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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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Figures need to be of high quality. Vector graphics, scanned line drawings and line drawings need to be in bitmap format and should have a minimum resolution of 1,200 dpi. Halftones (photographs, drawings or paintings) need to be in TIFF or JPEG format, up to 174 mm wide and up to 234 mm high and in minimum resolution of 300 dpi.

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

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or

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

- Book chapters:

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

- Online document:

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

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The echo of Silence

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ABSTRACT

We perceive the world around us through synapses, neurons, and cells. Nevertheless, some of us fall to the temptation of doubting their own senses, seeking comfort in technology and the "infallible" artificial intelligence. Others have reconciled the idea that they see the world through a peephole. Others do not even bother and instead they leave it all to the experts. Questions remain unanswered, creating the root of the question of the current paper: How do we define silence? How do we capture in words and shapes the complete absence of sound? Our senses fail to detect silence. However, they do prove able to describe the world that surrounds them. This is because, around the (apparent) absence of sounds, we witness events that require our attention and stimulate our thoughts. Through afterimages and aftermaths, we form our opinions on all things. There is no need to see the Higgs boson. We need only observe the effects of the actions of the energy derived from its existence. In the physical world, everything enlarges upon the field of human cognition, which constantly searches for ways to decode guarded secrets that define our own existence. It is thus worth to think about the labyrinths of comprehension in order to touch the essence of silence, carefully pondering the echo of its aftermath.

KEYWORDS. silence; echo; absence of sound; pause; noise; scream.

Introduction

We live in a chaos of natural and human noise, in bustling cities that are characterized by boisterous sounds and multilingual soundscapes. The spectacle of people verbally jousting in stadiums, cafes, and television channels is common. This happens even in the halls of parliaments, where we would expect the decency of democratic discourse to prevail. The loud disagreements and quarrels prevail even in school settings, be it in classes or in playtime. We have learnt to express our opinions loudly, using rude gestures and body language and we teach our children to do so as well.

The perspective of those who defiantly remain silent creates, at the very least, mistrust (**Figure 1**). Silent are usually those who do not know how to express themselves, those who -being aware of their ignorance of the subject at hand- choose to hermetically close their mouth as well as those who remain temporarily silent or those who wait to hear the opinions of others before they weigh in.

Nowadays, when our discourse has degraded to all sorts of vulgarity, falsehood, swear and cursing, silence has something to say. In times that we are consumed in unending sycophancy, ironic comments, slander and shameless gossip, we can gain unimaginable powers from our delicate and still purposeful silence.

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Figure 1. *Introverts are treated as suspicious*

Figure 2. *The Silence of God at Auschwitz*

Our ancestors had comprehend it before we even perceived it. They used to say: *"Η γάρ τῆς γλώττης ἀκολασία πολλοῖς λύπην καί αἰσχύνην φέρει" (The pointless use of language shall bring sadness and regret) and "Η γλῶττα πολλῶν ἐστί κακῶν αἰτία*" (Language *is the source of hardship*) [1].

The merit of silence

Plato taught his young students that it is greater to hush than to babble (*"Νέοις τό σιγᾶν κρεῖττόν ἐστί τοῦ λαλεῖν"*) and even that they could overcome anger by thinking logically before answering *("Νίκησον ὀργήν τῷ λογίζεσθαι καλῶς"*) [2].

Rudyard Kipling approaches the same in a similar way in his famous poem *If*:

If you can keep your head when all about you
Are losing theirs and blaming it on you;
If you can trust yourself when all men doubt you,
But make allowance for their doubting too. [3]

If we accept as an indisputable fact, that Art serves freedom in every form of expression, we should lean to come bravely closer and listen to what silence has to say.

In her poetry book with the title "Δημόσιος καιρός", *[Communal Time]* Kiki Dimoula [4] addresses to human curiosity, which she calls "savage" and notes that *"silently the words are loved/so that you don't hear them"*. This is an implicit, yet obvious, reference to the value of being soft-spoken.

Intellectuals and people of letters have expressed views on the subject of silence in a surprisingly similar way. In his masterpiece *"The Brothers Karamazov"*, Fyodor Dostoyevsky timely highlights that *"much unhappiness has come into the world because of bewilderment and things left unsaid."* [5]

In his autobiographic work Αναφορά στον Γκρέκο *(Report to Greco)*, Nikos Kazantzakis, after a tour (which he refers to as a "pilgrimage") of Greece, he inspires us to fall silent and listen for the screaming: *"Every Greek landscape is so drenched in happiness and unhappiness with a universal impact, so full of human struggle, that it becomes a stern lesson and you cannot escape it. It becomes a screaming, and you have a duty to listen"* [6].

Harry Klynn, a gifted Greek actor and writer, also known in Greece as "the modern day Aristophanes", had once said during an interview [7], in reference to a distinguished and famed Greek politician that *"He is such a good orator that he can talk to you for two hours to explain the value of silence"*.

A know question among theorists is why God remains silent. *"God's silence* - Nikos Dimou writes on his personal blog- *is the basic pattern of all Existential Philosophy - and Theology - of the past century. God was silent during Auschwitz* (**Figure 2**) *and in Rwanda and silent in Cambodia and in Srebrenica. He let unspeakable atrocities to occur without giving us any sort of sign. God stays silent not only during the large and public tragedies, but during the small and private ones as well. The mother who mourns her child's loss will get no answer"* [8, 9].

It is true that the world we live in is a valley of

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Figure 3. *Picasso breaks his silence by painting Guernica.*

tears and sorrowing. Wherever you may turn your gaze, you can see pain, sadness, injustice, and death. In an inspired text [10], Nikolaos, Metropolite of Mesogaia and Lavreotiki, bravely opines, *"every thought about the absence of God causes a sense of emptiness, deep disappointment, lack of purpose and direction, and inability to determine the deeper meaning of existence"*. At another point, he notes, *"The question isn't whether God is present, but whether He appears before us and whether we see Him and each of us can sense Him"*.

Silence in Life and Art

Artists comprehend silence in their own personal way and exploit it brazenly, as it is the only thing that can motivate creation and be a reservoir of inspiration. Artists call us all to feel and respect their plan. Pablo Picasso breaks his silence during the Spanish Civil War by painting *Guernica*, the most moving and powerful anti-war painting in History, after the barbaric destruction of Basque's holy city (**Figure 3**). Beethoven, sunken in silence, will construct exceptional musical syntheses, although isolated from his sonic environment. Yiannis Ritsos, the Greek poet, will write his *Eighteen Little Songs of the Bitter Homeland* (poems) while in exile at the soundless town of Partheni, Leros.

Luckily, it is not a necessary for us to go into exile in order to experience solitude and thus benefit from calmness. We can instead visit the remote islands of our homeland Greece and experience a deep and reverent sense of peace and tranquility. For those who seek transcendent wisdom, silence of the desert represents the perfect getaway [11]. Moreover, all that said, we can look for and find silence by listening our own body.

For people who lost their hearing early in their lives, their remaining senses were tuned accordingly in order to make up for the loss of the other ones. After all, the loss of sense of hearing can function in a compensatory manner as in the case of Beethoven as previously discussed. For the deafblind activist Helen Keller, her disability had a practical effect. Through the Braille Method (for the blind) and the Tadoma Method (for the deafblind), Keller managed to interact with the environment. She travelled across the world, conducted university studies, wrote articles, published books, gave talks and today is probably the most well-known deafblind person in History [12].

A vascular episode, which affects the left hemisphere of the brain, leads to aphasia, as it disturbs Wernicke's centre in the brain. Patients in intensive care units who are in coma or suppression unknowingly experience the same situation.

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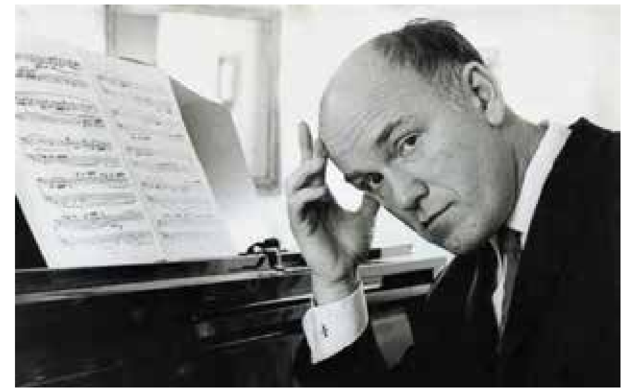

Figure 4. *Sviatoslav Richter made good use of absence of sound in his performances*

Figure 5. *Those that watched the launch of Apollo 11 witnessed a unique event.*

Saying this, we have trouble figuring out the inertia of death. Afterlife, like the philosophical *"επέκεινα"* ("hereafter"), that is the things beyond everyday knowledge, does not allow us to experience the stubborn silence of the great beyond. Dead tell no tales, they do not disclose the unsolved mysteries, they do not answer existential questions, nor do they enter in to self-reflection. They bravely imply, however, to all of us who hearken, the futility of earthly pursuits.

From Physiology, we know that Cheyne - Stokes respiration is characterized by progressively, deeper and sometimes-faster breathing followed by a gradual decrease (crescendo decrescendo) that result in temporary cessation of breathing (apnea). This is not always due to an underlying brain damage. This asymmetrical type of breathing is being manifested during normal conditions, such as in toddlers' sleeping or in people that live in high altitudes [13].

Actually, we know that after an extra systole of cardiac muscle a compensatory pause follows, as the cardiac muscle is in an unirritable period. However, immediately after the cavities of heart have filled with blood, a strong contraction follows with increased stroke volume [13]. In other words, our bodies for a new start use these small pauses of breath or cardiac function with increased intensity and with effects that are more apparent.

Music has mimicked nature and has added its silences in the form of musical pauses -yet another element in its long list of virtues. In symphonic works, in times when some instruments fall silent, other instruments shall highlight their own sound timbre. During the big pause, the composer shall cut off every musical sound, giving the audiophiles the chance to enjoy the harmonies from the last chord of the symphonic orchestra still present in their ears. Sviatoslav Richter, the famed pianist, had the unique ability to utilize the pause of the orchestra's instruments during a piano concert, before the beginning of the improvisational cadenza (**Figure 4**).

In Alfred Hitchcock's movies, especially those of his American creative period, almost exclusively Bernard Hermann had taken the music lining up. It is believed that even the slightest details of Hermann's music contributed to the culmination of agony and the climaxing of anticipation as desired by the master of suspense. In the movie *North by Northwest* the director and the composer decided that in the film's top scene no music was to be heard. [14].

Pantomime traces its origin to the period of Roman Empire and has maintained over the centuries the uniqueness of its on-stage presence, conditions, and setting, either as a special theatrical genre or as a part of the thespians' profession. All across the globe, *Silent theatre* has found fertile ground, while great artists in this genre have managed to elevate it to new heights.

In *Silent films*, recorded sound and any form of audible dialogue is of course absent. The genre bloomed up to the end of the 1920s. Great actors, such as Charlie Chaplin, Buster Keaton and Harold

Figure 6. *A Hebrew proverb defines five steps of knowledge.*

Lloyd were emblematic in this genre, which gave us unforgettable moments of sheer entertainment. The impact of silent dramatization continues to move audiences in cinema, the so-called "seventh art", even today.

The Sound of Silence, as an idea, inspires Paul Simon and Art Garfunkel to write their musical score and sing in Mike Nichols' landmark movie *The Graduate*, at the end of the 1960s. Actually, from Ingmar Bergman's *The Silence* (1963) to Finos Film's *Maria of Silence* (1972), cinema has done nothing else but flirting with silence.

Art shows interest in anything that attracts the psyche of man or pulls at our heartstrings. The artistic world observes speechlessly the various approaches on that. Films have been shot, musical compositions have been recorded and books have been written.

It is clear that in authors' creative vein flows blood saturated with metaphysical searches, autobiographical recollections, and nostalgic shivers of childhood, historical reports, and allegorical mind games, spiritual and moral forces that found their way in writing. Writing on paper is truly a remedy. Silence and -mainly- its echo plays a leading role in this process. [15-18].

Everyday experiences

In a music concert, the audience knows well and everyone has an understanding: During the show, they all ought to stay silent. To the musical rainbow that unfolds, they have to demonstrate this unique agreement of silence. In some performances, cough pastilles are provided.

A few days ago, in a metro station, some moronic faced youths boarded while listening to trap music at max volume from their earphones. The verses sounded deafening, harsh, vulgar, and provocative. Yet, none of their fellow passengers in the train car reacted.

This experience of silent harmony, shared never before until this unique event, was lived by those who stood to watch the launch of Apollo 11 (**Figure 5**) on a summer day of 1969. Everyone was left speechless before the wonder of technology, which at that very hour was sending man to the Moon.

A few years ago, in the eve of the authentic marathon, the organizers had scheduled a meet and greet in a big hotel in Athens. Among the speakers were big names of the world of sports to address their greetings. The renowned pasta party would follow, giving athletes energy for the next day. It was the idea of one of the directors to put one of the Kenyan runners up on the stand. The runner indeed rose from his seat, got on the stand and remained silent for five minutes, awkwardly facing the audience with a shy and reluctant smile. The next day, however, he chose to let his actions speak for him by

being the first athlete to cross the finish line.

In the end of the First World War, the minute of silence was introduced and today is a period of silent contemplation in the memory of a tragic historical event or as a gesture of respect, particularly in mourning. Silence is considered the greatest form of sympathy to the grieving. In the case of the recent death of Queen Elisabeth II, the silence lasted two whole minutes across Great Britain.

Silence is also essential for the illegal operations of the world of organized crime. *Omerta* is exactly that: The code of silence, loyalty and solidarity among Mafia members in the face of authority. Its violation is punishable by death. With this code of silence, comes the Sicilian proverb: *"He, who does not listen, does not see and does not speak, lives for 100 years"*.

In the period of Pythagoras of Samos, the dominant view was that *"you should either remain silent or only say something superior to silence"*. After all, the code of silence, meaning voluntarily withholding of essential information useful to an organization, is a known code in secret societies or brotherhoods as a necessary precondition for their members' devotion.

The *Me Too* movement fights to overcome the code of silence regarding suppression. The present deputy minister of labor Maria Syreggela expressed her opinion with these words: *"The culture of silence finally wanes, as there are sympathetic ears to listen to the traumatic experiences of women, as well as theorists to support and advise women on how to escape abusive relationships"* [19].

Beneficial knowledge

A Hebrew proverb delineates knowledge in four steps (**Figure 6**). The first step is to have the strength to be silent and not pretend to be a knower in fields you have not a thorough knowledge. The second is to pay attention to your teachers. The third is to study ceaselessly, to observe the details of a subject and to keep notes. The fourth and final step is to pursue teaching as pretext for transmission of knowledge and experiences to the younger ones [20].

It is not coincidental that we got used to associate silence with gold. When you choose to answer a challenge by remain silent, tension is being lowered, escalation is interrupted, rage is being cut to pieces, anger is reduced. The faithful have glorified the silence of the saints in their countless hours of ascetic isolation; they have praised the holy silence of the blessed who have given answers to confusing problems; they have preached the reflective silence of a hero before his or her self-sacrificial act. Saint Arsenios used to say: *"I have regret speaking, but not being silent"* as well as *"We have two ears and a mouth. More for listening and less for talking"* [21].

For the people who have chosen remoteness and quietism, silence determines humbleness, seeing through the heart, and fulfillment of the soul. Monk Moses in Mount Athos, the Greek Orthodox Holy Mountain, have said: *"Silence gives birth to clear, beautiful and rich reason"* [21].

These are challenging times. We are called upon, on a daily basis, to react with screams, protests, placards and banners. We can, however, reduce uneasiness (to the degree that this is translated to pointless talking), and also our worries and fussiness to make room for studying, reflection and introspection. In the poem "As much as you can", published in 1913, Constantine Cavafy captures in his verses the merit of whispering and the trouble of everyday conversation that focuses on unimportant topics

And even if you cannot make your life the way you want it,
This much, at least, try to do
As much as you can: don't cheapen it
With too much intercourse with society,
With too much movement and conversation [22].

Conclusions

A difficult subject, such as that of silence, can be analyzed only by blending scientific writing and non-fictional creative writing. This is because any author's inner nature and its relation to the phenomenological "essence" of silence can only subjectively and poetically be comprehended. However, useful conclusions can be drawn from such a pursuit that can inform our life, making it more beautiful and peaceful.

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Thought travels uncontrollably with dizzying speed to places inaccessible and unexplored by our bodies. Thought also struggles to listen to the wake of silence of deep space and the bottomless depths of the oceans. Utopia, a world without suffering, hatred and war, is one of its targets as well. Nothing can resist thought's unsurpassed charm. There is not *terra incognita* that can hide from its penetrating gaze.

The article is based on a specific lecture that was given by the first author (N.G.M.) during the works of 78th Congress of the Hellenic Association of Orthopedic Surgery and Traumatology, which took place from 12 to 15 October 2022 at the Megaron Athens International Conference Center.

Conflict of interest
The authors declared no conflicts of interest.

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Platelet Rich Plasma for the management of knee osteoarthritis: a review of biological role and potential mechanism of action

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ABSTRACT

Knee osteoarthritis (KOA) is a progressive degenerative disease characterised by joint cartilage damage, interindividual variation in clinical manifestations and severe end-stage clinical symptoms. It is one of the most common arthritis types, with increasing prevalence as life expectancy and obesity rise. It is quite a significant public health issue as it reduces physical function, causes chronic pain, and severely impacts the quality of life. The early and middle KOA stages are usually managed conservatively, and the end-stage KOA with knee arthroplasty. Emerging evidence suggests that platelet-rich plasma (PRP) has a potentially regenerative effect on various tissues. Intraarticular PRP has been shown to provide symptomatic relief in early KOA, at least as effective as hyaluronic acid and steroid injections. The combined effects of PRP positively impact inflammation, angiogenesis, cell migration and metabolism of many degenerative joints. However, the PRP's biological activity and mechanism of action are not yet fully understood. This article aims to resume the critical evidence highlighting all reported biological, biochemical and cellular PRP actions in KOA to help physicians better understand this molecular treatment type.

KEYWORDS: platelet-rich plasma, osteoarthritis, knee, PRP

Introduction

Knee osteoarthritis (KOA) is a degenerative disease with gradual joint cartilage damage. KOA is mechanical arthritis with a multifactorial origin[1]. Click or tap here to enter text. It is one of the most common arthritis types, with increasing prevalence as life expectancy and obesity rise[1]. Knee pain, stiffness, and swelling are the typical clinical symptoms[2]. End-stage KOA eventually leads to disability. Conservative treatment is used for the early and middle stages, and knee arthroplasty is for end-stage KOA. Conservative management includes pharmacologi-

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cal and non-pharmacological therapies. Non-pharmacological interventions involve orthotics, weight loss, activity modification and physiotherapy. Pharmacological treatment includes analgesics, anti-inflammatories, opioids to manage painful crises, and orally or intraarticularly administered disease-modifying osteoarthritis drugs to deal with the KOA progression[2].

However, new metabolic and biochemical pathways have been recognised in KOA aetiopathogenesis. Emerging evidence suggests that platelet-rich plasma (PRP) has a potentially regenerative effect on various tissues. Intraarticular PRP has been shown to provide symptomatic relief in early KOA, at least as effective as hyaluronic acid and steroid injections[3]. However, the PRP's biological activity and mechanism of action are not yet fully understood[3]. This article reviews PRP biology and all reported biological, biochemical and cellular PRP actions to help physicians better understand this molecular treatment type.

Anatomy and structure of the knee cartilage

KOA affects mainly the joint cartilage, subchondral bone, and capsule[1]. Cartilage comprises chondrocytes and the collagenous extracellular matrix (ECM) rich in proteoglycan and elastin fibres. Chondrocytes are specialised metabolically active cells synthesising variable components, providing a stable anabolic and catabolic ECM equilibrium[4]. ECM contains organic ingredients, mainly water, aggrecan, proteoglycans, collagens, glycosaminoglycans and glycoproteins. Proteoglycans are protein complexes formed by negatively charged glycosaminoglycans. They are bound to aggrecan, which is linked with hyaluronic acid at the inner matrix part. The outer part is made of a cross-linked collagen type II network. Pericellular matrix encircles chondrocytes and is formed by other proteins such as collagen VI, fibromodulin and matrilin[4].

Histologically, the articular cartilage consists of four layers, the tangential, transitional, radial, and mineralised zone. Chondrocytes and collagen fibers' number, scheme, and orientation differ between zones. The superficial tangential area consists of disk-shaped chondrocytes and collagen fibrils. The middle transitional zone has round-shaped chondrocytes, and the deeper radial zone has chondrocytes' stocks and aligned collagen fibrils[4]. Tidemark is a small, mineralised zone in calcified cartilage, separating the non-mineralised cartilage layers from the subchondral bone[5].

KOA Pathogenesis and Pathophysiology

KOA is mainly caused by articular cartilage integrity loss; however, bone, synovial and other joint changes are described. In the early KOA stages, the atypical action of aggrecanases imbalance the ECM. Aggrecanases are degrading enzymes that cleave the aggrecan core proteins from superficial layer proteoglycans. Subsequently, chondrocytes increase their synthetic activity to restore the aggrecan loss[6]. ECM degradation is also caused by the matrix metalloproteinases (MMPs), mainly MMP3, that disrupt the collagen type II network[7]. On the other hand, chondrocytes form clusters increasing their synthetic activity and trying to repair the ECM structure and cartilage stability—however, the released synovial inflammatory factors and mechanical loading further damage the cartilage[7]. The subchondral bone alterations may further promote KOA development[8]. During KOA progression, subchondral bone osteoblasts and osteoclasts adapt their metabolic activity, secreting pro-inflammatory factors and degradative enzymes, leading to abnormal cysts, osteophyte formation and subchondral bone sclerosis.

Typically, the synovial membrane produces the synovial fluid providing essential nutrients and products for cartilage metabolism. In KOA, the synovial membrane is inflamed by inflammatory macrophages, growth factors and highly active synoviocytes[9]. Synovitis induces the T, B lymphocytes and mast cell infiltration[15]. Inflammatory mediators stimulate MMPS and proteinases production, causing the regulatory cells (chondrocytes, synovial cells and lymphocytes) to extensively produce interleukins (ILs 6,8,15,17) and prostaglandin E2 (PGE2), further damaging the extracellular matrix[10].

Cytokines are signalling molecules playing a vital role in OA pathogenesis[11]. The cytokines' secretion regulates the inflammatory response that causes

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symptoms and controls genes' expression in KOA. Various studies support that IL-1β, IL-6, IL-8, IL-17 and Tumor Necrosis Factor-a (TNF-α) are the principal inflammatory cytokines, and IL-1Ra, IL-4, IL-10, and IL-13 are the main anti-inflammatory factors[11]. Especially for KOA, IL-1β, type IX collagen and TNF-a, stimulates the expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), extracellular signal-regulated kinases (ERKs), Jun N-terminal kinases (JNKs) and p38 mitogen-activated protein kinases that enable the chondrocytes' catabolic pathway[12]. Activating NF-κB promotes osteoarthritis inflammation, producing many inflammatory factors, including hypoxia-inducible factor 2α (HIF2α), cyclooxygenase-2 (COX2), IL-1 and nitric oxide synthase (NOS2). The activated NF-kB pathway induces degrading enzymes and enzymes that enhance chondrocyte apoptosis[13]. IL-8 promotes the NF-kB path attracting neutrophils in the knee, and IL-6 promotes the Janus kinases signal transducer and activator of transcription proteins (JAK/STAT) pathway leading to MMP production and joint inflammation[14,15]. Growth factors such as the VEGF and Transforming growth factor β (TGF-β) are also involved in KOA pathology. VEGF produced by affected chondrocytes suppresses the ECM's aggrecan and type II collagen synthesis. In healthy individuals, TGF-β has an anabolic effect; however, during abnormal catabolic function, TGF-β activates stem cells that inhibit cartilage and bone degradation[16].

