significant difference. Regenerative strategies targeting the repair of the annulus fibrosus and end-plates are also lacking[50]. In addition, the questions of cultivation, storage and adequate supply of the administered cells also have to be answered. In order to bolster and confirm the positive results and address the issues above, further investigation with bigger patient populations and comparison between different treatment options are required.

***Conflicts of Interest***

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