PRP: Definition, production, and main components

PRP is an autologous biological product, a part of the blood plasma fraction with a high platelet concentration above the standard, various cells and growth factors[17]. Platelets are 2-3 μm in diameter discoid anucleate elements produced by the bone marrow megakaryocytes and released into the bloodstream. Biomolecules present in platelets interact with plasma components to maintain homeostasis. Several platelets' glycoprotein receptors enable numerous functions every time the extracellular matrix is exposed. The platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptor is critical to platelet aggregation, thrombus formation and tissue repair. Upon activation, platelets secrete hundreds of active molecules from their intracellular granules, involved in hemostasis or tissue healing. Platelets secrete seven essential protein growth factors [platelet-derived (PDGF), TGF-β, VEGF, epidermal (EGF), fibroblast (FGF), connective tissue (CTGF) and insulin-like (IGF)] in the wound healing process and three secretory proteins acting as cell adhesion molecules (fibrin, fibronectin and vitronectin)[17]. Platelets contain three different granule types:

a. **Lambda granules** (lysosomes)[18] contain enzymes necessary for carbohydrate, lipid, and protein degradation that remove debris from damaged tissues and eradicate infectious agents. They also include various proteins such as cathepsin D and E, lysozyme, elastase, and hydrolases; their role has not been fully clarified yet.

b. **Delta granules** (dense bodies)[19] contain several factors (serotonin, dopamine, calcium ions, histamine, adenosine polyphosphates, and epinephrine) involved in coagulation, platelet activation and immunomodulation. Histamine and serotonin increase the capillaries' permeability, allowing the inflammatory cells' migration and stimulating Mesenchymal Stromal Cells (MSCs), fibroblasts and autologous chondrocytes.

c. **Alpha-granules** contain growth factors (PDGF, IGF1, VEGF, FGF, CTGF, TGF). PDGF, IGF1, TGFβ and bone morphogenetic proteins (BMPs) are anabolic GFs, inhibiting pain and inflammation and enhancing the bone matrix and cartilage[20-21]. GFs recruit and activate immune cells, induce endothelial cell inflammation, and inhibit the local inflammatory response and pain caused by TNF-α, IL-1, IL-1b and IL-6[22]. GFs are responsible for cartilage matrix synthesis, chondrocyte stimulation, cellular proliferation and microenvironment regulation. Alpha-granules also contain chemokines and cytokines (pro-platelet basic protein, platelet factor 4, P-selectin) that can stimulate cellular chemotaxis involved in maturation, clotting, migration, cell proliferation growth, angiogenesis, and inflammatory regulation[17-18,23]. Literature supports that a-granules secrete more than 300 soluble proteins, bioactive molecules with heterogeneous functions (inflam-

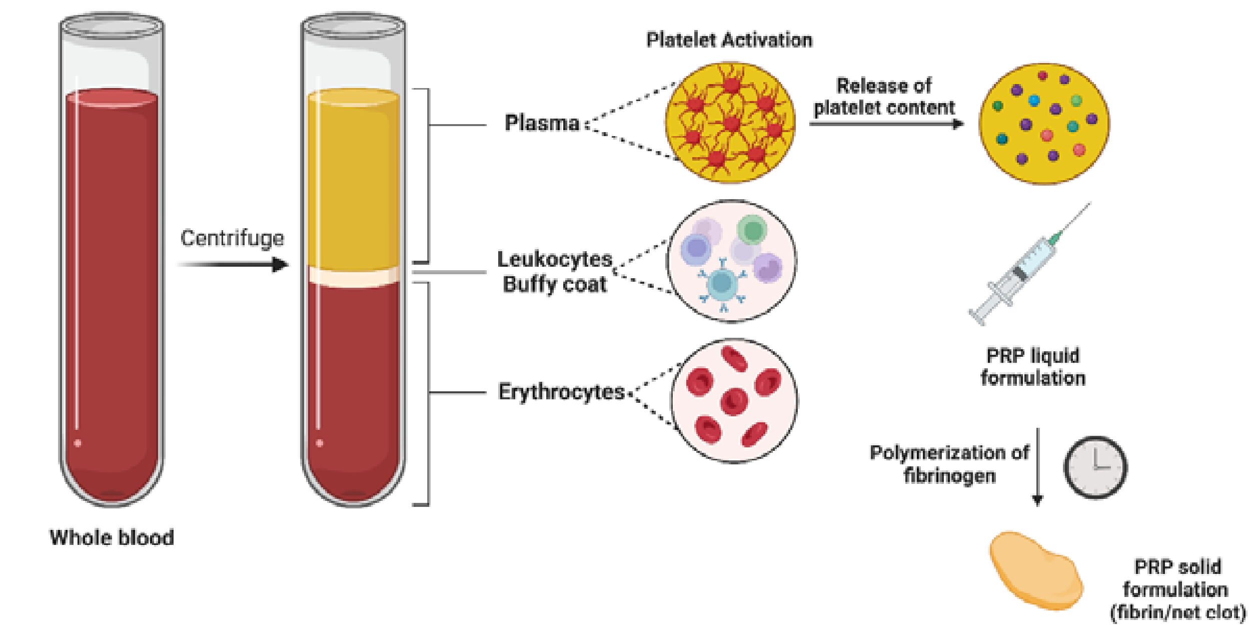

Figure 1: *PRP is obtained by the patient's whole blood sample. After blood collection, a centrifugation process is performed separating the PRP from other blood components.*

mation, clotting, cell adhesion, cell growth, host defence)[24].

The preparation method critically affects the PRP composition and therapeutic potential. PRP is prepared by the patient's whole blood sample. After blood collection, the blood sample is placed in tubes with anticoagulant (sodium citrate)[25]. Centrifugation separates the PRP from other blood components by applying centrifugal force between 350-2000g for 3-15 minutes. Centrifugation must be performed in a sterile microbial environment and can be single or double, depending on the protocol used. Following spinning, the blood separates into layers; the bottom layer, almost half of the blood amount, including mainly red blood cells; a thin intermediate layer lying above RBCs and consists of leukocytes (buffy coat) and the superficial layer containing the plasma fraction and platelets (Fig. 1)[25]. The PRP products may include the leukocyte layer or not. The PRP that has a leukocyte concentration above baseline is named Leukocyte Rich-PRP (LR-PRP), and this with leukocyte concentration below average Leukocyte Poor-PRP (LP-PRP). LR-PRP can release high levels of pro-inflammatory cytokines inhibiting cell proliferation, chondrogenic differentiation and articular cartilage regeneration, and it is not recommended as a KOA treatment. However, further studies are needed.

After centrifugation, PRP activation initiates; this is a crucial step in efficient PRP protocols leading to the platelet degranulation process, involving the fusion of activated platelets granules to the cell membrane and the GFs release promoting cell mitosis, chondrogenesis, angiogenesis and chemotaxis. Platelets secrete almost 70% of GFs stored within the first ten minutes of activation and more than 95% of the pre-synthesized GFs within one hour. However, they continue to produce additional GFs for approximately eight days. The activation begins with the blood clot formation but lasts ten minutes after the clot is complete. Therefore, PRP should be generated in an anticoagulant environment and used within ten minutes of the onset of thrombus formation.

On the other hand, several limitations of PRP preparation exist. The platelet aggregate must be extracted from the whole blood precipitate without

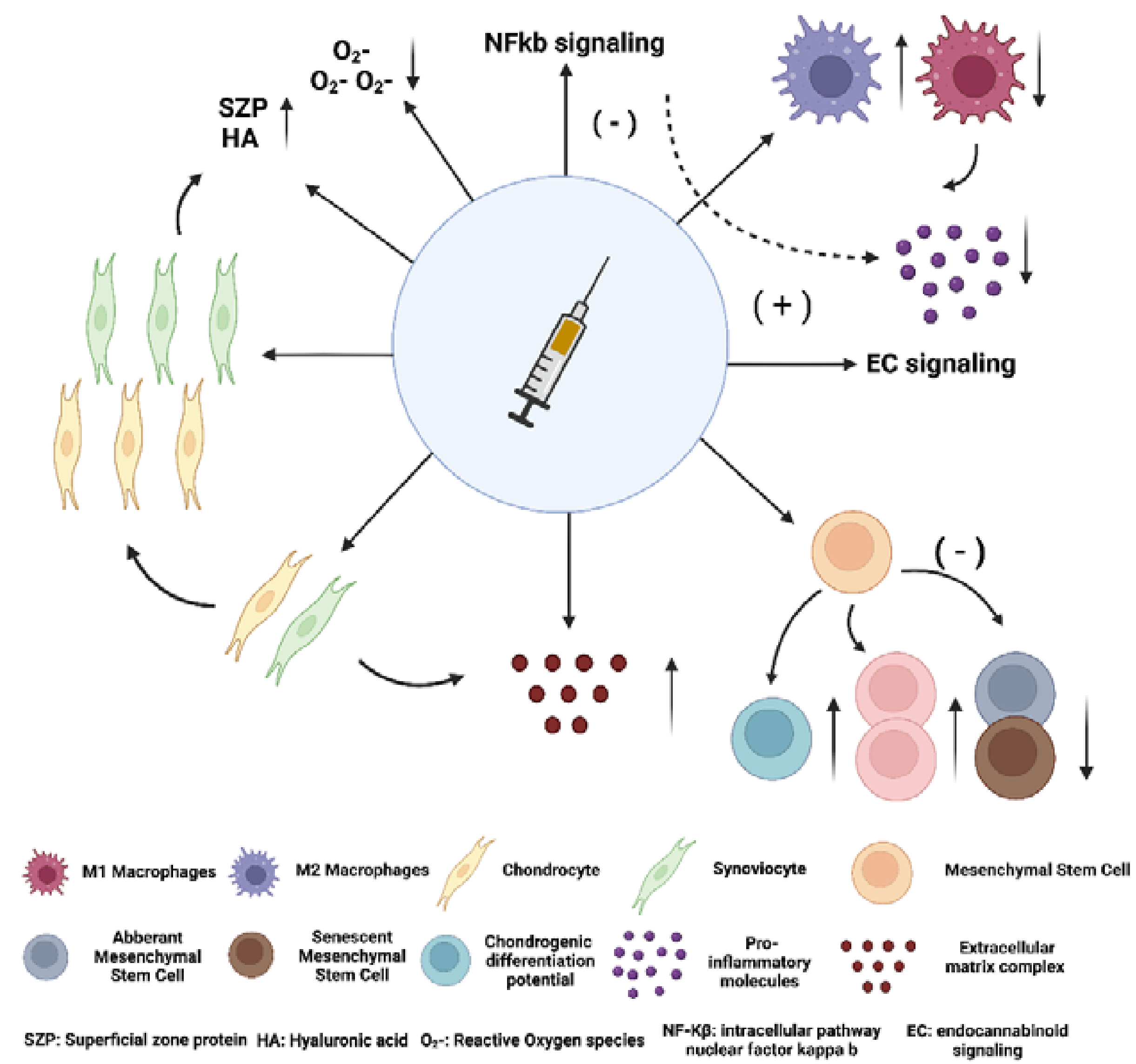

Figure 2*: Intra-articular PRP injections are involved in numerus molecular and biochemical mechanisms affecting the cartilage.*

mixing or damage; if this happens, it can no longer actively secrete GFs. The apparatus of PRP production must be certified by internationally recognised organisations. Improper production may reduce the platelet concentrate content and the number of released active agents. The lack of standardization is another limitation of PRP production. Different PRP compositions may result in various biological and clinical outcomes. Thus, PRP protocol standardization for KOA treatment is necessary.

The PRP role in KOA

PRP contains numerous GFs with a variety of biological functions:

1. **CTGF**: stimulates angiogenesis and enhances cartilage regeneration[26].

2. **EGF**: promotes angiogenesis, endothelial cells chemotaxis, MSCs mitosis, and epithelisation and significantly shortens the healing process. EGF also increases MSCs and epithelial cells' cytokine secretion[27].

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3. **FGF**: stimulates osteoblasts and chondrocyte differentiation and growth. It positively affects cartilage repair and, together with VEGF, promotes angiogenesis[28].

4. **Hepatocyte growth factor (HGF)**[29] involves cartilage regeneration and chondroinductive actions. HGF reduces IL-6 production, increases the anti-inflammatory cytokine IL-10 release and contributes to the NF-κB pathway inhibition.

5. **IGF**: enhances the other cartilage GFs effects, the MSCs differentiation and mitogenesis and stimulates cell growth and bone formation through osteoblasts' differentiation and proliferation[30,31]. Together with PDGF, it enhances collagen synthesis and prevents the NF-κB pathway activation.

6. **PDGF**: stimulates collagen and extracellular matrix synthesis, enhances macrophages, fibroblasts and neutrophils chemotaxis and promotes TGF secretion from macrophages. PDGF also prevents the NF-κB pathway activation[30,31].

7. **TGF-β:** stimulates collagen production, inhibits collagen breakdown and enhances angiogenesis. TGF-β may also enhance osteoblast proliferation, prevent osteoclast formation and enable connective tissue regeneration and immune cells chemotaxis[32].

8. **VEGF:** regulates angiogenesis and tissue regeneration, crucial in nutrient transport and higher blood flow to the injury site[33]. VEGF stimulates neutrophils and macrophages through chemotaxis.

Some GFs can interact with each other, thus activating a variety of intracellular signalling pathways and enhancing tissue repair[32].

Numerous molecular and biochemical mechanisms are involved in cartilage healing following PRP intraarticular injections (Fig. 2):

a. Anti-inflammatory effect

1. NF-κB pathway inhibition

PRP therapy aims at anti-inflammatory action, restoring articular cartilage homeostasis and promoting tissue repair. Many PRP GFs (IGF-1, HGF) have anti-inflammatory activity by inhibiting the NF-κB pathway and chondrocyte, fibroblast, and macrophage activation. The NF-kB plays a crucial role in KOA's pathogenesis. NF-kb comprises five homo- or heterodimers; the p65/p50 heterodimer is the prototype. In normal conditions, the NF-kB dimers are unstimulated and bound with the inhibitor proteins IkB into the cytoplasm. Following a pro-inflammatory signal stimulation, NF-kB complexes can bind into NF-kB response elements, enabling immunomodulatory proteins and pro-inflammatory factors[34]. The NF-kB pathway expresses matrix-degrading enzymes and abnormal catabolic pathways that affect the cartilage, causing hypertrophy and inflammation[35]. Numerous studies have demonstrated that PRP inhibits the NF-kB pathway. In vitro and in vivo studies supports that PRP secretes HGF, IGF-1, and PDGF that inhibit the NF-kB signalling pathway by either acting directly on the NF-kB transcription factor or suppressing the NF-kB-produced inflammation factors such as macrophages and fibroblasts[36,37]. Thus, the NF-kB signalling pathways understanding and their role in KOA may provide insight into possible pharmaceutical targets.

2. Macrophage phenotype alterations and suppression of reactive oxygen species

Many studies demonstrated the phenotype shifting of inflammatory M1 macrophages into reparative M2 macrophages resulting in tissue repair[38-39]. The increase in anti-inflammatory macrophage action mainly affects the synovial membrane. Another PRP anti-inflammatory action involves suppressing reactive oxygen species (ROS), achieved by activating the antioxidant pathway NrF2-ARE in osteoblasts.

b. Analgesic action and cartilage healing

OA patients experience high pain levels, limiting activities and affecting their quality of life. The analgesic PRP mechanism of action is complicated. The macrophage phenotype change mentioned above suppresses the PGE2 production, mainly produced by pro-inflammatory macrophage M1[40]. The NF-Kβ pathway inhibition also reduces joint synovitis[40]. The PRP's GFs reproduce the tissue healing complex process, improving angiogenesis, inflammation and immune response[27]. GFs reduce the local inflammatory response, enhance cartilage healing and promote chondrocyte antiapoptotic properties, mediating beneficial anabolic effects in KOA[41,42]. Intra-articular PRP injections may decrease the pain mediators' expression (PGE2, dopamine, 5-hydroxytryptamine and substance P) and contribute to tissue and cartilage healing, regulating catabolic enzymes and critical pro-inflammatory mediators and maintaining joint homeostasis[43-44]. Studies have shown that intra-articular PRP injections enable the healing process by inhibiting chondrocyte apoptosis, remodelling bones and vessels, modulating inflammation and stimulating collagen synthesis[29]. PRP stimulates the healing process through cell differentiation and proliferation[41] and reduces the expression of inflammatory enzymes[18].

c. Cellular regulation

Preclinical studies have shown that PRP improves KOA symptoms by stimulating the MSCs' migration, proliferation and differentiation into articular chondrocytes[29]. PRP contains the essential cytokines (EGF, TGF-β, PDGF, IGF-1) to support and stimulate the MSCs' growth and differentiation. Literature supports that the MSCs' recruitment to the injury site is due to PRP cell adhesion molecules and chemotactic properties[29]. Other studies demonstrated that PRP could promote cell migration, maintaining the adipogenic, chondrogenic and osteogenic differentiation capacity of MSCs, enhancing the cell clones' formation and maintaining an immunosuppressive state. Zhang et al. discovered that PRP promoted a variable cell osteogenic ability but restrained cell adipogenic ability, in line with other studies[29]. The PRP chemotactic properties are also mediated through the chemokine stromal factor 1 (SDF-1a), which is stored in a-granules and acts through CXCR-4 to promote cell migration and homing[45].

Discussion

A thorough understanding of KOA pathogenesis is needed to produce disease-modifying drugs. PRP may be the future new KOA treatment. Platelets' granules secrete several essential protein GFs and secretory proteins that may be beneficial in KOA. The PRP preparation method critically affects its composition and therapeutic potential. PRP is produced from the patient's blood, thus avoiding an immune response, disease transmission or other allografts side effects. The main PRP limitation is the lack of standardization of protocols of therapeutic efficacy, such as platelet concentration, dose number and cost-effectiveness. Anti-inflammatory, analgesic, tissue healing, and cellular regulation are PRP's primary modes of action in KOA. The main reported PRP biological actions include the NF-κB pathway inhibition, macrophage phenotype alterations, suppression of reactive oxygen species and the other regulatory and tissue healing processes mediated through GFs.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Closed Reduction and Casting Versus K-wire Fixation of Gartland Type II Supracondylar Fracture Humerus in Children: Radiographic Outcome and Complications

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ABSTRACT

Background: Supracondylar fracture is the most common elbow fracture in children. There is substantial agreement on managing Gartland type I (conservative) and type III (operative) fractures. The treatment of type II fractures is still debatable. This study aimed to review the radiographic outcome and complications of type II supracondylar fractures in children treated by closed reduction & casting and closed reduction & K-wire fixation, respectively.

Methods: We retrospectively reviewed 61 children with type II fractures treated with closed reduction and casting (Group 1;32) and closed reduction K-wire fixation (Group 2;29). Radiographic outcomes and complications were analysed and compared between the two groups.

Results: Overall higher radiographic loss of reduction (LOR) was noted in group 1 compared to group 2 (40.62% vs 13.79%, *p*=0.0405). Higher LOR was observed in both IIA and IIB fractures in group 1, managed with closed reduction and casting (p=0.1257, *p=0.0437*).

We found higher LOR in group 1 with IIA fractures, where the anterior humeral line (AHL) was not intersected the capitellum (*p=0.0224*). We noted more complications in group 1 patients compared to group 2 (28.12% vs 17.24%, p=0.316), and most of these complications were due to reoperation following the loss of reduction.

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Conclusion: Higher LOR and complications were noted in type II fractures managed by closed reduction and casting (Group 1) alone. Our study supports K-wire fixation in some cases of type IIA fracture, where the AHL is not intersecting the capitellum and in all cases of type IIB fractures.

Keywords: Supracondylar fracture, Gartland type II, Closed reduction & casting, K-wire fixation, Radiographic outcome, Complications

Introduction:

Supracondylar humeral fractures are the most common elbow fractures among children and adolescents, about 85% of all elbow fractures [1]. These fractures typically occur transversely through the medial and lateral columns of the distal humerus [2]. This area of the bone is relatively weak because of the metaphyseal remodelling during the first 10 years of development; therefore, the incidence of this injury peaks between 5 to 8 years of age [2]. Gartland classified supracondylar fractures in type I (no displacement), type II (posterior displacement of the distal fragment without posterior hinge disruption) and type III (complete displacement) [3]. Wilkins modified this classification by dividing type 2 fractures into IIA (posterior displacement only) and IIB (displacement plus translation/rotation of the distal fragment) [4].

There is generally no controversy in the treatment of type I (conservative) and type III (surgical approach) supracondylar distal humerus fractures in children [5]. The treatment of type II fractures is, however, less well-defined. Although some authors have recommended treating all type II fractures operatively (reduction and pinning) to maintain reduction and avoid further deformity [6-8], others suggest treating some nonoperatively [9,10]. Some reported a higher risk of compartment syndrome and decreased range of motion (ROM) following nonoperative treatment; others reported satisfying clinical and radiological outcomes without exposing the patient to surgical and anaesthetic risks [8,11].

Wilkins modification has often been used to solve this dilemma, addressing type IIA to casting and type IIB to surgery; however, many doubts about the validity of this distinction. Several authors have reported low intra- and inter-observer agreement rates in distinguishing IIA and IIB [12,13]. Many of these fractures are stable after closed reduction and casting in 90°of flexion. If more than 90° of flexion is required to maintain reduction, fewer complications may be found with closed reduction and percutaneous pin fixation. Furthermore, percutaneous pin fixation is needed to address rotational deformities [14].

We are reporting our experience treating Gartland type II supracondylar fractures in children. The purpose of this study is to review the radiographic outcome and complications of Gartland type 2 supracondylar fractures in children treated by closed reduction & casting and closed reduction and k-wire fixation, respectively.

Materials and methods:

Sixty-one cases of Gartland type 2 fractures were retrospectively reviewed between January 2014 and July 2020. Data was collected from Electronic Medical records and PACS radiographs to identify demographics, side of the fracture, type of fracture, timing of surgery, type of fixation, number & size of K-wire, loss of reduction, pre-operative and iatrogenic neurovascular injuries, stiffness of elbow, number of weeks at K-wire removal, need for physiotherapy, cubitus varus deformity and other complications, numbers of weeks to final follow up.

Out of 61 cases, 32 children were treated with closed reduction and casting (Group 1) and 29 with closed reduction and cross or lateral wire fixation

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Table 1 Characteristics of all type II supracondylar fractures in Group 1 and Group 2

Variable	Closed reduction and casting (Group 1, n=32) *Mean/N/%/+/-SD*	Closed reduction and wire fixation (Group 2, n=29) *Mean/N/%/+/-SD*
Age	5.96+/- 1.42	6.17+/-1.94
Range	(4-10 years)	(3-11Years)
Sex		
Boys	20 (62.5%)	19 (65.5%)
Girl	12 (37.5%	10(34.5%)
Side		
Right	17 (53.1%)	13 (44.8%)
Left	15 (46.%9)	16 (55.2%)
Fracture type		
IIa	22 (68.8%)	10 (34.5%)
IIb	10 (31.3%)	19 (65.5%)
A/E presentation and surgery Interval		
<24hrs	29 (90.6%)	23(79.3%)
Pre op nerve injury	1(3.12%) (Ulnar N-sensory only)	0
Type of reduction		
Open	0	0
Closed	32	29
Type of K-wire Fixation	NA	
Cross		10(34.5%)
Lateral		19(65.5%)
Size of wire	NA	
1.6mm		10(34.5%)
2mm		17(58.6%)
1.6 mm & 2mm		2(6.9%)
No of k wire	NA	
2 wires		25 (86.2%)
3 wires		4 (13.8%)
Mean BA angle	73.96 (63-87 degrees)	73.65 (63-88 degrees)
Mean BA changes (3-6wks)	5.81+/- 4.76 degrees	4.13 +/- 3.79 degrees
Anterior Humeral Line (AHL) not intersecting capitellum (3-6wks)	10	4
Physiotherapy	7 (21.9%)	14 (48.3%)
Average follow-up	7.68 weeks (6-18)	11.48 weeks (6-36)

(Group 2). We excluded cases with type I and type III fractures, flexion type fractures, cases with inadequate follow-up or X-ray, and children under three years old.

Patients were reviewed in the follow-up clinic 5-9 days after the initial procedure for a complete cast and check X-ray. Both groups had a further x-ray done at 3-6 wks. We compared perioperative radiographs with postoperative radiographs taken at 3-6 weeks of all 61 children.

Loss of fracture reduction was determined by comparing the perioperative and post-operative follow-up x-ray. We reviewed radiographic loss of reduction (LOR) by evaluating changes in the Bauman angle (BA)>12 degrees in the coronal plane [15] and the Anterior humeral line (AHL) not intersect-

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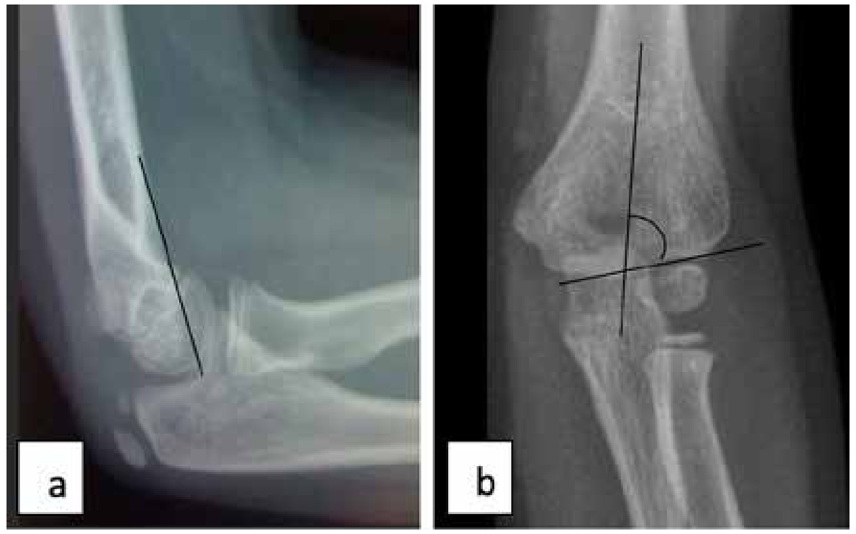

Figure 1 *a) Normal elbow X-ray –lateral radiograph showing Anterior Humeral line (AHL) intersecting capitellum. b) AP radiograph showing Bauman's angle*

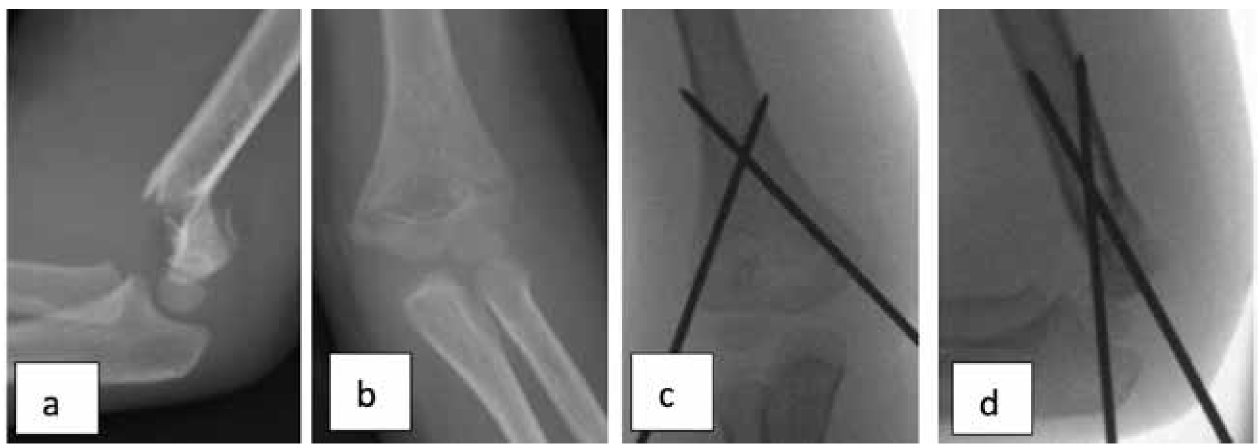

Figure 2 *(a, b) Pre-operative AP and lateral radiograph showing type IIb fracture. (c, d) Intraoperative AP and lateral radiograph showing adequate reduction and fixation with crossed K- wire*

ing capitellum in the sagittal plane (Figure 1) [15].

Statistical analysis was performed using open-source online resources. Data of all variables were analysed to determine differences between the closed reduction & casting and closed reduction & K-wire fixation group. Statistical significance was tested using Fisher exact test, and P<0.05 was set as the threshold for statistical significance.

Results

In group 1, the mean age was 6 years (range 4-10 years); there were 20 boys (62.5%) and 12 girls (37.5%), and the right arm was affected in 17 children (53.1%). In group 2, the mean age was 6.2 years (range 3-11 years); there were 19 boys (65.5%) and 10 girls (34.5%), and the right arm was affected in 13 cases (44.8%) (Table 1).

In group 1, 22 (68.8%) cases had Gartland IIA fractures, and 10 (31.3%) had Gartland IIB fracture.26 (81.3%) cases were treated with closed reduction and casting within 24hrs of presentation to the Emergency department.

In group 2, 10 (34.5%) cases had Gartland IIA fractures, and 19 (65.5%) had Gartland IIB fractures. 21(72.4 %) cases were operated (closed reduction and K-wire fixation) within 24hrs of presentation to

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Table 2 Loss of reduction in type II supracondylar fracture

Variable	**Closed reduction and casting (Group 1, n=32)** *Mean/N/%/+/-SD*	**Closed reduction and wire fixation (Group 2, n=29)** *Mean/N/%/+/-SD*	**P value**
Radiographic loss of reduction			
Yes	13(40.6%)	4 (13.8%)	***0.0404***
No	19	25	
IIA	7 (31.8%)	0	0.1257
IIB	6 (60%)	4 (21%)	***0.0437***

Table 3 Relationship of the preoperative intersection of AHL to capitellum and loss of reduction in closed reduction and casting (Group1)

	AHL intersecting capitellum	**AHL NOT intersecting capitellum**	**P value**
Radiographic loss of reduction in group 1 (Gartland 2A, n=22)			
Yes	1	6	*0.0224*
No	11	4	

of type IIA fractures. We found higher LOR in group 1 with IIA fractures, where the anterior humeral line (AHL) was not intersected the capitellum (p=0.0224) (Table 3).

the Emergency department. In Group 2, 19 (65.5%) cases were treated with lateral wire, and 10 (34.5%) cases were treated with crossed wire (Figure 2). Most commonly, the fracture was fixed with 2 wires (86.2%) using 2mm (58.6%) K-wires (Table 1).

Mean BA was 73.96 degrees (range 63-87 degrees) and 73.65 degrees (range 63-88 degrees) in group 1 and group 2, respectively. At 3-6 weeks follow up, mean changes in Bauman angle were 5.81degrees +/-SD 4.76 in group 1 and 4.13 degrees +/-SD 3.79 in group 2. At 3-6 weeks follow up, AHL was not intersecting capitellum in 10 (31.3%) cases in group 1, 4 (13.8%) cases in group 2, whereas BA changes >12 degrees in 3 cases in group 1 and none in group 2.

In our series, LOR was noted in 27.9% (17) cases. LOR was noted in 13 (40.6%) cases in group 1(Figures 3 and 4) and 4 (13.8%) cases in group 2. This was statistically significant (*p= 0.0405*) (Table 2).

We further analysed the LOR in group 1 cases. Higher LOR was observed in both IIA and IIB fractures in group 1, managed with closed reduction and casting (p=0.1257, *p=0.0437*) (Table 2).

In group 1, out of 13 cases with loss of reduction, 7 cases were type 2A (Figure 3), and 6 cases were type 2B (Figure 4). AHL was not intersecting the capitellum (Figure 3) in 6 cases

We reviewed all the complications in both groups (Table 4). Revision /reoperation (within three months) was done in 6 (18.75%) cases in group 1 but none in group 2. All instances of reoperation were due to loss of reduction. Remanipulation and casting were done in 4 cases, and 2 cases were treated with manipulation and K-wire fixation. One patient had the pre-operative ulnar nerve (only sensory) involvement in group 1, which improved fully in 6 weeks, but no pre-operative nerve injury was noted in group 2. There were no patients with vascular involvement or compartment syndrome in either group. Only one (3.4%) child had post-operative median nerve involvement in group 2, but none

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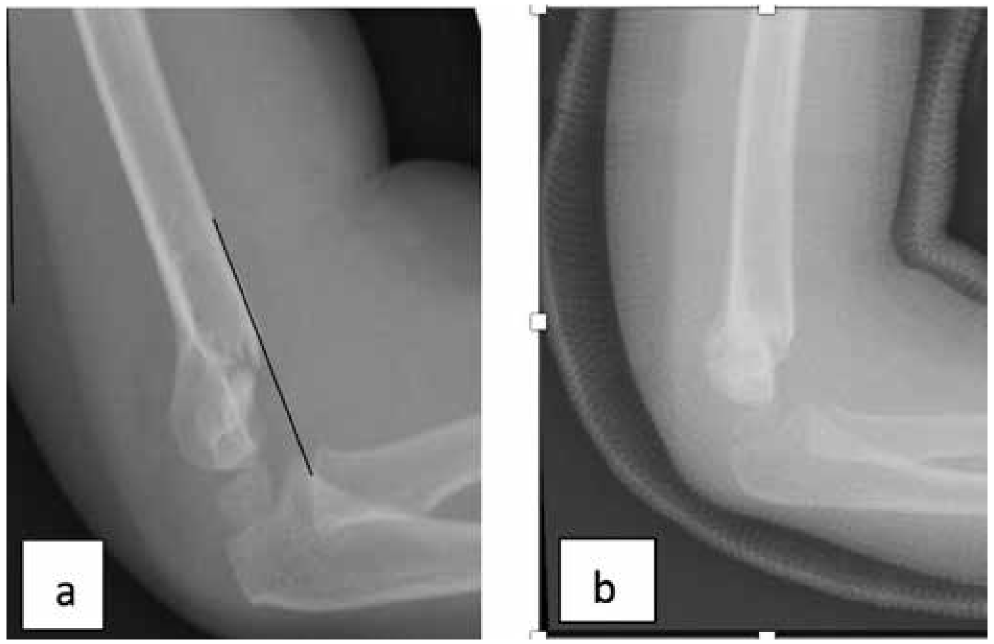

Figure 3 *a) Lateral radiograph showing type IIA fracture (AHL not intersecting capitellum). b) Lateral radiograph showing loss of reduction following closed reduction and casting*

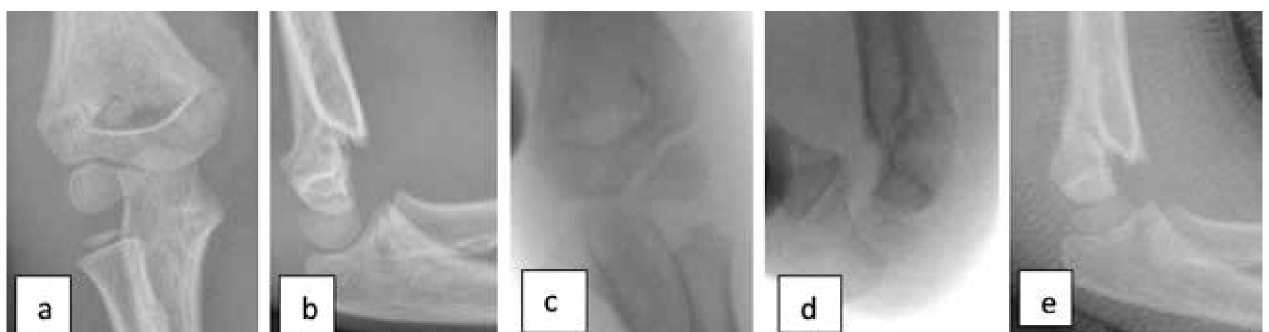

Figure 4 *(a, b) Pre-operative AP and lateral radiograph showing Gartland type IIB fracture. (c, d) Intraoperative AP and lateral radiograph showing adequate reduction (closed reduction and casting). (e) Lateral radiograph showing loss of reduction 3 weeks postoperatively*

was noted in group 1. It was resolved fully in 12 weeks. In 1 (3.4%) case, pin site infection was noted in group 2, treated with antibiotics. There was 1 (3.4%) case of cubitus varus in group 2 but none in group 1. Moderate elbow stiffness was noted in 1(3.4%) case in group 1 and 2 (6.9%) cases in group 2. Hyperextension was mentioned in 2(6.3%) cases in group 1 but none in group 2. None of the patients in our series had intraoperative complications related to anaesthesia. Higher overall complications were noted in group 1 compared to group 2 (28.1% vs 17.2%, p=0.316). The overall complication rate in our series with type II supracondylar was 23 %, and around 40 % were due to reoperation.

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Table 4 Complications in Group 1 and Group 2

	Closed reduction and casting (Group 1, n=32)	Closed reduction and wire fixation (Group 2, n=29)
Overall complications	9 (28.1%)	5 (17.2%)
Iatrogenic nerve injury		1(3.4%)
Elbow stiffness	1(3.12%)	2(6.9%)
Hyperextension	2 (6.25%)	0
Cubitus varus	0	1(3.4%)
Infection	0	1(3.4%)
Any Revision/reoperation procedure (within 3 months)	6 (18.8%)	0

Mean follow-up was 7.68 weeks (range 6-18 weeks) and 11.48 weeks (range 6-36 weeks) in group 1 and group 2, respectively.

Discussion

The treatment of Gartland type I and III fractures is commonly accepted as non-operative and operative treatment, respectively. However, controversy persists over the management of type II supracondylar fractures.

Overall, in our study, radiographic LOR was 27.9%. LOR was noted in 40.6% of group 1 and 13.8% of cases in group 2 (*P= 0.0405*). We recorded a LOR in the closed reduction and casting group higher than some of the reported literature. We further analysed the LOR in group 1 cases. Higher LOR were observed in IIA and IIB fractures in group 1, which were managed with closed reduction and casting (p=0.1257, *p=0.0437*). We also noted higher LOR in Group 1 with type IIA fracture where AHL did not intersect capitellum pre-operatively (Table 3).

Revision /reoperation (within 3 three months) was done in 18.8% of cases in group 1 (all due to loss of reduction) but none in group 2.

Lucas et al.[16] reported up to 48% chance of losing reduction without pinning for Gartland type 2 fractures. Parikh et al.[10] found that 28% of patients lost reduction after closed reduction and cast immobilisation. Hadlow et al.[9] reviewed 148 patients with type II supracondylar fractures treated with closed reduction and casting. Of these patients, 23% required a second procedure owing to loss of reduction (either re-manipulation with the placement of a new cast or closed reduction and pin fixation). In a retrospective review of 189 patients with type II supracondylar fractures treated nonoperatively, 21% of patients eventually underwent operative treatment [17]. Camus et al.[18] reported that 80% had radiographic evidence of extension deformity with long-term follow-up of 155 patients treated nonoperatively with cast immobilisation. In contrast, in a retrospective review of 189 cases of type II supracondylar fractures treated with percutaneous pin fixation, Skaggs et al. [8] found no loss of reduction. Most surgeons agree that Gartland type IIB fracture should be treated with K-wire fixation, but disagreement persists regarding the management of IIA fractures. In our study, we found a significantly higher loss of reduction of fractures in type IIA where AHL was not intersecting capitellum and in type IIB fractures treated without K-wire fixation.

Most type IIA fractures with AHL intersecting capitellum are stable after closed reduction and casting in 90° of flexion. However, if more than 90° of flexion is required to maintain reduction, fewer complications may be found with closed reduction and K-wire fixation.

In our cohort, one case had the pre-manipulation ulnar nerve (only sensory) involvement in group 1, which improved fully in 6 weeks, but none was noted in group 2. Only one (3.1%) child had (group 1) post-operative median nerve involvement, which was resolved fully by 12 weeks. Our finding is somewhat higher than previous reports (0%, 0/189

Skaggs et al. [8]; 0.8%, 3/399 Larson et al.) [19].

In our series, there were no patients with vascular involvement or compartment syndrome in either group, and this is similar to other reported literature. Little data exist about the incidence of infection after percutaneous pinning, but rates up to 2.5% of superficial [8,21] and around 0.2% of deep[22] pin tract infections have been reported. Our series detected a single case (3.4%) of superficial pin site infection, successfully treated with oral antibiotics.

Moderate elbow stiffness was noted in 1(3.1%) case in group 1 and 2 (6.9%) cases in group 2. Hyperextension was mentioned in 2(6.25%) cases in group 1 but none in group 2. An extension malunion provokes an increase in extension and a lack of flexion. Hyperextension of the elbow causes only cosmetic problems. However, a lack of flexion can cause an inability to perform activities of daily living. It has been described that functional elbow motion is from 30° to 130°.

In our study, one patient (3.1%) developed cubitus varus deformity in group 2 but none in group 1. Most authors believe that cubitus varus is the consequence of malunion of the fracture rather than growth arrest. Angular deformity and rotational deformity are thought to cause cubitus varus deformity. Distal physis of the humerus has limited potential for remodelling. A child aged eight to ten years has only 10% of the total growth of the humerus remaining. While sagittal and coronal mild deformities can be remodelled in children aged < 4, rotational deformities cannot [23]. In literature, this percentage varies between 0% and 26.1% [24]; even though this deformity was considered an aesthetic problem, more recently, it has been linked to chronic pain [25], ulnar neuropathy [21], and late postero-lateral instability [25]. Hence, the best way to avoid cubitus varus seems to be to achieve and maintain anatomical reduction of the fracture with particular attention to replicating the contralateral rotation of the humerus.

Our study certainly has some limitations. It is a retrospective study, so it has some selection bias. Different surgeons have carried out procedures. No standard protocol was used; pin configuration depended on the surgeon's preference. Our patient sample size was relatively small, and we did not do long-term follow-up.

Conclusions:

Many studies support that satisfactory outcomes should be expected in closed reduction and casting or closed reduction & K-wire fixation management of Gartland type II supracondylar fractures as long as correct treatment criteria are known and applied.

In our study, higher radiographic loss of reduction (LOR) and complications were observed in type II fractures managed by closed reduction and casting alone. So current study indicates that the natural history of type II supracondylar is not entirely benign. It is essential to check the relationship of AHL to capitellum and the presence of any rotational deformities to decide the management of Gartland type II supracondylar fracture. Our study supports K-wire fixation in some cases of type IIA fracture, where the AHL is not intersecting the capitellum and in all cases of Type IIB fractures.

However, long-term prospective randomised studies comparing closed reduction and casting versus reduction and K-wire fixation are needed to define the best treatment options for Gartland type 2 supracondylar fracture in children.

Statements and Declarations:

Conflict of interest

The authors declared no potential conflicts of interest.

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Research involving human and animal rights statement

This article does not contain any studies with human or animal subjects.

Ethical approval

An ethics committee approval is not required for this study type.

Informed consent

No human subjects were used in this study which necessitates informed consent.

Sanjay Jain et al. Closed Reduction and Casting Versus K-wire Fixation of Gartland Type II Supracondylar Fracture Humerus in Children: Radiographic Outcome and Complications

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The role of the gastrocnemius muscle flap in the treatment of failed Total Knee Arthroplasty.

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ABSTRACT

Introduction: Total knee arthroplasty (TKA), although generally a safe operation, fails in a small number of patients with substantial morbidity. Muscle flaps and especially the medial gastrocnemius offer a viable treatment option for limb salvage. The surgical technique is described and the senior author's personal experience is reviewed.

Patients and methods: A retrospective study of patients treated with a medial gastrocnemius flap for failed TKA was conducted. Five patients were found, 4 female and one male. Mean age was 63.8 years (range, 38 – 85 years). Four patients were operated at the Middlesex and UCH Hospitals, London and one at Metropolitan General Hospital, Athens. All patients had a preexisting skin defect of the knee area with exposed tendon, bone and/or implant. The surgical technique used is briefly described. Postoperative antibiotics were administered to all patients for a minimum of 6 weeks.

Results: There were no flap or donor site complications. All flaps and skin grafts survived. One patient died at home five weeks postoperatively of unrelated causes. One patient presented with a wound breakdown three weeks after the flap operation. The defect was covered with a lateral tibial fasciocutaneous flap. The Oxford Knee Score improved in all patients.

Conclusion: The medial gastrocnemius muscle flap remains the first line of treatment of failed total knee arthroplasties. Early use of the flap is recommended in order to achieve the best possible outcome.

Key words: Total knee arthroplasty, infection, surgery, failure, muscle flaps, gastrocnemius muscle, reconstruction.

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Introduction

Total knee arthroplasty (TKA) provides excellent results for most patients with osteoarthritis. A number of complications, however, including infection, delayed wound healing, wound dehiscence, and skin necrosis pose substantial risk to patient morbidity (prosthetic infection, amputation etc.) and mortality. Soft tissue coverage by means of flap reconstruction is a viable treatment option which can save the limb and, occasionally, even the patient's life.

Various local (rotation) and distant (free) flaps have been utilized to cover wound defects of the knee and improve vascularization and antibiotic/nutrient delivery to the area: muscle flaps (medial gastrocnemius, lateral gastrocnemius, rectus abdominis, latissimus dorsi, gracilis), chimeric and fasciocutaneous flaps (random pattern, perforator). Size of the defect, donor site morbidity and condition of the patient are the main considerations dictating flap choice.

The gastrocnemius flap, basically the medial gastrocnemius, remains the commonest method of reconstruction for defects at or distal to the inferior pole of the patella (1-5). This axial pattern muscle flap is supplied by the medial sural artery and can be rotated to cover soft tissue defects of the anterior distal aspect of the knee (6, 7). It is a versatile flap due to its substantial size, mobility, ease of harvest, and minimal functional loss and donor site morbidity (1, 8). The flap ranges from 5 to 9 cm in width and from 13 to 20 cm in length (8). It improves the delivery of oxygen, systemic antibiotics, and immune modulators to an infected joint (1, 9).

Aim of this paper is to evaluate the personal experience and the results of the senior author (Ch. I). A small series of 5 patients operated on because of a preexisting knee defect after total knee arthroplasty (TKA) have been reviewed. The surgical technique is described, the advantages and disadvantages of the medial gastrocnemius muscle flap are discussed and a comparison with other reconstructive methods according to recent literature reviews is presented.

Patients and methods

A retrospective study of patients treated with a medial gastrocnemius flap after failed TKA was conducted. The study group consisted of 5 patients, 4 female and one male. Mean age was 63.8 years (range, 38-85 years). The left knee was involved in 3 cases and the right in two (Table 1). Four patients were operated on at the Middlesex and UCL Hospitals, London and one at Metropolitan General Hospital, Athens (all five Ch. I.). The indication for using a gastrocnemius flap in this setting was deficient soft tissue over the anterior knee (Fig. 1). All five patients had a preexisting skin defect with exposed (or ruptured) tendon, bone or implant (Fig. 2). The medial head of the gastrocnemius muscle was used in all five cases and the muscle flap was covered with a split thickness skin graft in four of them. Three patients met Musculoskeletal Infection Society criteria for periprosthetic joint infection (10), with the most common infecting organisms being Staphylococcus species. In one case, a concomitant pre-flap patellar tendon reconstruction was performed; a rectus femoris tendon turnover was utilized for this purpose.

Antibiotics were administered for a minimum of 6 weeks (two weeks i.v., then per os) to all patients. Postoperatively, all patients were assessed clinically at regular interval

Surgical technique

The patient is positioned supine and a thigh tourniquet is placed high on the ipsilateral thigh. After obtaining tissue cultures, debridement of osseous, soft tissue and retained implant surfaces as well as sinus tracts and devitalized tissue is carried out. Once the revision is completed, the residual soft tissue defect is assessed (Fig. 3). An incision is placed 2 to 3 cm posterior to the middle border of the tibia (Fig. 4A), from the distal end of the muscle belly to the level of the popliteal fossa. The skin bridge to the knee defect ought to be at least 7 cm wide in order to prevent skin necrosis. After skin incision, bilateral skin flaps are elevated (above the gastrocnemius fascia); the saphenous vein is preserved. The medial gastrocnemius muscle is exposed along its length, the fascia is opened and the avascular plane between gastrocnemius and underlying soleus muscle is developed (Fig. 4B). Care is taken to preserve the plantaris, which lies between these muscles. The median raphe is identified (between the two heads

TABLE 1. Data of the five patients

Patient	Age	Sex	Side	Comorbidities	Complications	SSG	Latest Outcome
M F	38	F	RI	RA	None	Yes	OK
C F	49	F	LE	None	None	Yes	OK
G L	82	M	LE	DM HTN	Dehiscence Second(Skin) Flap	Yes	OK
P N	65	F	RI	None	None	Yes	OK
B B	85	F	LE	HTN HF	None	No	Died 5 weeks postop.

RA: Rheumatoid arthritis
DM: Diabetes mellitus
HTN: Hypertension
HF: Heart failure
SSG: Split thickness skin graft

in the proximal third of the leg), so is the sural nerve which traverses the midline between the two heads. The dissection of the muscle is completed and this is sharply detached from its distal attachment leaving approximately 1 cm of Achilles tendon attached to the flap (Fig. 5). The muscle is carefully elevated proximally, with care not to sever the sural nerve, up to the level of the popliteal fossa. The dominant blood supply of the medial gastrocnemius is the sural artery (branch of the popliteal artery) accompanied by one or two veins and a branch of the tibial nerve (Fig. 6). Proximal dissection to the level of the popliteal fossa crease will protect the more proximally located flap pedicle even without direct visualization. After elevating the flap, this is rotated and transposed (under the skin tunnel) over the defect on the anterior part of the knee (Fig. 7). The flap should cover the defect without tension. It is secured with peripheral sutures (within the remaining cuff of aponeurosis and peripheral fascia) so as to minimize strangulation of the muscle and its blood supply (Fig. 10A). The donor site is closed in layers over a vacuum drain. The remaining parts of the recipient site (skin) are closed without tension. The extent of feasible closure should have been estimated prior to insetting the flap so that appropriate flap positioning is achieved. Where the skin cannot be approximated, the skin flaps should be sutured directly to the underlying muscle flap. A split thickness skin (SSG) graft is harvested from the ipsilateral thigh (Fig. 8), meshed (or not), placed and secured on top of the flap (Fig. 9). The wound is dressed with a non-adhesive dressing (paraffin gauze, Jelonet R, Smith & Nephew, Watford, England), sterile swabs, natural fiber padding (Velband®, Essity, Hull, England) and an elastic bandage. The skin graft donor site is covered with an adhesive dressing (Tegaderm® Film, 3M, Saint Paul, Minnesota, USA or Opsite® transparent adhesive wound dressing, Smith & Nephew, Kingston upon Hull, UK), sterile swabs and a compressive elastic bandage.

Results

There were no flap or donor site complications.

Fig.1. The soft tissues over the anterior knee after TKA are deficient.

Fig.2. Skin defect with exposed tendon.

Fig.3. Exposed knee prosthesis and soft tissue defect after completion of TKA revision.

All flaps and skin grafts survived (flap success rate 100%). One patient (BB) died at home of heart failure five weeks postoperatively. She had been discharged from hospital six days after flap cover of the exposed left knee prosthesis, which had resulted after a fall and subsequent scar breakdown and knee infection. Because of her medical history and in order to shorten anesthesia time, no skin graft was used. One month postoperatively, healthy granulation tissue had covered the muscle and there were clear signs of epithelialization (Fig. 10). The other four patients survived and were fit at last follow-up (median 12 months, range 1 to 30 months) (Fig. 11). There was one postoperative complication (operation success rate 80%). The male patient (GL) presented with a wound dehiscence three weeks after gastrocnemius transfer. Cover of the small defect was achieved with a lateral tibial fasciocutaneous flap (Fig. 12). The Oxford Knee Score improved in all four patients.

Discussion

Total knee arthroplasty (TKA) is a common and safe orthopedic procedure worldwide; complications, however, can be devastating. Soft tissue compromise or periprosthetic joint infection may cause failure of prosthesis, requiring knee fusion or amputation (2). Fortunately, the incidence of failure of TKA has been reported low. In a review of 20,184 TKAs, merely 58 patients required flap reconstruction (4). Other authors have reported that the rate of infection or wound healing complications in patients who have undergone TKA ranges from 0.33% to 10.5% (11, 12).

Muscle flaps represent a valid treatment option in cases of failure; they cover the wound defect, improve vascularization and antibiotic/nutrient delivery to the knee area. Muscle provides a well-vascularized and substantial tissue mass for elimination of dead space. Muscular flaps have been shown to be advantageous compared to fasciocutaneous flaps when covering chronically infected wounds due to increased collagen deposition and greater inhibition of bacterial growth (8). Several local and free flaps have been utilized; the gastrocnemius muscular flap, however, is the most widely used method (1-5, 13, 14) of reconstruction for knee defects due to its reliability and ease of harvest (8). The medial head of the gastrocnemius is supplied by the medial sural artery and can be rotated to cover soft tissue defects of the medial, anterior and upper knee. Its

Fig.4. A. The skin incision has been drawn 2-3cm posterior to the middle border of the tibia. B. Bilateral skin flaps have been elevated and the plane between gastrocnemius and soleus has been developed.

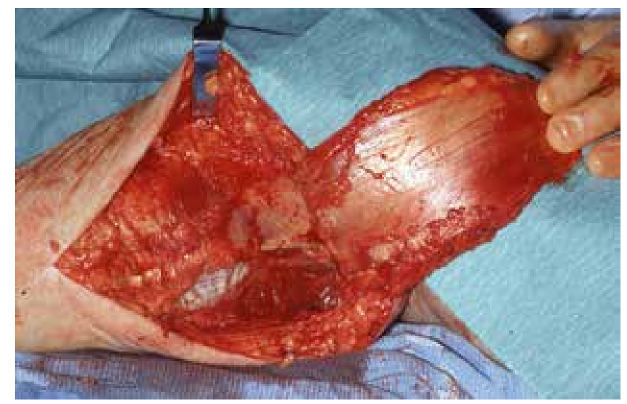

Fig.5.The gastrocnemius muscle has been detached from its distal attachment.

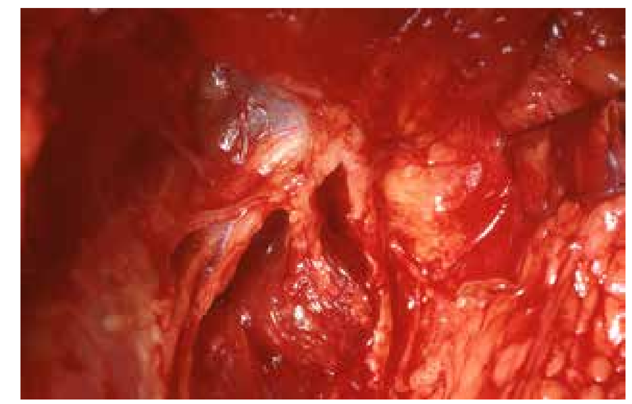

Fig.6.The dominant blood supply to the muscle is the sural artery.

width ranges from 5 to 9 cm and its length from 13 to 20 cm. Its calculated area in anatomical position was 32.5 ± 8.55 cm2 (range 22.3 to 47.5 cm2) (7). It is commonly used for wounds between 3 and 7 cm in width and with surface areas between 33 and 49 cm2 (7, 8). The flap can be easily rotated to cover medial and distal defects in the area of the tibial tubercle or patellar tendon (8). The arc of rotation can be further extended by 20% to 50% or 5 to 8 cm with dissection of the muscle of origin and the pes anserinus (7). Some authors have reported division or excision of the superficial and deep fascia in order to extend the width and length of the muscle or increase the chances of skin graft take (8). We do not support the notion that fascial excision facilitates the healing of the skin graft and consider it therefore an unnecessary act. The skin graft is not indispensable, as it was shown in this study. Granulation of the fascia and reepithelialization will occur in 4 to 6 weeks (Fig.12), provided meticulous wound care is provided to the patient. The above may prove useful when one wishes to reduce operating time especially in compromised or overaged patients.

The lateral gastrocnemius muscle can also be used for cover of anterior as well as lateral knee defects. It is smaller (5 x 12 cm) and has a lesser arc of rotation (obstructed anterior rotation caused by the fibula) compared to the medial gastrocnemius. An additional difficulty is the eventual dissection and decompression of the common peroneal nerve. It is therefore less frequently used than the medial gastrocnemius. Occasionally, both heads can be used

Fig.7. The muscle flap has been rotated and transposed (under the skin tunnel) into the defect.

Fig.8. A split thickness skin flap is harvested from the ipsilateral thigh.

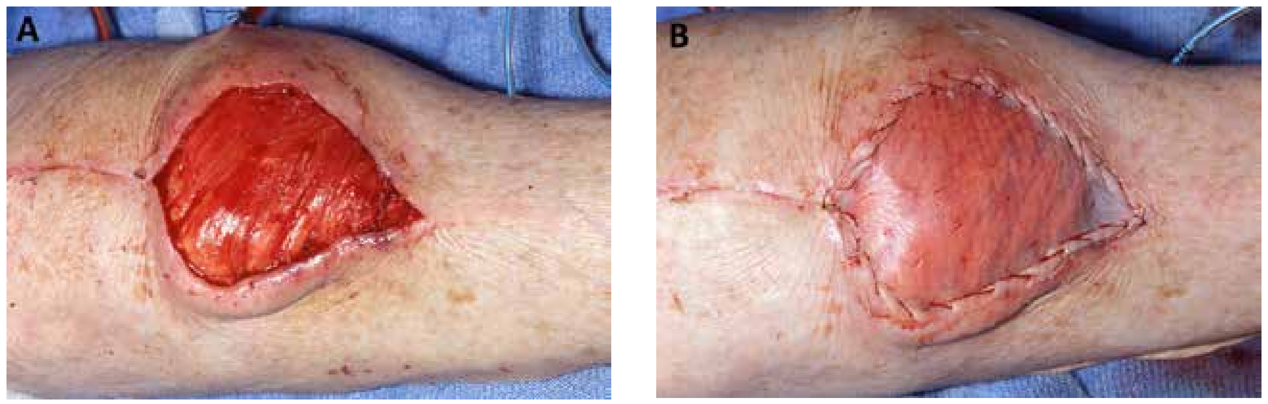

Fig.9. A.The muscle flap in situ.B. A skin graft has been placed and secured on top of the flap.

Fig.10. A. Fibrin covers the gastrocnemius flap 5 days postoperatively. B. Healthy granulation tissue has covered the muscle flap (no skin graft was used) and signs of epithelialization are evident.

for the reconstruction of large defects centered over the patella.

Medial gastrocnemius defect coverage may be performed at the time of TKA debridement with exchange of modular components, prosthetic explantation and antibiotic spacer placement, antibiotic spacer exchange, or second-stage prosthesis reimplantation (1). The decision regarding timing of the flap procedure is made on the basis of when the soft tissues are deemed insufficient and not on the basis or belief that placement at one stage or another is advantageous (1). Early cover of the defect has fewer complications and improves end results with respect to tissue loss from infection, healing time, and hospitalization and rehabilitation (15, 16).

Defects exceeding the size of the gastrocnemius muscle are a contraindication to its use. The technique may also not be ideal in very thin patients who may have smaller gastrocnemius muscle bellies. In cases of a previous arterial bypass, an arteriogram should be obtained to confirm the patency of the sural artery pedicle (17).

Reported success rates after use of a medial gas-

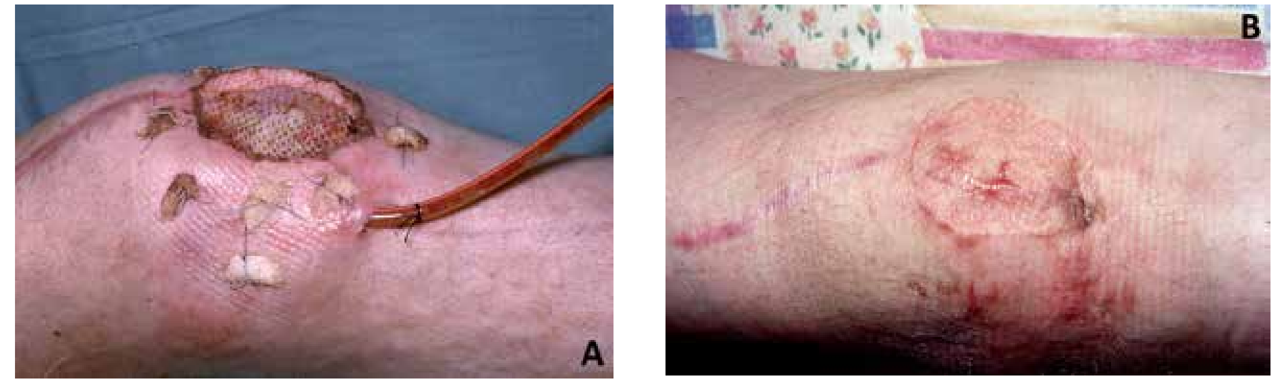

Fig.11. A. gastrocnemius flap covered with meshed skin graft. B.The same patient depicted one year postoperatively.

Fig.12.A. Intraoperative aspect of patient GL immediately after extensive debridement second to an infected TKA; a gastrocnemius flap has been dissected in order to cover the defect. B.A lateral medially based tibial fasciocutaneous flap was used to cover a small gastrocnemius dehiscence. C. Close up view of the fasciocutaneous flap.

trocnemius flap vary widely (3). Despite adequate tissue coverage, several patients experience recurrent infection requiring additional surgical treatment. Persistent or recurrent infection rates have been reported in ca 50% of patients by various authors (1, 3, 14). Satisfactory results have been reported in 80 - 92% of patients (4, 13, 18, 19), which coincides with the findings of the present small case series. In a series from Johns Hopkins Medical Institutions, Baltimore (17), secondary plastic surgery procedures were necessary in 5/29 knees (17%), and secondary orthopedic procedures were necessary in 4/29 knees (14%). Cepas et al (4) observed superior functional knee joint salvage rates in the group of non- infected patients compared to the infected group (97.1% vs. 75.0%, p=0.004). The trans femoral amputation rate was nearly three-fold in the infected group (8.3% vs. 2.9%, p=0.36). Estimated 5-year survival with functional knee joint was higher in the non-infected group (p=0.03) (4). The amputation rate reported by Warren et al (3) was considerably higher (23.1%); the same authors reported a high rate of arthrodesis (19.2%). Kwiecien et al (20) retrospectively reviewed 73 patients with TKA. The first group (patients with preexisting defects requiring reactive flap reconstruction) had a higher rate of implant reinfection compared to the second group (patients with no preexisting soft tissue defects but with extensive debridement during revision TKA requiring immediate flap coverage) (58% vs. 27%, p<0.05). The first group had a higher rate of amputations (25% vs. 0%, p<0.05) and subsequent prosthesis revisions (2.2 vs. 0.9, p<0.05). Functional joint was preserved in 54% and 80% of cases, respectively. Mean gain in range of motion and quality of life were significantly better in the second group (20).

Colen et al (2) commented that patients referred to their institution with complicated periprosthetic wounds were significantly more likely to lose their knee than patients treated only within their system. Patients with multiple prior knee operations before definitive soft tissue reconstruction had significantly decreased rates of prosthesis salvage and an increased risk of amputation. Knee salvage significantly decreased with positive joint cultures and particularly at the time of definitive reconstruction, which also trended toward an increased risk of amputation (2). Tetreault et al (14) investigated a number of risk factors to which failure could possibly be attributed, with failure defined as recurrent or new periprosthetic joint infection or inability to reimplant TKA prosthesis. With the patients available (n= 27), treatment failure was not associated with age, sex, BMI, Charlson comorbidity index, diabetes mellitus, smoking status, coronary artery disease, number of knee arthrotomies before flap coverage, extensor mechanism rupture, prior completed two-stage revision, area of skin defect, surgical service that performed the flap, knee procedure being performed at the time of the flap, spacer type or growth of staphylococcus aureus, Gram-negative rods or antibiotic-resistant bacteria (p>0.004 for each) (14). There was a trend toward failure when flap coverage was performed at the same time as antibiotic spacer placement or exchange compared with at the time of irrigation and debridement or replantation of prosthesis, but this did not reach statistical significance (14). Other authors, based on small(er) patient series identified the growth of multiple organisms, a history of smoking and the presence of methicillin-resistant staphylococcus aureus on wound cultures as factors predicting a poor outcome, whereas age<30, the absence of comorbid conditions and a favorable microbiological profile predicted success (21). Colen et al supported the notion that in revision TKA, prompt soft tissue reconstruction improves the likelihood of success, and protracted surgical courses and contamination increase failure and amputation. The same authors showed a benefit when plastic surgeons were early involved in the course of TKA complications (2).

The functional loss and comorbidity associated with the medial gastrocnemius flap is generally minimal for non- high level sports people because of compensation provided by the remaining hemi gastrocnemius (muscle) and the soleus muscle (7, 14). The aesthetic after effects are very acceptable. If there are concerns regarding the aesthetic appearance of the calf, an autologous fat transfer can be further associated with the procedure in order to minimize the cosmetic impact at the donor site (7).

In cases of larger or more proximal skin defects with deficiency of the anterior capsule and quadriceps tendon, a gastrocnemius flap alone may be of insufficient size. These composite defects affecting the extensor mechanism can be managed with transfer of the vastus lateralis, in conjunction with the gastrocnemius, if necessary (8). Another locoregional muscle option for coverage of knee defects is the distally based pedicled gracilis muscle flap, which is based on minor pedicles from the superficial femoral or popliteal artery (8, 22). It carries a high risk of partial flap loss and is reserved for use when a pedicled gastrocnemius flap seems inadequate and when the patient is not a suitable candidate for a free flap (8). The complication rate after use of a gracilis muscle flap has been reported 55.6% (20).

Fasciocutaneous flaps (pedicled or perforator) are occasionally utilized for cover of, especially, small defects around the knee. They are thin, pliable and easy to contour, however they provide merely cover and lack the necessary bulk and rich vascular supply offered by muscle flaps. Patient 3 of the current series is illustrative of our viewpoint regarding indications for these flaps. Proximately based fasciocutaneous flaps preserve cutaneous innervation and have been advocated for coverage of areas of skin necrosis (23). Healing rate and complication rate after use of fasciocutaneous flaps has been reported 70% to 90% and 19.2%, respectively (22, 24).

Free tissue transfer is occasionally indicated. The most common muscular flaps are the latissimus dorsi and the rectus abdominis flaps (25). The commonest fasciocutaneous free flap is the anterolateral thigh flap (ALT). Free flaps require microvascular expertise; furthermore the duration of the operation, the longer recovery and the higher donor site morbidity (e. g. rectus abdominis) render free tissue transfer a second – line treatment option. It is for the above reasons that free flaps constitute less than 10% of all flaps used in cases of failure of a TKA (22).

Conclusion

The results of this retrospective study support the notion expressed in the literature that the medial gastrocnemius muscle flap remains the first- line treatment of failed total knee arthroplasties (TKAs). Early use of the muscle flap is recommended in order to achieve the best possible outcome. Timely involvement of plastic surgeons seems to be beneficial.

Conflict of interests

No conflict of interests to declare.

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The Constraints-led Approach Framework in Training and Coaching.

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ABSTRACT

Movement "constraint" is defined as a variable that defines the way a movement can be organized and controlled. The "constraint model" emphasises the important interactions of individual constraints, environmental constraints, and those of skill - in a balanced perspective - and suggests that constraints can shape the manifestation of movement patterns, cognitive processes, and decision-making processes. According to the Constraints Model, any learning / teaching environment should be arranged in such a manner as to provide any learner with capability or protentional into movement. Therefore, in this way, each youngster will feel that they have accomplishing something, improving their perception of their abilities and, thus, their self-confidence. The application of the Constraint Model within PE can help to 'shape' young people who will progress in life with fluency and skill, will be creative and confident, and have acquired a deep understanding and knowledge of how they interact within a dynamic and ever constantly changing environment.

Key words: constraints, representative learning design, physical education

Introduction

In a school / (an academic) curriculum, Physical Education (PE) is the subject that aims to contribute to the holistic development of students - at a physical abilities level, cognitive and emotional. The content of PE lessons aims to help pupils to develop knowledge and skills, to grow their ability and confidence and therefore to perform fundamental and progressively specialised movements, which will result in them adopting a more physical active way of life for the rest of their life. An essential component of physical education programmes is developing independent, innovative, and self-sufficient 'learners' (Roberts, Newcombe, & Davids, 2018).

The theoretical model 'constraints-led approach' is a contemporary pedagogical approach that can be applied in the school environment and serve the afore-mentioned purposes of PE. In this paper, the term 'Constraints Model' will be used for the 'constraints-led approach'.

The development of the "Constraints Model" has been based on the Dynamical Systems Theory and on ideas related to Ecological Psychology. It is an ecological model that focuses on the relationship that arises between the interaction of the individual with an environment of efficiency. According to

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the constraints model, the most skilful execution/performance of a movement occurs through self-organization in the presence of constraints as individuals become perceptually attuned to important sources of information that can regulate individuals' actions in specific performance environments (Renshaw, Araujo, Button, Chow, Davids, & Moy, 2015).

In this paper, we refer to the constraint model and the categories in which constrains are classified. It is explained how the Constraints Model contributes to the formulation of appropriate PE contents, with the aim of learning and developing of motor skills, and the management of the information provided it results from the "performer-environment" interaction. It also discusses how the management of constraints is related to cognitive skills and self-organization ability. The final part of the paper (**Appendix**) describes examples of PE lessons using the traditional teaching method and the constraint model approach.

Ecological Dynamics and Constraints Model

Ecological dynamics is a theoretical model that has evolved combining the theories of Dynamical Systems and Ecological Psychology. The Ecological Dynamics model emphasizes the importance of the relationship between "performer and environment" for the design of learning contents and for the process of developing skills. Adopting such an approach leads coaches / trainers to view learners as complex, adaptable dynamic systems, that adapt to events, objects, significant others, in a constantly changing performance environment.

The Constraint Model pedagogical approach supports the development of intelligent, internally motivated pupils, who are engaged in PE lessons (Moy, Renshaw, & Davids, 2016). The Constraint Model is an expression/manifestation of the Ecological Dynamics theory and is based on ideas and concepts such as: the combination of information-movement, representative learning plan, modification of constraints, acceptance of variability / diversity, external focus of attention, alignment to opportunities for movement (Renshaw et al., 2015). The constraint model focuses on the performer-environment' relationship and proposes that functional motor solutions are an inherent characteristic of humans, who are considered as self-organised, non-linear motor systems. It is argued that behaviours - actions/movements, perception, knowledge - arise from the ongoing interaction of each performer's unique individual constraints with the constraints of abilities and performance (Renshaw, Chow, Davids, & Hammond, 2010).

The constraint model provides a framework for understanding how individuals learn, each person's constraints, the skill / ability and the environment that shape the learning process. Valid categorization of constraints for each practitioner helps to understand how differences lead to different, appropriate performance outcomes. Constraint model approaches help develop a model for the trainee and for the learning process that will further improve practice. This logic supports the creation of novel kinetic solutions by designing learning contents that provide controlled "frontiers" of exploration within dynamic environments by providing skill-relevant constraints. According to the constraint model, motor skill learning depends on self-organization in relation to the constraints of the individual, the skill / ability, and the environment, as well as the effective combination of perception and movement (Brymer & Renshaw, 2010).

Classification of the Constraints

Constraints are defined as "boundaries" or characteristics that shape the manifestation of a behaviour. The interaction of various constraints 'forces' the performer to adopt stable and efficient motor patterns when performing physical activities and dynamic target interception movements (Brymer & Renshaw, 2010; Renshaw et al., 2010).

According to constraints-led theory, a movement constraint is defined as a variable that defines the way in which a movement can be organized and controlled. The 'constraints model' proposes that constraints drive the dynamics of the evolution of movement. They can shape the manifestation of motor patterns, cognitive processes, and decision-making processes (Chow, Davids, Button, Shuttleworth, Renshaw, & Araujo, 2007; Renshaw et al., 2015).

Due to the interdependence of the various processes in the motor system, a small change in one part of the system can bring about large changes in the motor-sensor outcome (Renshaw et al., 2010). According to Newell (1986), the constraints are classified into three categories: individual or organismic constraints, environmental constraints, and task constraints (Brymer & Renshaw, 2010; Renshaw et al., 2010).

The **individual constraints** refer to the unique structural and functional characteristics of each individual and relate to biological, physical, and psychological - cognitive parameters. These parameters influence/shape how individuals approach a motor skill. Personal - individual factors provide affordances for actions and play an important role in determining how a motor behaviour is performed/executed. These different individual constraints demonstrate various possible strategies/techniques that can be used to manage specific skill / abilities characteristics, as well as lead to individual adaptations (Brymer & Renshaw, 2010; Renshaw et al., 2010). Obviously, the ways of approaching or managing a kinetic energy (ability to move) will vary, as each performer will try to "meet" their individual limitations and "manage" specific situations through their own adaptations. For example, when adjusting the straddle before crossing over a puddle, individuals with different lower limb lengths will use different ways of performing the skill (task solutions) based on their own (individual) physical characteristics. Unique individual constraints can influence behaviour and provide specific 'individual pathways' to achieve similar performance outcomes.

The term 'affordance' is also used in the literature to describe a possibility for action/movement that combines the objective nature of the environment with the subjective nature of the performer (Brymer & Renshaw, 2010; Renshaw et al., 2010). This means that a specific environment will have certain properties/characteristics and an individual perceives possibilities for movement/energy within it from their own unique perspective. For example, two performers performing the same exercise with a canoe, in the same environment, but with different physical characteristics (body height and length of body parts) will come to different conclusions and different ways of performing the task- solution. In the same environment, performers with different individual characteristics will perceive the same motor demand differently and will result in a different - individual - motor outcome (Brymer & Renshaw, 2010). In dynamic performance environments, the influence of environmental constraints is very important. **Environmental constraints** relate to physical and socio-cultural factors. Physical factors refer to the immediate environment in which a motor skill is performed, and the information provided within it (dimensions and characteristics of the skill performance area, weather conditions, lighting level, gravity, altitude). Socio-cultural factors relate to the role of social structures/contents and cultural - intellectual expectations (group expectations, the relationship with significant others such as the teacher and peers in the school environment).

Skill constraints are all about the objectives of the skill / ability, regulations, spatial boundaries, and requirements related to the performance of the skill, applications or equipment used in the learning process. Unlike other constraints, skill constraints are easier to modify (e.g., modifying the equipment available to the trainees or the dimensions of the practice area, identifying specific motor objectives). Small modifications to the skill constraints result in big changes in the performer's behaviour.

Skill constraints play an important role in influencing performer's intentions and can be modified in a learning/practice environment to encourage specific behaviours or motor solutions. An effective modification of a skill's constraints should direct performers towards 'discovery' of functional coordination patterns and into decision-making behaviours (Chow et al., 2007; Renshaw et al., 2010). However, decisions to modify the constraints of an ability should be related to the performer's cognitive level and their level of motor development (Chow et al., 2007; Gagen & Getchell, 2006; Rudd, O'Callaghan, & Williams, 2019). Such modifications to the content/learning environment can lead to large changes in motor patterns during the learning process. Newell's (1986) constraint model emphasises the important interactions of individual constraints, environmental constraints, and skill constraints - in a balanced perspective. Understanding the unique - for each performer - skill constraints will assist in designing effective learning content (Renshaw et al., 2010).

Teaching contents design based on the Constraints Model

Physical education (PE) subjects should take place in learning environments that have a specific learning objective, are 'playful' and information rich. According to the Constraints Model, each learning environment should be designed in such a way that it provides possibilities for movement for each student. Therefore, in this way, every youngster will feel that they have accomplishing something, his abilities' perception and self-esteem will improve. The rules of the game or activity, the dimensions of the practice area, the number of children in each group, the amount and size of the equipment should be modified to create appropriate learning content, which - in an implicit way - will provide possibilities for movement aligned with the intended goal. In such a learning content, learners are 'silently directed' towards the desired motor solutions. They discover, self-act, gain knowledge, understanding and learn (Roberts et al., 2018). According to Constraints Model to design the appropriate learning context / boundaries in PE the below principles need to be applied (Roberts et al., 2018):

1) Teachers should design appropriate learning environments, considering the cognitive level of the trainees and their level of motor development (Chow et al., 2007; Gagen & Getchell, 2006; Rudd, et al., 2019), which "provide" the desired possibilities for movement. Teachers should identify the most important sources of information - which performers can use to coordinate movements/actions - and confirm that this information is available in specific practice environments. It is important that the learning environment facilitates problem solving when regulating motor actions. Observing children engaged in the decision-making process is a sign that they are building knowledge from different domains. Deciding when and how to act should be motivated by information in relation to the possibilities for movement in the environment.

2) The learning environment should encourage the trainee / performer to discover possibilities for movement relevant to the objectives pursued. Decisions for actions should come from the trainee's choice to align with the information related to the possibilities for movement in the environment (information-movement combination). A well-structured learning content should implicitly lead the trainees to knowledge and understanding of movement - tailored to their own individual characteristics.

3) Management of constraints. Modifying the constraints of the skill / ability is considered a common way to direct performers towards functional information-movement combinations that will facilitate the creation of functional motor patterns and enable them to achieve the goals of the skill / ability.

4) Collaboration and co-adaptation. The performer's interaction with teammates and opponents in a learning environment will have the greatest impact on the discovery of innate self-organizing tendencies. Skill constraints should be modified in such a way as to provide performers with the opportunity to cooperate and co-adapt, understanding how their interaction with others can affect both their own development and that of others. Having students work in pairs or small groups on the various games emphasizes collaboration and is also a useful method of differentiation.

5) Management of unstable conditions. When teachers design practice contents, it is important to manage the "performer-environment" system so that it is balanced at a critical point - on the edge of chaos - i.e., in a performance area that is neither too stable, where the resulting behaviours will be static, nor in a continuously unstable area that is unmanageable. When the "performer-environment" system is in equilibrium in an area, where many motor-related performance solutions are available, non- stable conditions are created for performers, who are forced to discover different options and create problem-solving behaviours.

6) Skill and adaptability. The need for flexibility in skill development is emphasised to encourage performers to seek different solutions to the same or similar problems. Creating learning environments that have some volatility in the learning contents, which provide many possibilities for problem solving, allow performers to discover effective adaptive motor (skill) solutions. The modification of skill constraints in a practice environment should provide characteristics of repetition and variability, so that performers can move deftly while also interacting with the performance environment. Coaches / trainers should incorporate a variety of appropriate constraints to help performers effectively seek successful motor (skill) solutions in a practice environment. The search process should create conditions for adaptability so that performers can find unique solutions compared to their individual and skill constraints and of the environment. The development of this functional variability in motor models facilitates a 'discovery approach' during the learning process (PE lesson/training) allowing practitioners to create effective coordination models that meet skill constraints (Brymer & Renshaw, 2010; Renshaw et al., 2010). While variability features have traditionally been classified as non-functional, the constraint model proposes that variability in motor models is viewed as an intrinsic feature of adaptive motor behaviour that is necessary to consistently achieve a motor goal in a dynamic learning and performance environment (Brymer & Renshaw, 2010; Renshaw et al., 2010).

The application of the Constraint Model in the context of physical education can help 'shape' young people who will move with fluency and dexterity, be creative and confident, and have gained a deep understanding and knowledge of how they interact with a dynamic and ever-changing environment (Roberts et al., 2018).

Management of the information provided through the Constraints Model

The constraint model could facilitate the learning process through the approach of "managing the information provided to performers/ trainees".

Teaching motor skills by 'decomposing' the skill into 'manageable' components (task decomposition) is a teaching method commonly used to manage the amount of information provided to performers (Thomas, 2007). However, 'decomposing' complex coordination models can cause the information-movement combination to 'break down', making it difficult for performers to perform the skill / ability. The constraint model encourages a method of "task simplification" of motor skill. This is a teaching method that allows different components of complex motor coordination models to be learned together, thus preserving the information-movement combination. According to this approach, skill development - learning should take place in the real environment, but where needed the learning content (e.g., environmental characteristics, target of the performed motor skill) can be simplified to explore effective movements. It is also argued that additional modifications of the skill constraints can facilitate the learning outcomes of this method (Renshaw et al., 2010).

For example, using larger and softer balls or smaller handles on rackets could allow performers to successfully complete the overhead service movement without affecting the important time-position relationship in the movement. To make such modifications to the learning environment, it is essential that the coach / trainer has full knowledge of the skill and environmental constraints and the ability to observe and interpret individual constraints (Brymer & Renshaw, 2010; Renshaw et al., 2010).

Effects of constraints management and cognitive abilities

Physical activity, in addition to improving motor skills, is being explored as a method of enriching cognitive skills. Cognitive skills are linked to the development of the self-organisation required for a child to be able to coordinate movements with a specific goal. During motor skill learning, cognitive skills - inhibitory control, working memory, cognitive flexibility - work cooperatively and independently through the processes of decision-making, planning, problem solving, attention, perception, and coordination actions (Rudd, et al., 2019). The design of learning contents, through the Constraint Model approach, could support performers in the process of searching for and developing functional and adaptable motor solutions. The process of searching for alternative movement solutions requires the suspension of previously used solutions and the continuous updating of information retained in working memory. Children will need to use the same information but will come up with different solutions, possibly generating unusual and/or novel solutions, thus developing their cognitive flexibility (Rudd, et al, 2019). Closely related to this is the enhancement of competence and sense of autonomy, as the child who has successfully discovered their own motor patterns experiences a sense of accomplishment and satisfaction that comes from their own self and does not rely solely on feedback or praise from the teacher, as in linear pedagogy (Moy et al, 2016). Using non-linear pedagogy, students are asked to find multiple solutions to a motor problem, demonstrating not only their ability but also their creativity. This will result in enhanced decision making and a strong sense of self-organisation.

Conclusions

In the process of learning a motor skill, performers need simplified, realistic performance environments where they can be attuned to information that enables them to make intelligent and appropriately informed decisions based on a comprehensive understanding of their own abilities/possibilities in any environment (Brymer & Renshaw, 2010). The constraint model perspective can generate novel -movement- solutions by designing learning contents that provide controlled exploration 'frontiers' in dynamic environments - through the provision of skill-relevant constraints (Brymer & Renshaw, 2010; Renshaw et al, 2010). The constraint model (Newell, 1986) provides useful ideas on how to practice / train as it adequately 'captures' the rich range of different constraints that act on performers during motor skill learning. The constraint model emphasises the importance of a balanced interaction between the constraints of the individual, the environment, and the ability (task). According to this perspective, those involved in promoting effective motor skill learning should expect variability in motor-related solutions. It is, therefore, suggested that the academics seeking to design effective learning experiences need to understand the unique limitations of the ability / skill, environment and individual that provide references for creating a learning pattern in a specific way for each performer (individual-level adaptation) (Brymer & Renshaw, 2010; Renshaw et al., 2010).

The effectiveness of the constraint model approach for designing representative learning/practice contents has been evaluated in some complex motor skills such as long jump (Panteli, Smirniotou, & Theodorou, 2016) and springboard diving (Barris, Davids, & Farrow, 2013, 2014), and in physical activities such as canoeing and kayaking (Thomas, 2007) and rock climbing (Seifert, Wattebled, L'Hermette, Bideault, Herault, & Davids, 2013), with application in a training environment. However, the practical application of this model is not yet well developed in the school environment. Future research could examine the practical application of the constraints model - with intervention programmes - in a wider range of sport activities included in the proposed PE curriculum (gymnastics, classical sports, group games) and in different educational / academic settings (different levels of education).

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Appendix

Traditional learning approach courses examples vs constraints-led approach

Traditional approach	**Constraint-led approach**
Goal: Teaching – learning skill ability: «hitting / swinging the ball with a bat»	Goal: Teaching – learning skill ability: «Hitting the ball with tools»
The trainer / coach is preparing to teach the ability «hitting / swinging the ball with a bat». This skill is associated to group sports such are baseball, softball, cricket (game-related skill). He explains and presents the skill to the students and asks those in the class to perform this skill, trying to imitate the same movement as originally presented to them. They all have the same equipment – a bat and a ball – and they must be used in the same way.	To teach motor skills in a developmentally appropriate way, more than just the characteristics of the skill should be considered - such as the characteristics of everyone performing a dynamic skill (with specific goals, rules, equipment) in a such environment (physical and social). The teaching of the skill "hitting the ball with a bat" will be transformed into a lesson aimed at developing the skill "hitting the ball with tools". The learning content will include: • hitting with tools (small paddles, rackets, bats) of different sizes and weights, • using balls of appropriate size and colour (even balloons), • available at different locations within the practice area, and • each child will be able to choose the hitting tool they feel comfortable hitting with, and the object they wish to swing.
	(Gagen & Getcchell, 2006)

Traditional approach	**Constraint-led approach**
Goal: Teaching – "hurdling" / "obstacle race" motor ability	
The traditional teaching method is characterised by: • Descriptive analysis and demonstration of a skill - isolated from the competitive performance environment. • The repeated attempts by students to reproduce the movement as presented by the coach / trainer. • The provision of verbal, correct feedback by the coach / trainer. • A final game or performance of the motor skill in its entirety, where students attempt to apply the movements learned. ⇒ In obstacle lesson, the trainer / coach «decomposes» the obstacle technique and demonstrates isolated areas/ items of the movement for the 1st and 2nd leg, respectively. ⇒ students practice, through multiple repetitions, performing/reproducing these «ideal» movement patterns individually in a progressive sequence of specific exercises (e.g., 2nd leg movement from the side of the obstacle by walking, jogging, skipping). ⇒ The teacher regularly provides verbal feedback in relation to observed errors while performing the movement. ⇒ Having practiced individually, students try to apply the overall movement model in race conditions: 50m race with 3 obstacles of specific height, placed at specific distances (for girls: obstacle height 76cm and intermediate distance 8m, for boys: obstacle height 84cm and intermediate distance 8.5m).	According to the Constraints Model, the curriculum plan, and the instructions / or feedback are designed based on the nonlinear pedagogy approach. ✓ The learning/exercise environment consists of 8 routes with 4 obstacles on each route, placed at different distances and different heights per route. ✓ The skill constraints - obstacle height and intermediate distance - are progressively increased from the 1st to the 8th route. E.g.: Route 1: obstacle height 60cm and intermediate distance 5m. Route 4: obstacle height 68cm and intermediate distance 6.5m. Route 8: obstacle height 84cm and intermediate distance 7m. ✓ Students are given the opportunity to choose which course they wish to start their training on. ✓ In relation to feedback, the trainer provides "general" phrases that act as constraints on the students' search for appropriate movements/actions. These phrases mainly relate to the outcome of the movement, reinforcing an external focus of attention, e.g., "try to make 3 jumps between the obstacles». ✓ Students are given time to discover the practice environment and seek their own ideal functional motor solutions, with self-generated feedback. ✓ When the performers feel able to achieve these results, they are encouraged by the coach / trainer to practice the next difficult route. ✓ The last skill has a racing character (simulates real-life conditions) - 50m race with 3 obstacles - with the students choosing their «opponent» and the preferred racing route.
	(Moy, Renshaw, & Davids, 2016)

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Surgical versus non-surgical treatment of degenerative lumbar spondylolisthesis: systematic review of randomized control trials.

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ABSTRACT

Background: The best management for degenerative spondylolisthesis patients is still controversial. Low-grade spondylolisthesis without neurologic deficits used to be treated non-surgically as a first-line. Many studies stated that in patients with degenerative spondylolisthesis with or without spinal stenosis, surgery had superior outcomes. The aim of this systematic review was to describe the effectiveness of surgery versus conservative treatment for lumbar degenerative spondylolisthesis.

Methods: A comprehensive literature search was performed for relevant studies in Medline, EMBASE, CINAHL, Scopus, Centre for Review and Dissemination databases and Cochrane databases were searched. The search included English studies, and all conservative and surgical interventions were included.

Results: Two studies met the inclusion criteria. The number of patients was 650 (355 treated with surgical intervention and 295 treated conservatively). Surgery was found to be more effective than conservative care in the two studies.

Conclusion: Patients with lumbar degenerative spondylolisthesis treated with surgery had significantly better results in pain and function compared with patients treated with nonoperative treatment.

The study is retrospectively registered.

Level of evidence: II

Keywords: spondylolisthesis, degenerative, surgical treatment, conservative treatment, systematic review.

Introduction

The degenerative spondylolisthesis is displacement of one vertebra over the other, associated with degenerative changes (1-3). The pathological process is started with disc degeneration, with narrowing of the disc space and settling of the motion segment leading to "micro instability" and vertebral slippage (4,5). This is followed by degenerative changes, as osteophyte formation, ligamentous hypertrophy, and facet arthrosis (6).

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The optimal management for patients with degenerative spondylolisthesis is controversial. Patients with low-grade spondylolisthesis without neurologic deficits could be treated non-surgically primarily (7). This includes restriction of activities, bracing, anti-inflammatory medications, epidural steroid injections, and physical exercises that may help to reduce pain and strengthen spinal musculature to restore range of motion and stabilize the spine (8-10). For diagnosis and treatment of lumbar degenerative lumbar spondylolisthesis, North American Spine Society (NASS) guidelines in 2014 were inconclusive about the role of nonoperative medical/interventional therapies. Most of the studies denoted that the main indication for surgical treatment of degenerative lumbar spondylolisthesis is symptomatic spinal stenosis associated with low-grade spondylolisthesis in patients who have been refractory to conservative treatment (11). Also, many studies mentioned that in patients with degenerative spondylolisthesis with or without spinal stenosis, surgery had superior outcomes (12).

Management of degenerative spondylolisthesis are difficult when applying evidence-based guidelines, because of the few reports of high quality that compare conservative and operative management within the study population. Even in an expert panel survey including more than 30 questions concerned with the management of degenerative lumbar spondylolisthesis, no questions had consistent Level I evidence to support any recommendation, and half of the questions had insufficient evidence (13,14).

Clear evidence about the best treatment for patients with degenerative spondylolisthesis are not available in the literature. This systematic review summarizes the current literature on the nonsurgical and surgical management of lumbar degenerative spondylolisthesis aimed to determine the effectiveness of treatment for lumbar degenerative spondylolisthesis.

Method

Inclusion Criteria and Study Selection

The published studies were systematically reviewed according to the following criteria: prospective randomized control studies in patients older than 18 years with degenerative lumbar spondylolisthesis of at least 3 months duration with prospectively collected SF-36 and ODI scores and minimum follow-up period of 24-months for surgically and non-surgically treated patients. Editorials, comments, case reports, and conference papers were excluded.

Electronic Literature Database

Systematic search was conducted in MEDLINE, EMBASE, CINAHL, Scopus, Centre for Review and Dissemination databases and the Cochrane Collaboration Library for literature published from January 1965 through December 2021. only studies published in English language were considered. The following search terms were used to find relevant literature specific to the topic: “degenerative lumbar spondylolisthesis” OR “lumbar degenerative spondylolisthesis”), (nonoperative OR nonoperative management OR operative versus nonoperative OR conservative treatment OR observation OR observational treatment) AND (operation OR surgical treatment OR surgery OR fusion OR reduction OR fixation OR in situ fusion OR operative procedures) AND (Spondylolisthesis).These results were filtered to include only clinical trials, prospective analyses, and studies in English and with human subjects, yielding 2532 results. Manuscripts involving basic research, case reports, editorials, and nonstructured reviews were excluded. Titles and abstracts were reviewed to identify studies that held (1) comparative data and (2) a population of patients with degenerative lumbar spondylolisthesis. A total of 43 studies were found relevant by title and abstract alone. After full text reviews and searching the reference sections of these studies, only 2 randomized control studies were included in the present review (Figure 1).

Quality Assessment

The Newcastle–Ottawa quality assessment scale (NOS scale) was used to assess the quality of the included studies (15). The scale assigns a maximum of 8 points for case-control studies and 9 points for cohort studies. Validity scores of NOS- Scale were

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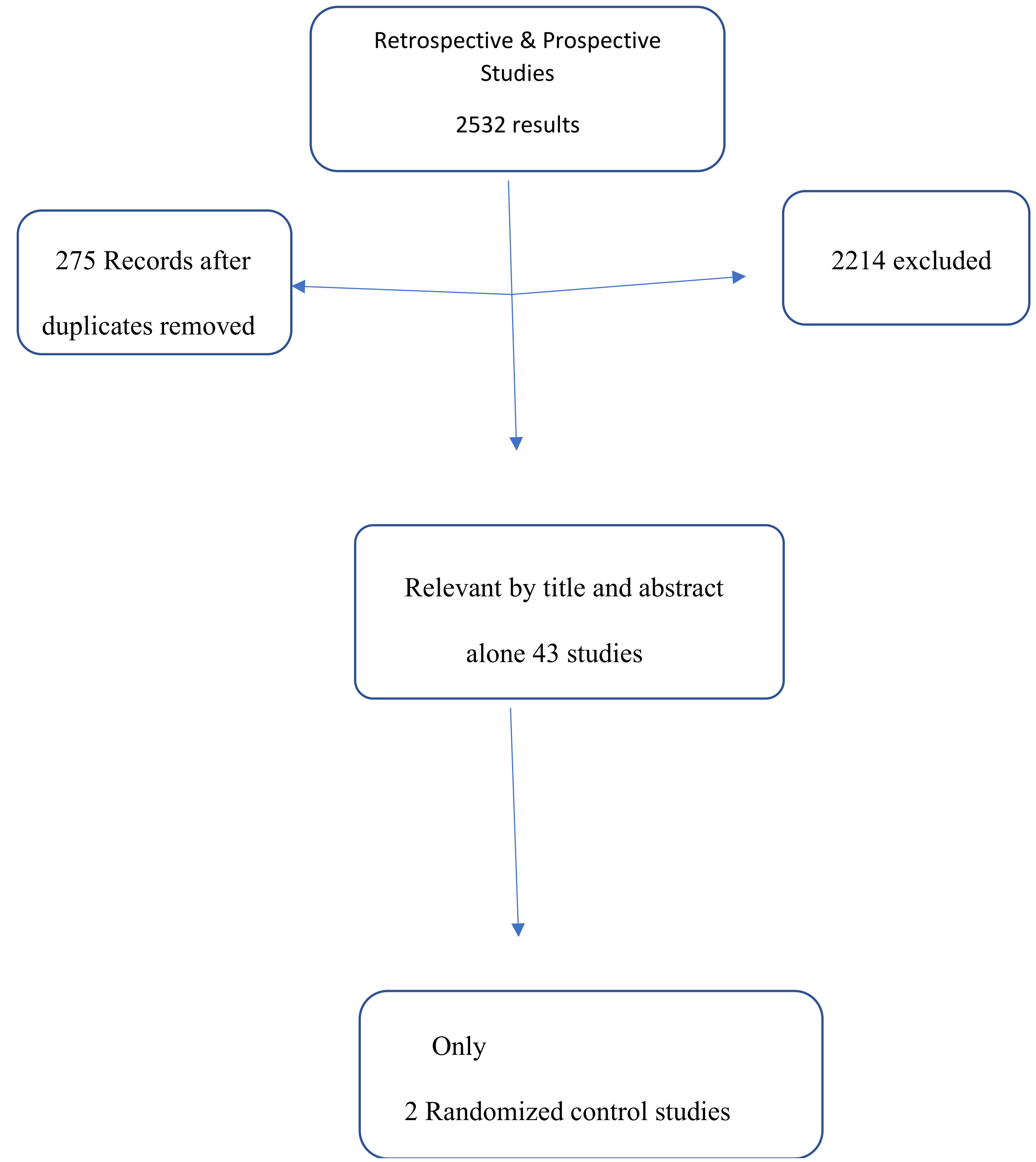

Figure 1- Flow diagram of the study selection

evaluated as follows: 8 to 9, high quality; 6 to 7, medium quality; 5, low quality.

Data Collection

Data extraction was done. Details describing each study and results on effectiveness in promoting the outcomes of interest extracted from papers included in the review using the standardized data extraction tool from the Joanna Briggs Institute-MAStARI. In addition to extraction of the results for outcomes relevant to the review question and specific objectives, the information extracted included details

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about populations, and the interventions method, of the included studies.

Results

Search Results

Initially, 2532 articles were found during search strategy. Forty-three articles remained for screening based on the inclusion criteria after reviewing the titles and abstracts. Of these 43 articles, 25 full text articles were selected for further evaluation. Twenty-one manuscripts were excluded after reviewing full-texts. Finally, 4 eligible articles were identified.

Four publication (two studies) only fulfill the inclusion criteria (17-20). The number of patients was 650 (295 treated conservatively and 355 treated with surgical intervention). One study was cross sectional study while the other was divided into randomized control trial and observational cohort study. Both studies scored as being of high quality, although the sample size of one of them was small (17).

The mean age of patients included in the studies ranged between 56 and 66 years. Imaging had documented lumbar degenerative spondylolisthesis in all the participants. The percentage of females was larger than males in the two studies (66% to 78%).

The follow up period ranged from 3 to 8 years.

The non-surgical management

In the first study (17), only 20 (46.5%) patients were treated conservatively. Sixty percent of the patients were grade 1 spondylolisthesis while 40% were grade 2 according to Meyerding's classification (21). L4-5 level was involved in 40% of the patients while L5-S1 level was involved in 60%. Two patients (10%) had good outcomes, 10 patients (50%) had regular outcome and eight patients (40%) had a poor outcome (according to Fischgrund's criteria (22). The average VAS score was 8 for the back and 6 for the leg. Results on SF-36 function score showed a mean of 35 (Standard Deviation: 24). On the ODI scale (the Oswestry Disability Index), the mean was 46 (Standard Deviation: 21). No complications occurred. Progression of the slippage from grade 1 to grade 2 occurred in two patients (10%).

In the second study (18-20), 192 patients (32%) were assigned to nonoperative treatment. L3-4 level was involved in 8% and L4-5 was involved in 92%. Back pain bothersomeness (22) was 4.1 while Leg pain bothersomeness (22) was 4-3. SF-36 was 36.9. ODI was 36.5 (18.8%). Of those patients assigned to nonoperative care, 54% underwent surgery by 2 years and 46% underwent surgery between 4 and 8 years.

Surgical management

In the first study (17), 23 patients were included (53,5%). Forty eight percent of the patients were grade 1 spondylolisthesis while 52% were grade 2. The affected levels were as follow: L3-L4:(5%), L4-L5:(43%), L5-S1:(43%), and L4-S1:(9%). According to Fischgrund criteria, nine patients (39%) had excellent outcomes, 10 patients (44%) good outcome, four patients (17%) regular outcome and no patients (0%) had a poor outcome. The VAS score was 4 for the back and 3 for the leg. SF-36 function score showed 77 (Standard Deviation: 16). ODI was 17 (Standard Deviation: 14). Two cases of infection were detected successfully treated with antibiotics. Progression of the slippage from grade 1 to grade 2 occurred in two patients (9%).

In the second study (18-20), 409 patients were included (68%). L3-4 level was involved in 10% of cases while L4-5 level was involved in 90%. Back pain bothersomeness was 4.4 while Leg pain bothersomeness was 4.6. SF-36 was 31.6 and ODI was 43.9 (Table 1).

Discussion

Degenerative lumbar spondylolisthesis is an anterior displacement of one vertebra over the subjacent vertebra, associated with degenerative changes. Progression of slip correlates with the activities that require repetitive forward movements of the spine. Progression of clinical symptoms does not correlate with progression of the slip.

Evidence-based decision-making is needed for management of the medical conditions and especially required for conditions that required surgical interference. Recommendations can be strong when high level evidence is available. A few studies com-

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pared surgical and conservative treatment of lumbar degenerative spondylolisthesis patient (24,25). The debate about surgical versus nonoperative interventions for the treatment of degenerative spondylolisthesis always present.

Although many studies have been published on the results of various treatment methods for lumbar degenerative diseases, clear conclusions are difficult to draw because of differences in patient inclusion criteria, fusion technique, nonoperative treatment regimen, and clinical outcome measures used to determine success. The few randomized controlled trials directly comparing surgical and nonsurgical treatments have been criticized for the variations in treatment regimens used within the studies and the number of crossovers (26-30).

Surgery is usually recommended for treatment of patients with symptomatic low-grade degenerative spondylolisthesis with spinal stenosis whose symptoms have been not improved to a trial of non-surgical treatment (31-36).

In the treatment of degenerative spine disorders, the Medical Outcomes Study Short Form SF-36 (SF-36) and the Oswestry Disability Index (ODI) are widely used to measure treatment outcomes. The SF-36 measures the health-related quality of life, allowing comparison across disease and treatment groups. The ODI is an outcome measure specific to lumbar degenerative disorders.

The results of this analysis of collected SF-36 and ODI data revealed the problems in designing trials to determine the efficacy of treatments for symptomatic lumbar degenerative conditions. Many studies did not report important characteristics of their patients's samples, which make a difficulty to compare the results of those studies with other studies. Some studies did not mention the diagnostic indication for treatment, other studies collected ODI data but did not report them and some studies had very short follow up of less than 12 months.

Two studies included in this systematic review. The first study (17) showed the results of the cross-sectional study that showed better scores for back VAS, leg VAS, SF-36 function score and ODI scales were attained by the surgical treatment group with significant statistical difference. In the surgical group, 83% of patients rated their general health post treatment as excellent or good compared with 10% of patients in the nonoperative group. However, the surgical procedure was associated with a higher number of complications. The second study (18-20) was multicenter study compared patients with degenerative spondylolisthesis associated with vertebral canal stenosis treated nonoperatively or surgically.

A large number of articles are available in the literature comparing nonoperative and surgical management of patients with lumbar stenosis, but these studies included patients with a broad diagnosis of degenerative lumbar spondylosis, lumbar disc herniation, spondylolisthesis and vertebral stenosis (37).

Overall, the outcomes of nonoperative and operative management of patients with spondylolisthesis depend on patient selection and effective surgical management. Operative treatment provides significant benefits for patient outcomes and improved quality of life. However, the heterogeneity of selected patients for surgical intervention remains a limitation of published studies.

Conclusion

Patients with lumbar degenerative spondylolisthesis treated with surgery had significantly better results in pain and function compared with patients treated with nonoperative treatment.

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Table 1- Results of the two included studies.

Author	Type of study	Surg/Non	VAS (Back)	VAS (Leg)	SF-36	ODI
Corredor (2015)	Cross-sectional 23/20	4/8	3/6	77/35	17/46	
Wenstein (2007)	Prosp. Random. 159/145					
[2 ys follow up]	Observant. Coh. 173/130					
Weinstein (2009) [4ys follow up]						
Abdu (2018)				33/ 25	42/22	
[Weinstein 8 ys follow up]						

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Bilateral simultaneous bony skier's thumb. A case report.

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ABSTRACT

Injuries of the thumb during winter sport activities usually occur amongst skiers, followed by snowboarders. Rupture of the ulnar collateral ligament (UCL) is most common injury, as a result of fall or an entrapment of the hand in a ski pole. We present a simultaneous bilateral bony rupture of the thumb UCL in a female recreational snowboarder, sustained after a simple fall during a snow ride. Surgical intervention with open reduction and stabilization with 1 mm Kirschner wires was performed at one time on both hands by the same orthopedic surgeon. A thumb plaster cast was applied for protection on either thumb. K-wires and the thumb cast were retained for a period of 4 weeks. The patient regained full function of her thumbs at 6 months postoperatively.

Keywords: Hand trauma, ulnar collateral ligament, skier's thumb, metacarpophalangeal joint

Introduction:

Stability of the metacarpophalangeal (MCP) joint of the thumb is maintained by a complex ligamentus mechanism. The ulnar collateral ligament (UCL) of the thumb is a primary static stabilizer of the MCP joint and its untreated injury can lead to chronic laxity. Winter sports and especially skiing have an incidence up to 40% of all injuries, [1] a condition which led to naming the acute type of this injury with the general term "skier's thumb". We present the first ever reported case of a simultaneous bilateral bony avulsion of the UCL in a 27 years old female snowboarder.

Case report:

A 27 year old female was evaluated at the emergency department after sustained a fall during snowboarding two days before administration. The patient suffered from pain at the ulnar side of both thumbs and inability to perform a strong fist. Clinical evaluation revealed pain at the ulnar side of metacarpophalangeal (MCP) joint on both thumbs with simultaneous laxity on valgus stress test under local anesthesia with lidocaine (Oberst anesthesia). Macroscopically edema and mild hematoma on the thenar was documented bilaterally. The flexion and extension mechanisms were intact, while no neurovascular deficit was detected. Radiographic imaging (figure 1) revealed avulsed fracture of the UCL at the base of the proximal phalanx of the thumb, bilaterally.

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Figure 1. *Posteroanterior radiography of the hands revealing bilateral bony avulsion of the thumb UCL.*

Figure 2. *Postoperative Posteroanterior radiography of the hands. Two 1mm K-wires were used for stabilization of the right fragment, while only one 1mm K-wire was considered adequate for the left fragment. A thumb spica was applied postoperatively for protection and rest.*

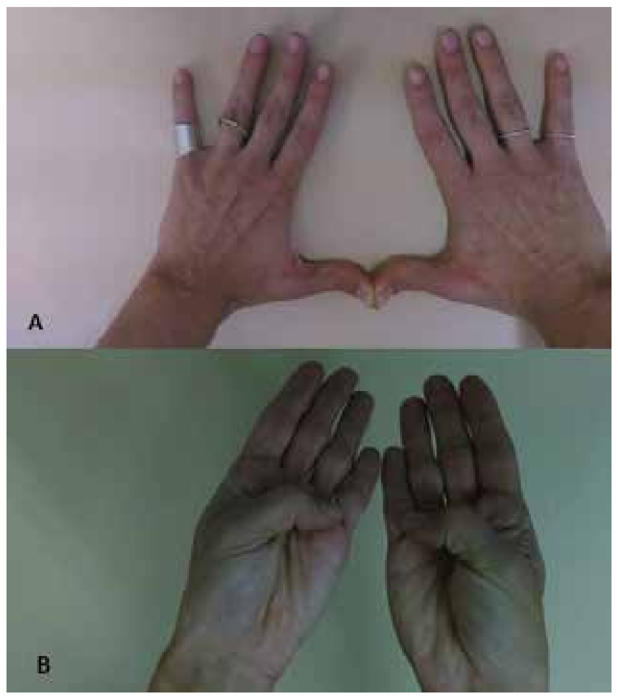

Figure 3. A. *Thumbs were stable under valgus stress at 6 months postoperatively. Scar wound was cosmetically acceptable by the patient.* ***B.*** *Range of motion was complete and painless on both hands.*

Figure 4. *Posteroanterior radiography at 6 months postoperatively. Porosity of both fragments was complete. Under valgus stress the MCP joint was stable bilaterally.*

Under brachial block anesthesia, open reduction using a longitudinal incision and stabilization with 1 mm Kirschner wires was performed (figure 2). During surgical exposure the bone fragments were found displaced and rotated a condition which favored our decision on surgical management of the lesions. The small bony fragment of the left UCL led to the use of only one k-wire, an intervention which provided enough stability to the reattached structure, as it was tested intraoperatively. A dorsal thumb plaster cast for rest and protection was applied, as well as an arm sling on every extremity. K-wires were removed four weeks postoperatively and progressive kinesiotherapy was consulted.

At 6 months follow up the patient restored full thumb mobility (figure 3), MCP joints were stable

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on valgus stress test and porosity of the fractures was sufficient on plain radiographs (figure 4). Grip strength was almost equal between the two hands, as well as the lateral pinch grip strength. The young snowboarder returned to her previous activities, being completely functional.

Discussion:

Thumb's UCL is a complex structure consisting of two main parts, the proper and the accessory collateral ligament, acting as restrainers of the MCP in flexion and extension respectively. Watson-Jones [2] in 1943 was the first who pointed that deficiency of the ulnar ligament at the base of the thumb leads to widening of the MCP joint under pressure. It was until 1981 when Gerber [3] used the term "skier's thumb" in order to describe the acute rupture of the UCL of the thumb, due to the high prevalence of this injury in winter sports athletes, mostly skiers [4].

Rupture of the ligament is a result of extended valgus stress in an abducted MCP joint. In winter sports a fall, as in our case, or an inadvertent stress force [4] applied by a ski pole leads to skier's thumb. Edema and pain at the ulnar side of the thumb's base, hematoma at the thenar area are commonly detected during clinical evaluation. The clinician should test the stability of the MCP. Under local anesthesia with lidocaine (Oberst anesthesia) and placing valgus stress in 30° of flexion and 0° of extension to the thumb, with the metacarpal head stable, a rupture of the proper or accessory collateral ligament can be identified respectively. [5] A possible ligamentous laxity should be differentiated to a rupture by examination of the contralateral thumb, something which in our case was impossible due to the simultaneous and similar type of injury of both thumbs.

Following clinical examination, posteroanterior (PA) and lateral radiographies of the thumb are the next step in evaluation. PA images show a radial deviation of the thumb, while the lateral x-ray provides information about the volar subluxation of the proximal phalanx. When an ulnar bone fragment of the UCL at the base of proximal phalanx is not present, imaging studies should be concentrated on stress radiographies, usually under local anesthesia. PA views of bilateral thumbs under valgus stress can reveal a possible rupture and distinguish between ligamentous laxity and a true injury of the collateral ligament, as well the stability of the MCP joint postoperatively. In cases where doubt for the diagnosis still exist Magnetic Resonance Imaging (MRI) is the study of choice. [6]

Anatomical reduction and stabilization of the UCL is mandatory for restoring kinematics of the MCP joint. Best results are obtained when treating acute bony injuries, rather than lesions being diagnosed 3 weeks after the actual accident. Palmer and Lewis [7] set a classification of skier's thumb and its treatment options, which was later modified by Hinterman. [8] Based on their classification system, our case is considered a type II injury. Regarding avulsion fractures and the high incidence of non union as the result of conservative treatment, which in some series rises up to 60%, [9] a displacement of more than 2mm, joint incongruence and rotation of the fragment are the main indications for surgical treatment. [10] Open reduction and stabilization can be performed either with 1mm K-wires or small diameter screws, when considering bigger fragments. Some authors suggest that small fragments should be excised, followed by anatomical reattachment of the ligament with anchors. The use of a thumb spica postoperatively is used for protection for a period of 4 to 6 weeks.

Intense graduate kinesiotherapy must follow after cast removal. Patients usually regain full mobility of the thumb 3 to 4 months postoperatively. Radial sensory nerve neurapraxia is common, but it subsides automatically. Joint stiffness of the MCP and interphalangeal joint of the thumb, complex regional pain syndrome and secondary osteoarthritis are also reported. Chronic valgus instability is a result of a failure of the conservative or surgical treatment. Poor outcomes are expected when dealing with complex injuries or late diagnosis.

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Spondylodiscitis: Surgical Treatment And Indications

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ABSTRACT

Spondylodiscitis is a serious infectious disease affecting the spine, causing inflammation of the vertebral bodies and intervertebral discs. It is caused by a bacterial infection and can lead to significant disability if left untreated. Initial management of the disease is conservative. Aiming to evaluate the indications and the methods of surgical management in patients with spondylodiscitis, a literature review was conducted searching the keywords: "spondylodiscitis" AND ("surgical treatment" OR '"surgical management" OR "indications") on Pubmed database. The search included only prospective studies. Initially, 308 studies were identified after primary search. At last, 26 studies remained for analysis. The study concluded that indications for surgical treatment include neurological deficits, spinal instability, abscess formation and failure of conservative treatment. Surgical management includes debridement of the infected tissues and spinal fusion with instrumentation, through an anterior, a posterior or a combined approach. The choice of material for spinal support and enhancement of spinal fusion does not influence the clinical result.

Keywords: Spondylodiskitis, treatment.

Introduction

Spondylodiscitis is defined as an infection of the intervertebral disc and adjacent vertebral body. It is a relatively uncommon condition, but it can lead to significant morbidity and mortality if left untreated. The epidemiology of spondylodiscitis varies depending on a variety of factors, including age, sex, underlying medical conditions, and geographic location. In general, spondylodiscitis is more common in older adults, with a peak incidence in the sixth and seventh decades of life. It is also more common in men than in women, with a male-to-female ratio of approximately 2:1. This may be due in part to a higher incidence of risk factors for spondylodiscitis, such as intravenous drug use and alcohol abuse, in men. The incidence of spondylodiscitis has been found to be increasing in recent years. This may be due in part to an aging population, as older adults are at increased risk for developing spondylodiscitis. Patients with conditions that weaken the immune system, such as HIV/AIDS, cancer, or chronic steroid use, are at increased risk for developing spondylodiscitis. Additionally, patients with diabetes mellitus are also at increased risk for spondylodiscitis, as high blood sugar levels can impair immune function and increase the risk of infection [1-3].

The pathophysiology of spondylodiscitis involves a complex interplay between host defenses and microbial virulence factors. The most common bacteria associated with spondylodiscitis are *Staphylococcus aureus* and *coagulase-negative staphylococci*, accounting for the majority of cases of spondylodiscitis, particularly in developed countries. Other bacterial species that have been implicated in spondylodiscitis include *Streptococcus species, Enterococcus spp, Escherichia coli, Pseudomonas aeruginosa, Brucella spp and Mycobacterium tuberculosis* [4]. According to the responsible pathogen, spondylodiscitis may be classified as pyogenic, tuberculous and brucellar [5].

The etiology of spondylodiscitis can be divided into two main categories: (a) hematogenous and (b) direct inoculation. Hematogenous spondylodiscitis occurs when microorganisms gain access to the vertebral body and disc space via the bloodstream, deriving from a primary infection elsewhere in the body. Direct inoculation spondylodiscitis, on the other hand, occurs when microorganisms are introduced directly into the vertebral body and disc space via invasive procedures, such as spinal surgery or injections [6-7].

Regardless of the route of infection, once microorganisms gain access to the vertebral body and disc space, they can cause a cascade of inflammatory events that ultimately lead to the characteristic clinical features of spondylodiscitis. The first step in this process is adhesion of microorganisms to the endothelium of the vertebral body and disc space. This is followed by invasion of the surrounding tissues and establishment of a biofilm, which serves as a protective barrier against host defenses and antimicrobial agents. The presence of the biofilm triggers an inflammatory response that is characterized by the release of pro-inflammatory cytokines and chemokines, which attract neutrophils and monocytes to the site of infection, where they phagocytose and attempt to kill the invading microorganisms. However, the virulence factors produced by the invading microorganisms can interfere with this process. For example, many bacteria produce enzymes that can degrade the extracellular matrix of the vertebral body and disc space, allowing the microorganisms to invade further into the surrounding tissues. Additionally, some bacteria produce toxins that can directly damage host cells and tissues, leading to further inflammation and tissue destruction. As the infection progresses, the inflammatory response becomes more intense, leading to the formation of an abscess. The abscess can compress adjacent neural structures, leading to neurological deficits and severe pain. In addition, the abscess can cause destruction of the surrounding bone, leading to vertebral collapse and spinal instability [8].

Clinical presentation of spondylodiscitis may vary, depending on the location and severity of the infection. In general, patients present with back pain that is typically localized to the affected vertebral level. The pain is often severe and unrelenting, and it may be exacerbated by movement or palpation. Additional findings may include muscle spasm, weight loss, lower back, groin, or buttock pain, as well as symptoms of rhizopathy and myelopathy (advanced stage). In addition, patients may present with fever, chills, and other systemic symptoms of infection [9].

Diagnosis of spondylodiscitis is typically made based on a combination of clinical findings, radiographic imaging, and laboratory tests. Radiographic imaging, such as magnetic resonance imaging (MRI) and computed tomography (CT) can identify the characteristic changes in the vertebral body and disc space that are associated with spondylodiscitis [10]. Blood cultures and inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can help to identify the causative microorganism and monitor the inflammatory response. Isolation of the pathogen is of vital importance and should be attempted in any case. CT-guided biopsy is the method of choice because it allows a sample to be taken from inside the lesion [11-14].

Antimicrobial therapy is a crucial component of the treatment of spondylodiscitis. The choice of antimicrobial agent(s) depends on the suspected or identified pathogen(s), as well as the patient's clinical status and underlying medical conditions. In general,

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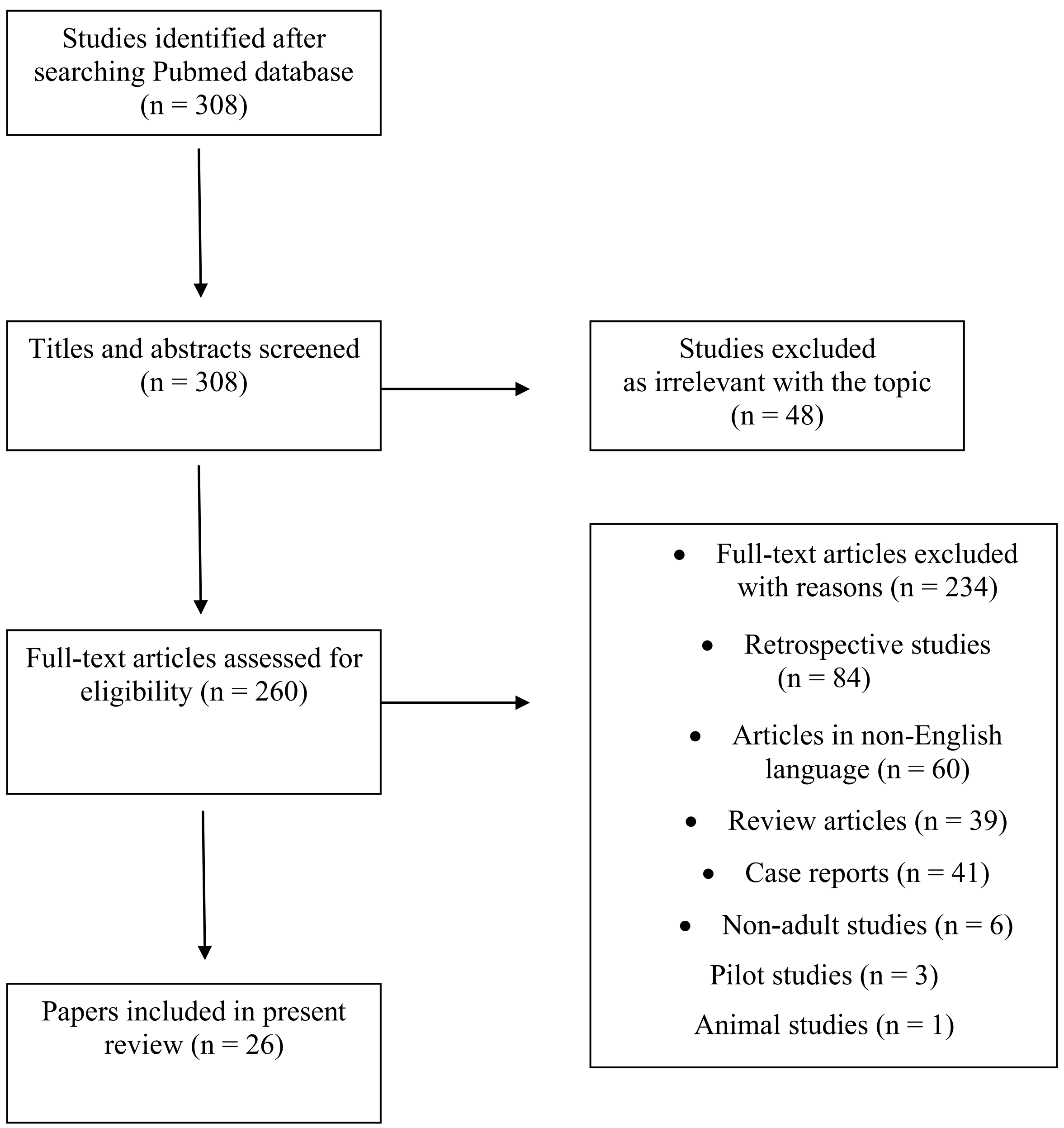

Figure 1. Study flowchart

broad-spectrum antimicrobial therapy should be initiated empirically in patients with suspected spondylodiscitis, pending the results of culture and sensitivity testing. Empiric therapy should cover the most common pathogens associated with the condition, such as *Staphylococcus aureus* and *coagulase-negative staphylococci*. Once the causative pathogen has been identified through culture and sensitivity testing, antimicrobial therapy can be tailored to the specific organism and its susceptibility to antibiotics. The duration of antimicrobial therapy typically ranges from 6 weeks to 12 weeks, depending on the severity and extent of the infection, as well as the patient's response to treatment. Antibiotic treatment should not be ceased until the normalization of inflammatory markers return to normal. Although rest is indicated for the early stages of treatment, early mobilization of the patient with the help of a brace is recommended [15-17].

The aim of the present review is to summarize the surgical treatment and its indications in the management of spondylodiscitis in adults. A literature review was conducted based on the Pubmed internet database, following the PRISMA Guidelines. Article titles were searched with the use of the keywords: "spondylodiscitis" AND ("surgical treatment" OR '"surgical management" OR "indications"). The search included only prospective studies, evaluating the indications and the methods of the surgical treatment in patients with spondylodiscitis. Studies published in non-English language, retrospective studies, reviews, case reports, animal studies and pilot studies were excluded. Studies in children and adolescents were also excluded.

Discussion

Initially, 308 studies were identified after initial search on Pubmed internet database. After screening of titles and abstracts, 48 articles were excluded as irrelevant with the searched topic. Among the remaining 260 studies, 234 were rejected for various reasons (figure 1), leaving 26 studies for final analysis to be included in the present review.

Indications of surgical treatment

Surgical treatment is one option for patients with spondylodiscitis, and it is typically reserved for cases where non-surgical treatments have failed, or where there is a high risk of complications. Indications of surgical treatment include:

Failure of conservative treatment: In some cases, the infection may not respond to antibiotics or the patient may experience severe pain while inflammation markers are still high after 4 - 6 weeks. The thresholds of 50 mm/hr for ESR and 2.7 gr/dl for CRP have been proposed for consideration of surgical treatment [18]. Moreover, prolonged antimicrobial therapy may cause antibiotic resistance and pharmacological side effects, as renal or hepatic impairment. In these situations, surgical intervention may be necessary to remove the infected tissue and alleviate the pain [19-21].

Neurological deficits: When the infection spreads to the spinal cord or nerve roots, it can cause compression and damage to these structures, leading to neurological symptoms. Surgery may be necessary to decompress the affected nerves and prevent further damage [19, 22-23].

Spinal instability: As spondylodiscitis can cause significant damage to the spine, including the destruction of the vertebral bodies and intervertebral discs and leading to spinal instability, surgical fixation may be necessary to stabilize the spine and prevent further damage [22, 24].

Spinal abscess: In case a spinal abscess is formed, it can put pressure on the spinal cord and nerve roots, leading to neurological deficits. Emergency surgical treatment may be necessary to drain the abscess and allow neural decompression, correction of deformity and segmental stabilization, preventing further complications [19, 25].

Responsible pathogen: Tuberculous spondylodiscitis in adults are usually easily controlled by proper antimicrobial therapy and the indications for surgery are few [26]. Mycotic spondylodiscitis may cause rapid destruction of the spinal tissues and often need surgical eradication and fusion [27].

Multi-level infection may be difficult to treat with antibiotics alone. Surgery may be necessary to remove the infected tissue and prevent the spread of the infection to other parts of the spine [19].

Suspected malignancy: As spondylodiscitis can sometimes mimic the symptoms of cancer, and it may be necessary to perform a biopsy or other diagnostic tests to confirm the diagnosis [19].

The Brighton Spondylodiscitis Score is a clinical tool that has been introduced to aid in the diagnosis and management of spondylodiscitis. According to this score, the need for surgical management of spondylodiscitis depends on the presence of distant site infection, comorbidities, immunosufficiency, MRI findings, anatomical location and neurological signs [28].

Methods of surgical treatment

The primary goal of surgical intervention for spondylodiscitis is the eradication of the infection and the stabilization of the spine. There are several methods of surgical treatment for spondylodiscitis, and the choice of method will depend on various factors, such as the location and severity of the infection, the presence of neurological deficits, and the patient's overall health. Surgical options include debridement of infected tissues and spinal fusion with instrumentation. In general terms, posterior pedicle screw-and-rod instrumentation, along with decompression of the spinal canal, radical debridement of the infected disc and interver-

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tebral fusion using either titanium cages or autologous bone graft are considered today's gold standard [21].

Debridement and drainage: Debridement and drainage are the most common surgical procedures used to treat spondylodiscitis. These procedures involve the removal of infected tissue and drainage of any abscesses or collections of pus. Debridement and drainage may be performed through an open surgical approach or minimally invasive techniques, such as percutaneous or endoscopic procedures. In the open approach, the infected area is approached through a skin incision and a muscle dissection, either with a ventral or a dorsal approach. The infected tissue is then removed, and any abscesses are drained. [25]. Transpedicular curettage and drainage is also a useful option for patients with poor health and multiple comorbidities [29]. In case of brucella-related spondylodiscitis, simple laminectomy and debridement is an effective method for treatment [30]. In percutaneous or endoscopic procedures, the infected area is accessed through small skin incisions with the use of a camera and specialized instruments. Percutaneous irrigation and suction of pyogenic spondylodiscitis is a minimally invasive option for the management of recalcitrant spondylodiscitis. It is most effective in cases where the infection is localized and has not spread to adjacent vertebrae. During this method, one or two needles are inserted percutaneously into the intervertebral disk space. The procedure can be performed under local anesthesia and is typically done on an outpatient basis. Percutaneous procedures are less invasive than open surgery, and they often result in less pain and a quicker recovery time [31].

Instrumentation and fusion: Instrumentation and fusion are surgical procedures that are used to stabilize the spine after debridement and drainage. The affected vertebrae are fused together with the use of hardware. These procedures are typically performed in cases where there is significant damage to the vertebral bodies and intervertebral discs, or where there is spinal instability.

In instrumentation, hardware such as metal rods, screws, or other devices are inserted into the spine to provide stability and support. In fusion, bone grafts or other materials are placed between the affected vertebrae to encourage bone growth and fusion, which further stabilizes the spine. Tricortical autologous bone grafts for intervertebral fusion are widely accepted but they are associated with donor-site morbidity and increased risk of subsidence and non-union. Titanium cages may enhance fusion and restore kyphotic deformity [19]. Polyethyl-ether-ether-ketone (PEEK) is a biocompatible alternative to metal implants. PEEK cages are used in single-stage debridement and fusion [21]. Radiolucent carbon-fiber-reinforced (CFR) PEEK hardware has shown inferior results compared to titanium screws, due to higher loosening rare and potential stronger adhesion to bacteria [32].

Instrumentation and fusion may be performed through an open surgical approach or minimally invasive techniques, such as percutaneous or endoscopic procedures. The choice of approach will depend on the location and severity of the infection, as well as the patient's overall health [23].

Anterior transthoracic or retroperitoneal approach with radical surgical debridement and reconstruction of the anterior column using bone graft, titanium cages and plates is indicated in patients with intravertebral abscesses and without major bone destruction, deformity and instability. Anterior approach is also effective in spinal canal decompression if the anterior column is involved. In general, isolated anterior internal fixation is not recommended in the thoracolumbar region due to high invasiveness [33]. The use of antibiotic-loaded bone cement as an efficient gap filler in anterior approaches has been described, in combination with additional stabilization and oral antibiotics. Antibiotic-loaded bone cement is typically used in cases where the infection is localized and has not spread to adjacent vertebrae. The procedure is less invasive than debridement and fusion and can be performed using minimally invasive techniques. It may contribute to the reconstruction of anterior column and the local infection control [34].

The combination of anterior decompression and debridement with posterior instrumentation has been reported with success. Posterior spinal fusion after anterior decompression is indicated in cases with severe kyphotic deformity, loss of alignment or after radical surgical debridement and multiple-level corpectomy. Spinal fusion hardware and grafts can be used at the site of infection, provided that radical surgical debridement is fully achieved [20,35]. Combined posterior approach for circumferential debridement and anterior reconstruction with fibular allograft has been applied in patients with skipped multifocal pyogenic spondylodiscitis with good clinical outcomes [36].

Recent evolution in the development and design of titanium implants has offered the potential to complete both the requisite debridement of the infected disc and correction of deformity from a single posterior approach. Isolated posterior stabilization is indicated in case of spondylodiscitis without bone destruction or local kyphosis caused by disc loss and distraction of the vertebral bodies. In case of formation of segmental kyphosis and loss of alignment, posterior stabilization should be combined with additional anterior fixation [33]. Posterior stabilization and fusion is an effective method of treatment of brucella-related spondylodiscitis, in case surgical intervention is required [30]. In case of a single-level spondylodiscitis, continuous epidural irrigation combined with posterior debridement and posterior lumbar interbofy fusion is an effective method facilitating the eradication of residual infection [37]. Percutaneous posterior instrumentation with 4 - 8 screws bridging the level of infection and contoured rods is associated with high overall satisfaction and low complication rate, in a 10-years follow-up [38]. Single-stage posterior transforaminal lumbar interbody fusion (TLIF) with PEEK cages is a reliable and feasible surgical option [21].

Extreme lateral interbody fusion (XLIF) with percutaneous posterior instrumentation is a minimally invasive interbody fusion technique which spares the anterior longitudinal ligament and allows adequate visualization of the intervertebral discs and vertebral bodies in order to debride necrotic and infected tissue and place a large, lordotic cage. Studies have suggested that XLIF is a safe and effective alternative to ALIF for the treatment of spondylodiscitis [39].

In case of tuberculous thoracic and lumbar spondylodiscitis, both anterior and posterior approaches are effective. Posterior approaches are associated with better kyphotic angle correction, less angle loss, better improvement of pain, greater duration of surgery and greater blood loss [40]. In these patients, video-assisted thoracoscopic surgery (VATS) involving anterior debridement and fusion along with minimally invasive posterior pedicle screw instrumentation and mini open posterolateral debridement and fusion have produced encouraging functional results [22]. For elderly patients with pyogenic spondylodiscitis and intraspinal abscess, microsurgical decompression and debridement of the infective tissue, followed by posterior stabilization and interbody fusion with iliac crest bone graft in one or two lumbar segments has good results [41]. Chronic kidney disease and hemodialysis is not a factor that increases complications after spinal instrumentation for pyogenic spondylodiscitis [42]. In these patients, surgical debridement with posterior instrumentation is a sufficient surgical option with good clinical outcome [43].

Conclusion

In conclusion, spondylodiscitis is a relatively uncommon condition that can lead to significant morbidity and mortality if left untreated. Initial management is conservative, including antibiotics, rest and braces. Indications for surgical treatment include neurological deficits, spinal instability, abscess formation and failure of conservative treatment. Surgical management includes debridement of the infected tissues and spinal fusion with instrumentation, through an anterior, a posterior or a combined approach. The choice of material for spinal support and enhancement of spinal fusion does not influence the clinical result.

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The effects of hydrotherapy on people with cervical spinal cord injury

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ABSTRACT

The primary goal of this study was to systematically review the effects of hydrotherapy in individuals with cervical spinal cord injuries (SCI). The aim was to focus on results in the musculoskeletal, respiratory and cardiovascular systems, the effect on pain and spasticity, as well as the contribution of aquatic therapy to gait retraining and quality of life. Furthermore, it was considered important to identify gaps in the literature and suggest future studies of therapeutic intervention in the aquatic environment in the field of neurological rehabilitation for patients with SCI.

Key words: Hydrotherapy, Spinal cord inury, Cervical spine.

Introduction

Traumatic tetraplegia results in motor, sensory and autonomic deficits that are dependent upon the site and extent of spinal cord damage [13]. Individuals with cervical spinal cord injury (SCI) can present paralysis of the upper and lower limbs and respiratory dysfunction, due to the loss of supraspinal control over the respiratory muscles. Additionally, muscular atrophy and loss of sympathetic activation diminishes venous return and systolic function and as result, it compromises cardiovascular function [6]. The chronic phase of the condition is characterized by loss of motor and sensory function, but also includes symptoms such as autonomic dysreflexia, impairment of bowel and bladder control, pain and spasticity resulting in significant loss of quality of life [34]. Complete spinal cord lesions above the fifth cervical segment, will result in the loss of motor and sensory innervation to some regions of the arms and all regions of the legs, hips and trunk. The loss of the sympathetic division of the autonomic nervous system will also affect cardioacceleration and redistribution of blood flow [14].

The rehabilitation program requires a multidisciplinary approach. The patients can experience severe problems with great impact on their activities of daily living, physical and psychological well being and self-care, mobility, social interaction, accommodation, employment, family support and sexual function. The physiotherapists provide a complete assessment of respiratory status, passive range of motion of the joints above and below the level of injury, muscle strength, coordination and function, as well as level of sensation. Each program is then tailored to each patient's needs and the patient is encouraged to work on developing independence with transfers, maximal independence and functional ability [5].

There is evidence to support the use of aquatic therapy (AT) for individuals with spinal cord injury [22]. The wide variety and physical properties of water, like buoyancy, temperature, and hydrostatic pressure make HT a particularly suitable technique for people with SCIs as water facilitates a variety of therapeutic interventions. Buoyancy provides gravity-eliminated support, hydrostatic pressure compresses tissues and promotes lymphatic and venous return, the warm temperature reduces muscle spasm, and viscosity/turbulence provides velocity-dependent and resistance-building strength [29].

The primary goal of this study was to systematically review the effects of hydrotherapy in individuals with cervical spinal cord injuries. The aim was to focus on results in the musculoskeletal, respiratory and cardiovascular systems, the effect on pain and spasticity, as well as the contribution of aquatic therapy to gait retraining and quality of life. Furthermore, it was considered important to identify gaps in the literature and suggest future studies of therapeutic intervention in the aquatic environment in the field of neurological rehabilitation for patients with SCI.

Methods

The research was conducted in English in the following databases: Pubmed, Science Direct, google scholar and PEDro. The following keywords and their combination were used: hydrotherapy, aquatic therapy, rehabilitation, (cervical) spinal cord injury, tetraplegia, quadriplegia, ventilated patient, tracheostomy.

Inclusion and exclusion criteria:

Studies referring to participants with acute or chronic, complete or incomplete SCI, as well as participants with a clinical picture of tetraplegia or tetraparesis were included. Animal studies were excluded.

Studies that used hydrotherapy as an intervention were included. Studies that did not use water exercise as an intervention or part of it were ruled out.

In terms of the type of studies, they can be randomized controlled trials (RCTs), controlled trials, qualitative studies, case studies or case series studies.

Studies referring to the effects of hydrotherapy (improvement of respiratory and cardiovascular function, reducing pain and spasticity, improving function and quality of life) on people with SCIs were included. Due to the small number of studies available, the year the survey was conducted was not of great significance.

The systematic review revealed 902 search-related surveys. After the titles and, where necessary, the abstracts, were screened, 864 surveys were excluded due to non-relevance to the topic. After sorting, 38 articles were evaluated for eligibility, by reading the full text, according to the criteria for inclusion and exclusion of this systematic review. Of these, 21 articles were excluded (7: systematic reviews, 3: animal research, 2 without extensive reference to hydrotherapy, 6: other neurological diseases, 2: children with cerebral palsy). Finally, 18 surveys were included in this review.

The evaluation of the methodological quality of the RCTs in this review was based on the widely used 11-point PEDro scale [19]. The Pedro scale is a valid and reliable tool for evaluating the methodological quality of randomized controlled trials on physiotherapy and rehabilitation [26]. This scale includes eleven quality criteria of methodology. The presence of each criterion in the study is graded with one grade and its absence with zero. The first criterion that describes the origin and the criteria of the sample of a study, is not included in the final score of the study so the lowest and highest score of a study in the Pedro evaluation, ranges from 0 to 10 respectively

Results

Thermoregulation, cardiovascular and respiratory system:

Di Rocco et al. [7], wanted to examine the cardiorespiratory responses of wheelchair users in the aquatic environment. As a result, water has been shown to improve venous return, cardiac output and lung ventilation, and it appeared that nonambulatory

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individuals with low fitness levels were able to experience greater cardiopulmonary work outputs when exercising in the water. In another study, reductions in heart rate and improvement in cardiac output appeared to be the result of 2 months of exercise in the water by individuals with incomplete SCI [32].

Studies of thermoregulatory and cardiorespiratory adaptations after immersion in warm water (39°C) and after exercise in water have shown lower heart rate, higher rectal temperature, lower plasma noradrenaline concentration, and increased plasma volume in a tetraplegic group [16], while in a group of paraplegics (affected sympathetic system, except of one participant), warm water immersion did not produce a significant adaptive response [15].

Regarding to spirometric parameters, it has been shown that immersion at shoulder height improves the VC of people with quadriplegia [19], a fact to which hydrostatic pressure contributes significantly [18]. Finally, significant differences were reported in FVC, FER, FEV1 and FEV1 / FVC [16], while a comparison of 3 months of hydrotherapy and robotic therapy in individuals with chronic incomplete SCIs showed that neither intervention succeeded to statistically improve the maximum VO2 value, although the percentage improvement was greater in the hydrotherapy group [15].

Spasticity, gait retraining and quality of life

In 1999, Pagliaro and Zamparo [28] observed that hydrotherapy contributed to a reduced myotatic reflex response in people with spastic tetraparesis, while in another study where AT was used as an intervention, there was a significant increase in FIM scores, a statistically significant decrease in baclofen oral intake and a significant reduction in spasm severity [17].

Regarding to gait retraining and movement in water, it was shown that the aquatic environment influences the beginning of gait in terms of the center of pressure excursion, impulses, trunk acceleration, and perceptions of participants with incomplete spinal cord injury, improving physical function and the ability to walk [21]. Furthermore, it was proved that the walking pattern of people with SCI in water is related to kinematic parameters similar to those of healthy people, especially in terms of speed, stride length and stance phase [34]. Later, Recio et al [29] observed a significant improvement in the SCIM III score, in the motor part of the AIS scale, and an increase in distance to 6MWT in ambulatory patients.

From the health professionals' point of view, physical, psychosocial and functional benefits were identified through questionnaires. It was reported that in warm water there was a reduction in pain, improvements in well-being, mental health and self-confidence. The aquatic environment gave patients a sense of freedom, something they could not experience on land, but various challenges were also reported, such as lack of (trained) staff and resources, infection control, transportation and participation costs, caregiver support and accessibility [22].

Presence of tracheostomy and invasive appliances

Both Taylor [35] and Wegner et al. [39] in their case studies, applied AT to a patients with tracheostomy and mechanical respiratory support and they noted that through careful planning and proper preparation, hydrotherapy can be successfully and safely integrated into the patient's rehabilitation program. They observed that aquatic therapy can facilitate the patient's ability to actively participate in exercise and rehabilitation and can lead to improved respiratory function, allowing faster weaning from mechanical ventilation and consequently, reducing the length of stay and the cost of intensive care.

Felten-Barentsz et al. [10], after applying a hydrotherapy program to 25 critically ill patients in the intensive care unit with mechanical ventilation, concluded that hydrotherapy seems to be a feasible and safe intervention in critically ill patients, while, later [11], through interviews with critically ill patients with mechanical ventilation, it emerged that hydrotherapy helps patients regain control and faith in their recovery and that exercise in water was an important turning point in their recovery process.

Finally, Recio et al [29] evaluated the interventions used in hydrotherapy and the clinical benefits in people with SCIs who use invasive appliances (bandages for pressure ulcers, indwelling or suprapubic catheters, colostomy bags and tracheostomy tubes) and it was shown that they can safely participate in a specialized hydrotherapy program without complications and

that they seem to achieve clinically significant benefits.

Discussion

Cardiorespiratory system and thermoregulation

The effect on the cardiovascular system will depend on the extent of the damage to the spinal /central part of the autonomic nervous system. The cardiac changes are caused by loss of supraspinal sympathetic control and relatively increased parasympathetic cardiac control. Decreases in sympathetic activity result in heart rate and the arterial blood pressure changes, and may cause arrhythmias, in particular bradycardia, with the risk of cardiac arrest in those with cervical or high thoracic injuries [4].

Systemic muscular atrophy and loss of sympathetic activation compromises cardiovascular function by diminishing venous return and systolic function. Consequently, cardiopulmonary disease is the most common cause of morbidity following SCI [6].

When a person is immersed in water, the blood shifts to the heart, enhancing venous return, which in turn increases arterial and ventricular filling and leads to a consequent reduction in heart rate [9]. During exercise in the water, the maximum oxygen consumption is higher than that of the exercise on land, allowing greater energy expenditure at lower speeds and prolonged activity. During immersion an individual is subjected to external water pressure in a gradient, which within a relatively small depth exceeds venous pressure, blood is displaced upward through the venous and lymphatic systems [3].

Hydrostatic pressure applied to the thorax and abdomen beneath the surface assists in exhalation improving vital capacity and resists inspiration increasing muscle tension as a signal for growth of muscle mass (hypertrophy). Buoyancy can also act as an abdominal binder, supporting the contents of the abdomen and allowing diaphragm ventilatory parameters to optimize due to supportive pressure beneath the dome of the diaphragm, improving efficiency in contraction and passive exhalation [29].

Below the level of the SCI it is expected that there will be no centrally driven vasomotor or sudomotor activity, resulting in higher skin temperatures and a greater gain in core temperature when the person with a cervical cord lesion is thermally challenged. The reduction in sudomotor and vasomotor function resulting from injury to the spinal cord, combined with a likely reduced total blood volume may lead to higher heat storage for a given thermal stimulus, thereby raising the risk of a heat related disorder. Indeed, passive heat has been reported to be responsible for approximately 3% of all deaths in people with spinal cord injury [13].

Spasticity and pain

Spasticity is a major health problem for patients with SCI, which limits patients' mobility and affects their independence in activities of daily living and work. It may also cause pain, loss of range of motion, contractures, sleep disorders, and impair ambulation in SCI patients. Spasticity creates great difficulty for both the patient and the rehabilitation team. Current therapies for spasticity are far from ideal, and new therapeutic interventions are being explored. Physiotherapy, however, is an important component in the management of spasticity [17], but still, there is not enough research to prove it [2]. As for hydrotherapy, it not only promotes functional recovery, but it can also improve spasticity as part of the treatment program [29].

In a study of children with cerebral palsy, aquatic therapy was shown to be effective in reducing spasticity [1], while a study in patients after a stroke showed that hydrotherapy could increase muscle strength of the affected limb without increasing spasticity [40]. Finally, in a study of patients with peripheral neuropathies, it was found that only 'in-water' patients experienced a reduction in neuropathic pain [41].

Kesiktas et al [17] noted that the side effects of oral medication for the management of spasticity are known and that adding hydrotherapy to the rehabilitation program may be helpful in reducing the amount of medication required.

Muscular system and joints

Frye et al [12] in their study of people with cervical SCI observed that participants had limitations in forearm pronation and elbow extension and increased shoulder and wrist extension. One third of the participants presented elbow overextension and ankle plantar flexion contractures were found in many participants.

As the body is gradually immersed, buoyancy provokes offloading of immersed joints. With immersion to the neck, only the approximate weight of the head (15lb) is exerted on the spine, hips, and knees. With immersion to the symphysis pubis, a person has effectively offloaded 40% of his body weight, and approximately 50% when immersed to the umbilicus. Xiphoid immersion offloads body weight by 60% or more [3]. Buoyancy allows to individuals with SCI to become mobile in the water without the resistance of gravity and they can safely, spontaneously and independently exercise. The water stabilizes their lumbopelvic hip, thoracic and cervical muscles and they can exercise without relying on the use of their upper limbs in order to support their posture, as happens during land-based exercises. This can be a key in the prevention of upper limb overuse injuries [9].

Common techniques performed in hydrotherapy for patients with spinal cord injury include stretching, muscle strengthening, balance improvement and gait retraining. These techniques prepare the achievement of functional mobility using exercise focused on daily activities and are integrated into a patient-centered exercise program [29].

Early intervention

Early mobilization can improve outcomes in critically ill patients with or without mechanical ventilation support. Although the data available suggest that mobilization in a therapeutic pool is able to enhance recovery in very weak patients, there are potential challenges and safety issues when it is applied to mechanically ventilated patients [20]. The risks of taking anyone into a pool are already described in the Chartered Society of Physiotherapy's 2006 Guidance on Good Practice in Hydrotherapy, but as it is a relatively novel rehabilitation strategy, its wide use across international facilities seems to be low [39]. Criteria for excluding such patients from hydrotherapy program may include high ventilator support, vasopressors, severe agitation, large wounds, and colonization with multiresistant bacteria [10].

Airway management is critical when undertaking hydrotherapy with ventilated patients and planning must consider airway security and safety. Ventilator disconnection or aspiration of pool water through incorrect positioning or support by staff are the main risks to the airway. When in the water, one therapist should support the head and shoulders of the patient and have direct visualization of the ETT/tracheostomy site to ensure it is maintained above the water [39].

Maling et al. [20], reviewed eleven studies that mainly focused on laryngectomy patients and although they were mostly case studies that contained limited data, they provided information that was useful in creating a Risk Management Tool.

Chronic phase and quality of life

The increasing rates of injury hospitalizations, improved trauma systems and acute care units are giving rise to higher numbers of trauma survivors [8]. Severe neurological deficits limit functional independence, participation and perception of general health, and consequently decrease the physical activity [30]. Long-term lack of physical activity and excessive sedentary behavior are related to, cancer, heart disease, type 2 diabetes and all-cause mortality. This information may be used to help people resume and manage physical activity after trauma and potentially reduce avoidable health decline in the years thereafter [8].

The aim of rehabilitation in patients after SCI is to provide them with as much autonomy as possible. It is of high importance to focus on the ability to perform activities of daily living such as dressing, personal hygiene, eating, computer operation, or mobility in indoor and outdoor environments [31]. It is noted that there is a need for improvement in early counselling between the medical/surgical and rehabilitation teams, along with the patients and family, in order to set realistic goals early during the first days after the injury [30].

In the study by Ekegren et al. [8], it was shown that 3 to 5 years after the injury, participants perceived a high level of physical inactivity due to fear of re-injury, pain and lack of proper clinical guidance. These restrictions were a source of distress, given the perceived impacts on health, social lives and family roles. Participants who were participating in regular physical activity recognized the value of social supports, sources of funding and their own self-motivation in promoting participation.

Difficulties and obstacles

Unfortunately, hydrotherapy is not always available to all patients with SCI due to various comorbidities, neurogenic bowel-bladder, colostomies with attached collection bags etc that could potentially create barriers to their participation [29]. However, the reduced use of AT in people with SCI may not only be due to the presence of comorbidities. For example, lack of trained professionals, limited time for AT in rehabilitation centers, and lack of knowledge of its benefits can be potential barriers. Some of them could be mitigated by educating health professionals, patients and community stakeholders about the benefits of providing AT [22].

Restrictions

Some of the main limitations of this study were the number of databases used, as well as the limitation of the English language. The limited number of surveys available, as well as their low methodological quality, are also significant limitations of this review.

Results - Suggestions

The main finding of this study is that the use of hydrotherapy has been shown to cope with the rehabilitation requirements of people with SCI, from a very early stage, with the presence of tracheostomy and other invasive devices, in the hypoxic and chronic stages. Nevertheless, there is a great need for more research of higher quality and validity, in order to develop specialized protocols and safety measures, for not only the greater participation of these patients in the hydrotherapy program, but also for more appropriate information of the health professionals.

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Hyperbaric oxygen therapy after spinal cord injury. A systematic literature review

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ABSTRACT

Hyperbaric oxygen therapy is the inhalation of 100% pure O_2 at increased pressure, i.e. at ambient pressure greater than 1 atm. The basic principles of hyperbaric oxygen therapy (HBOT) are based on the way in which the various gases – and especially O_2 - behave and act upon the tissues and fluids of the human body, under the influence of different conditions of volume and pressure. Spinal cord injury (SCI) is a very serious and complicated medical condition which greatly disrupts the patient's life. Historically, this condition has been associated with very high morbidity and mortality rates.

In the present study, the latest research data on the effectiveness of this method regarding spinal cord injuries was studied. In order to achieve this purpose, the research tool of systematic literature review was chosen.

Discussion: The systematic literature review resulted in the detection of 13 relevant published articles after 2015. There were 3 randomized controlled studies, 2 non-randomized clinical studies, 4 case series and 4 case reports. In total, 557 patients participated in the study. The main result of the study was that HBOT is a totally safe and without any clinically significant side effects adjuvant therapy for the treatment of SCIs, producing various degrees of improvement of the motor and sensory neurological condition of the patients suffering from various types of SCIs, along with their psychological condition.

Conclusion: Hyperbaric oxygen treatment is a totally safe adjuvant treatment method for patients suffering from spinal cord injuries, having the potential to improve both the neurological status (motor and sensory) and the psychological condition of the affected patients. Further research is needed to obtain specific guidelines in relation to the indications and the application protocols of the method.

Key words: Hyperbaric, Oxygen, Spinal, Cord, Injuries

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Introduction

The history of hyperbaric medicine begins in 1662, when Henshaw, a British doctor, used compressed air in order to treat various diseases of the respiratory system, developing the first hyperbaric chamber, which was named by him "the domicilium". Oxygen was discovered more than 100 years afterwards, in 1775 by another British scientist, John Priestley, but in was not until the first years of the 20th century, when Orval J. Cunningham, an American professor of Kansas University used, for the first time, oxygen in elevated partial pressures in order to treat various hypoxic conditions [1].

Nowadays, hyperbaric Medicine has became a separate medical sub-speciality and is applied with great efficiency in a large number of pathological conditions, such as treatment of burns, severe wounds and chronic ulcers, treating the side-effects of radiation therapy, migraines, hearing problems and even severe neuromuscular pathologies [2].

Spinal cord injury (SCI) is a very complex medical condition, which greatly disrupts the patients' life and is associated with high morbidity and mortality. Although there has been a disagreement regarding the pathology characterized as "spinal cord injury", most of the authors agree that all the lesions of the spinal cord and the cauda equina, either traumatic or atraumatic, should be viewed as spinal cord injuries [3]. It is estimated that 250.000 – 500.000 people every year worldwide suffer from this pathology, while two to three million patients live permanently with its consequences.

The purpose of the present study was to investigate the data of the recent literature regarding the effectiveness of the use of hyperbaric oxygen on the treatment and rehabilitation after spinal cord injuries.

The databases used for this review were: *PubMed / NCBI, Google Scholar, Cochrane Library and Scopus*. The applied key-words (mesh terms) included: *Hyperbaric oxygen therapy, HPOT, Spinal cord injury, SCI, Treatment, Rehabilitation,* in various combinations of the specific terms, and with the use of the separators *AND* and *OR*.

The inclusion criteria for the selection of the relevant published articles were: (i) original articles (randomized and non-randomized trials, case-series and case reports' presentations), involving humans, (ii) both traumatic and non – traumatic SCI, (iii) studies published after 2015, (iv) language of the publication in English and the availability of full-text studies.

On the other hand, systematic and narrative reviews were excluded, along with experimental trials and trials involving animals. The flowchart of this systematic literature review, according to the PRISMA principles [4], is presented in Figure 1.

Discussion

The systematic literature review, which was carried out according to the criteria mentioned in the previous chapter, resulted in the detection of 13 relevant published articles. There were 3 randomized controlled studies, 2 non-randomized clinical studies, 4 case series and 4 case reports. In total, 557 patients participated in the study. The findings of all those articles are summarized in Table 1.

All the recent published clinical studies concluded that HBOT is a totally safe, without any clinically significant side effects adjuvant therapy for the treatment of SCIs.

Almost all studies showed various degrees of improvement of patients' motor and sensory neurological condition suffering from various types of SCIs, along with their psychological condition.

Bunul et al., (2021) [16], in a small case series of 3 patients suffering from radiation-associated myelopathy did not find any improvement by this treatment. Marrosu et al., (2021) [14], reported that along with the dramatic improvement of a patient's neurological status, there were indications of reshaping of the cortico-cortical connectivity after the HBOT.

Another novel finding of the present literature review is that HBOT is an effective method for the prevention of spinal cord ischemia – reperfusion injury (SCIRI) in patients undergoing extensive posterior laminectomy and fusion for severe cervical and thoracic spinal stenosis [11].

The pathophysiological mechanisms of SCIs are complex, involving both primary and secondary lesions of the spinal cord. Primary lesions are due to the mechanical injury produced by the traumatic event, whereas the secondary injuries are more complex, may occur after a fairly long period of time and involve various physiological processes of the human organism,

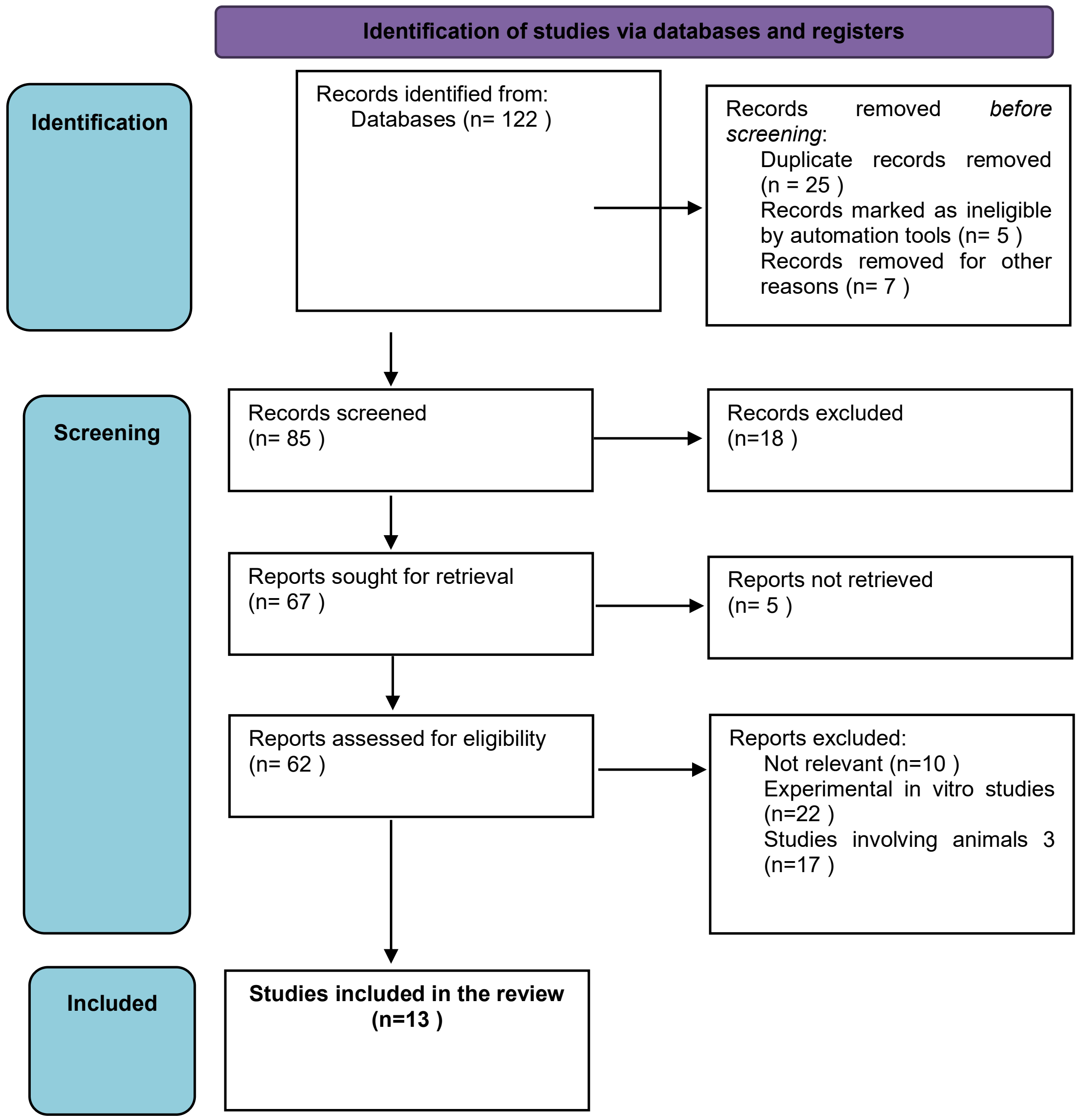

Figure 1: *The PRISMA flow diagram of the present systematic literature review*

including cellular death (apoptosis), injuries of the nervous system tissue due to oxidative stress, oedema and ischemia of the spinal cord, inflammation and toxicity produced by excitatory neurotransmitters like glutamate (excitotoxicity) [18].

Since in the majority of the serious SCIs, the primary spinal cord lesions are irreversible, recent scientific research focused on the successful treatment of the secondary spinal cord lesions. The medication used traditionally for these injuries is methylprednizole, in large therapeutic doses: the first dose is bolus, intravenous infusion of 30 mg/Kgr of patient's body weight, in the

Table 1: The results of the systematic literature review

Author, country	Type of study	Participants	Treatment	Results
Cheng et al., (2015) [5], Taiwan	Case report	Male, 30 years old, partial Brown-Sequard syndrome at the level of C4 – left side	HBOT 3 hours after the initiation of the symptoms	Significant improvement of the clinical and neurologic condition after two days of HBOT
Onen et al., (2015) [6] , Turkey	Case series	19 cases of iatrogenic SCI due to infections (mean age 54.6 years).	Average 20.1 HBOT sessions (10 - 40)	Safe and efficient adjuvant therapy
Xu et al., (2016) [7] , China	Case report	Male, 45 years old, acute paraplegia after needle biopsy – most probable due to air embolism	HBOT immediately after the incident	Partial improvement – paraparesis
Feng et al., (2017) [8], China	Randomized – controlled study	60 patients with incomplete spinal cord injury (20 patients in the HBOT group, 20 patients in the psychotherapy group, 20 patients in the control – conventional rehabilitation group)	HBOT at 2.0 ATA pressure, 6 days / week for 8 weeks	No side effects - Significant improvement of nerve function, psychological parameters and daily living activities. Further research needed, with larger sample and longer follow-up
Parotto et al., (2018) [9], Canada	Retrospective case series	7 patients with SCI after complex aortic repair	HBOT at 2.4 -2.8 ATA, once / twice daily until improvement or plateau of neurologic symptomatology	2 patients died (perioperative complications), 5 patients had varying degrees of neurological improvement – 1 patient had major complication (oxygen induced seizures). The method is beneficial for the neurologic recovery of patients with SCI.
Tan et al., (2018) [10] , China	Non – randomized controlled study	40 patients with acute SCI (29 in the BBOT group, 11 in the control group)	HBOT at 2ATA for 45 minutes, once/day for 30 days	HBOT group presented with significant improvement in the neurological parameters and the MRI findings ($p < 0.05$), in comparison to the control group. Is a very effective treatment at the early stages after an acute SCI
Chen et al., (2019) [11] , China	Randomized controlled study	186 patients with Spinal Cord Ischemia – Reperfusion injury	Group A: Combination of HBOT and methylprednisolone. Group B: Only dexamethasone	Statistical significant difference in the incidence rate of the SCI, in favour of the treatment group (Group A).
Wilson et al., (2020) [12] , Canada	Case report	Male, 68 years old, acute SCI due to degenerative thoracic and lumbar canal stenosis	Five sessions of HBOT at 2.8 ATA for 90 minutes during the first 3 postoperative days	Immediate improvement from ASIA B to ASIA E after the first session which sustained through the following sessions.

Ashton et al., (2020) [13], Australia	Retrospective case series	13 patients (median age 57 years), spinal cord infarction	Five of those patients received HBOT (average 15 sessions)	HBOT along with CSF drainage and pentoxifylline may reduce the disability caused by the disease
Marrosu et al., (2021) [14], Italy	Case report	Male, 45 years old, traumatic lesion of SCI at the level of C1 after a dive	Five cycles of HBOT, 18 session each cycle at 2.5 ATA	Dramatic improvement after the HBOT treatment. EEG recordings suggest reshaping cortico-cortical connectivity after the HBOT.
Li et al., (2021) [15], China	Randomized controlled study	80 patients with SCI after fractures of the thoracolumbar spine treated with posterior laminectomy and fusion	Group A: Control group (conventional treatment). Group B: HBOT combined with Riluzole and mannitol	Group B statistically significant superior to Group A for motor and sensory function scores.
Bunul et al., (2021) [16], Turkey	Case series	3 patients with radiation associated myelopathy	HBOT from the 12th till the 30th day after the occurrence of the symptoms	No significant improvement in the 2 patients – the third died because of his primary disease.
Zhang et al., (2022) [17], China	Retrospective non-randomized controlled study	78 patients with incomplete SCI, after spinal decompression and internal fixation	Group A: conventional treatment Group B: HBOT	HBOT is safe and effective method. Treatment group had superior results in comparison to the control group

first fifteen minutes, followed by continuous infusion of 5.5 mg/Kgr per hour, starting 45 minutes after the first, bolus infusion, and continuing for the next 23 hours [19]. The relatively limited effectiveness of this regimen, in combination to its limitations and side effects, made it necessary for further research in order to establish adjuvant therapeutic methods for the treatment of both acute and chronic SCIs.

One of the therapeutic methods, which has aroused the scientific interest during the last few years, is hyperbaric oxygen treatment therapy, in which 100% O_2 is administered to the patient at pressures between 1–3 ATA (atmospheric pressure). A number of experimental studies has shown that HBOT has the ability to offer strong protection to the patient's central nervous system (neuroprotection), with a broad variety of physiological mechanisms, including the following [18]: (i) decrease of the cellular death (apoptosis), (ii) reduction of the oxidative stress caused by the injury, (iii) reduction of the inflammation, (iv) reduction of the oedema of the spinal cord, (v) promotion of the creation of new vessels (angiogenesis) in the injured area and lastly, (vi) increasing the procedure of degrading and removing the injured and dysfunctioning neurones (autophagy).

After the beneficial effects of HBOT on the central nervous system were demonstrated in the experimental field, the first clinical, in vivo, studies on its effectiveness on humans gradually commenced.

Holbach et al., in 1977 [20], published one of the first case series regarding the effectiveness of HBOT in 13 patients suffering from compression SCIs, recording significant improvement in 6 out of the 13 patients, especially in their motor function. One year later, Jones et al.,(1978) [21], in another case series of 10 patients having sustained acute SCIs, recorded a more rapid and in a greater degree recovery of the motor function in 5 of them than the expected recovery through the traditional management.

Huang et al., in 2021[22], conducted a systematic review and meta-analysis of randomized controlled studies regarding the effectiveness of HBOT in patients who have sustained SCIs. In their study they covered the entire time period up to 2020 and finally included 11 clinical trials, involving 817 patients. The main results of this systematic review were the following: (i) HBOT improved statistically significantly the ASIA motor score, and the Modified Barthel Index (MBI), (ii) in 6 of the trials, HBOT improved statistically significantly the ASIA sensory score, (iii) in 4 of the trials, HBOT improved statistically significantly the needling score along with the light touch score and finally, (iv) HBOT decreased statistically significantly both the Hamilton Depression Scale (HAMD) and the Hamilton Anxiety Scale (HAMA).

The final conclusion of the authors was that the findings of the current literature indicate that HBOT most probably improves both sensory and motor function as well as the psychological parameters of patients suffering from SCIs, although more high-quality and with larger patients' sample was needed in order to definitely support the previous mentioned findings.

Limitations

The present study has a number of limitations: since the purpose of the dissertation was to study the most recent literature data, (after the year 2015), the high-quality randomized controlled studies published in that period were very few – only three, with another two non-randomized controlled studies and the rest of the articles being case reports or case series. Also, another limitation is the great heterogenity of the studies, which covered a variety of both acute and chronic, traumatic and non-traumatic spinal cord injuries. Definitely, further research with high quality of randomized – controlled studies, with larger numbers of participants in needed in order to prove the effectiveness of HBOT in the various context of SCIs

Conclusion

Hyperbaric oxygen treatment is a totally safe adjuvant treatment method for patients suffering from spinal cord injuries, which has the potential to improve both the neurological status (motor and sensory) and the psychological condition of the affected patients. Further research is needed in order to give specific guidelines in relation to the indications and the application protocols of the method.

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Physiotherapy interventions for enhancing neuroplasticity in people with spinal cord injuries: A systematic review of randomized control trials

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ABSTRACT

A systematic review of randomized control trials was conducted to provide an overview of the effectiveness of physiotherapy interventions for enhancing neuroplasticity and by extension functional recovery in people with SCI.

The appropriate MESH keywords were used in September of 2022 to search the global databases: PubMed, Science Direct, Cochrane and Scopus. In the review, only randomized controlled trials (RCTs) were included, which met the inclusion and exclusion criteria. The RCTs that were included in this review evaluate the effect of different physiotherapy interventions on neuroplasticity in people with spinal cord injuries. All studies were assessed for risk of bias using the Pedro scale.

In our study, we included 6 randomized control trials. Interventions such as massed practice with somatosensory stimulation, exercise with corticospinal neural stimulation, endurance training, intermittent hypoxia (IH) combined with Body weight supported treadmill training and paired transcranial direct current stimulation (tDCS) with Locomotor training with a robot-assisted gait orthosis (LT-RGO) were shown to enhance neuroplasticity and induce functional recovery in people with SCI. Therefore, further research needs to be done.

Keywords: Spinal Cord Injuries, Physical Therapy Modalities, Neuronal Plasticity

Introduction

Spinal Cord Injuries are serious medical conditions that often lead to severe disability. In spinal cord injuries, the nerve axons of the spinal cord are disrupted and this leads to loss of sensory and motor function [1]. The most frequent occurrence is the result of major trauma. Spinal cord injuries, depending on the severity of the trauma, are classified as complete or incomplete.

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This classification is based on whether there is some sensory and/or motor function below the injured level [2]. It is important to note that a clinically complete SCI is most of the times, not a pathological complete cut of the spinal cord and there are remaining neural pathways.

A certain degree of recovery for incomplete and even complete SCI can be achieved through physical rehabilitation. The amount and extent of recovery depends on multiple factors, including the level and extent of injury, post-injury medical care, and rehabilitative interventions. Plasticity as the Merriam-Webster's Medical Dictionary defines is "the capacity for continuous alteration of the neural pathways and synapses of the living brain and the nervous system in response to experience 5or injury''. It has been reported that there is a reorganization of cortical maps after spinal cord injury that occurs spontaneously [3]. Green et others showed that patients eventually regaining function after SCI, are initially presented with a posterior shift in cortical motor potential [4] The nervous system has the ability to enlarge cortical territories that are controlling functioning body parts and to invade cortical areas that have lost the peripherical target [5]. Also, another ability of the nervous system is to strengthen and weaken synapses in response to input. These synaptic changes are essential for learning, memory, and motor output under normal and pathological conditions. Decades of research revealed that the injured central nervous system retains the capacity for neuroplasticity even during the chronic phase of injury [3].

Plasticity is an incredible ability of the nervous system, giving it the capacity to learn and recover after trauma. Without the guidance of rehabilitation though, it yields limited functional improvements following SCI [6]. Existing physical therapy interventions for SCI mostly focus on minimizing secondary complications and compensating for lost function instead of targeting enhancing neuroplasticity and restoring pre-injury abilities [7]. Further research is urgently needed to be done in new physical therapy interventions approaches for facilitating physical function beyond conventional therapies and to promote quality of life among people with SCI [8].

The purpose of this systematic review was to provide an overview of the effectiveness of physiotherapy interventions for enhancing neuroplasticity and by extension, functional recovery in people with SCI.

We conducted a search of the literature using the key words: "Spinal Cord Injuries", "Physical Therapy Modalities", "Neuronal Plasticity" on September 2022. We used the following search strategies using Mesh Terms: (i) on PubMed and Cochrane: (("Spinal Cord Injuries" [Mesh]) AND ("Physical Therapy Modalities" [Mesh]) AND ("Neuronal Plasticity" [Mesh]) and (ii) on Science Direct and Scopus: ("Spinal Cord Injuries" OR "Cord Trauma" OR "Spinal Cord Injury") AND ("Physical Therapy Modalities" OR "Physiotherapy" OR "Physical Therapy") AND ("Neuronal Plasticity" OR "Neuroplasticity"). We included studies of people with Spinal Cord Injuries, no matter if the injury was acute or chronic, traumatic or non-traumatic and whether the classification of the injury was complete or incomplete. Only randomized control trials that were published in the last 20 years were included in this review. All the studies that were included were in English. All animal studies were excluded.

Risk of Bias: All studies were assessed for risk of bias using the Pedro Scale. The Pedro scale was developed in 1999 to evaluate the risk of bias and completeness of statistical reporting and is now commonly used in systematic reviews [9]. The Pedro Scale evaluates 11 items: inclusion criteria and source, random allocation, concealed allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, completeness of follow up, intention-to-treat analysis, between-group statistical comparisons, and point measures and variability. Each item is rated as "yes" or "no," and the total Pedro score is the number of items met (excluding criteria 1) (Maher,, Sherrington, Herbert, & Moseley, 2003). Eight items evaluate risk of bias and two completeness of statistical reporting. Depending on the Pedro score the study is consider to have poor (<3), fair (4-5), good (6-8) or excellent (8-10) methodological quality. Pedro scoring for each study is presented on **Figure 3.**

Results

We conducted our search on September 2022 on PubMed, Cochrane, Scopus and Science Direct and retrieved 649 studies. By applying the inclusion and exclusions criteria and by reading the full text and excluding duplicate publications, we identified 25 clinical trials. From the 25 clinical trials only 6 of them were randomized control trials that were evaluating physical therapy effects on neuroplasticity in people with spinal cord injuries and were included in our systematic review [11-16]. The studies are presented in **Figure 2.**

The evaluation of Risk of bias is presented on Figure 3. As is shown on the table only 2 studies were considered high quality and scored 10/10[16][15]. Three of the six studies were considered of good methodological quality by scoring 6/10 and 7/10 [1-13]. Only the study of Khan et al, 2016 was considered of fair methodological quality with score 5/10 [14].

The limitations of the included studies were the sample size, and in most of them, as with all exercise interventions, the fact that participants cannot be blinded to the intervention. In all of the studies, the sample size was very small, with the biggest sample size being only 38 people with SCI, in the research of Hang Jin Jo et al, 2020. Further research needs to be done with a larger sample size. Also, the fact that in most cases, reports of participants, therapists and evaluators were not blinded could have created bias.

Discussion

In both randomized Control Trials of Beekhuizen et al, in 2005 and 2008, their purpose was to evaluate the effect of massed practice with somatosensory stimulation on upper extremity hand function and cortical excitability in people with cervical spinal cord injuries [11,12]. In the study of Beekhuizen et al, 2008 the comparison groups were 4 massed practice group (MP), Massed Practice and Somatosensory stimulation group (MP+SS), Somatosensory Stimulation Group and Control group, contrary to Beekhuizen et al, 2005 when there were only 2 groups, MP and MP+SS. In both studies they hypothesized that the combined intervention MP and SS, would result in greater changes in the previously mentioned outcomes. Both studied used as outcome measures the Jebsen-Taylor Hand Function Test (JTHFT) scores, the Wolf Motor Function Test (WMFT) timed task scores, (3) the maximal pinch grip force, (4) the Semmes-Weinstein monofilament sensory testing, and (5) the intensity of the cortical stimulation required to evoke a motor threshold response (50-100 μV) in thenar muscles. The results of both studies indicated that practice of functional tasks combined with augmented afferent input was associated with the greatest change in hand and upper-extremity function, pinch strength, and sensory scores. MP+SS did not differ significantly from SS in several of the outcome measures though. The fact that there were significant improvements in the group receiving somatosensory stimulation alone suggests that afferent input may be a powerful tool in promoting neural plasticity. No measurable changes appeared in cortical excitability on the study of Beekhuizen et al, 2005 but this was probably due to the time of intervention, the small sample and the fact that they evaluated the same location as the pretesting measurement. This preliminary study did not find significant changes in cortical excitability after MP+SS or MP training, and the lack of significant results may be due to the low power (54.3%) to detect differences between the groups in this study. On the study of Beekhuizen et al, 2008 where the cortical excitability was evaluated via MEPs threshold, they identified a significant between-groups difference ($F=19.06$, $p=.001$) for the MEP threshold data, with the regression model explaining 78.5% of the variation in the data. All else being equal, both the MP+SS group and the MP group differed significantly from the control group ($t=-4.28$, $p=0.001$, $t=-4.25$, $p=0.001$, respectively).

In the study of Han Ji jo et al, 2020 the purpose was to investigate the effect of paired corticospinal-motor neuronal stimulation (PCMS) combined with exercise on augmenting changes in corticospinal transmission and motor output [13]. Thirty-five people with chronic incomplete spinal cord injury randomly assigned to three groups, exercise with PCMS, exercise with sham-PCMS and PCMS only. The primary outcome measures that were used were the Maximal voluntary contraction (MVC) and Motor evoked potentials (MEPs) of each of the muscle tested. MEP size increased after 10 sessions of PCMS + exercise and PMCS (64.6±65.0%, $p<0.01$). MVC increased after 10 sessions of PCMS + exercise (48.0±54.9%, $p< 0.01$) and PCMS (42.8±25.7%, $p< 0.001$) but not after sham-PCMS + exercise (1.3±13.5%, $p=0.7$) compared with baseline. The time to perform functional tests decreased in all groups: PCMS + exercise (by 24.4 ± 18.6%, $p<0.05$), PCMS (by 19.5 ± 9.1%,

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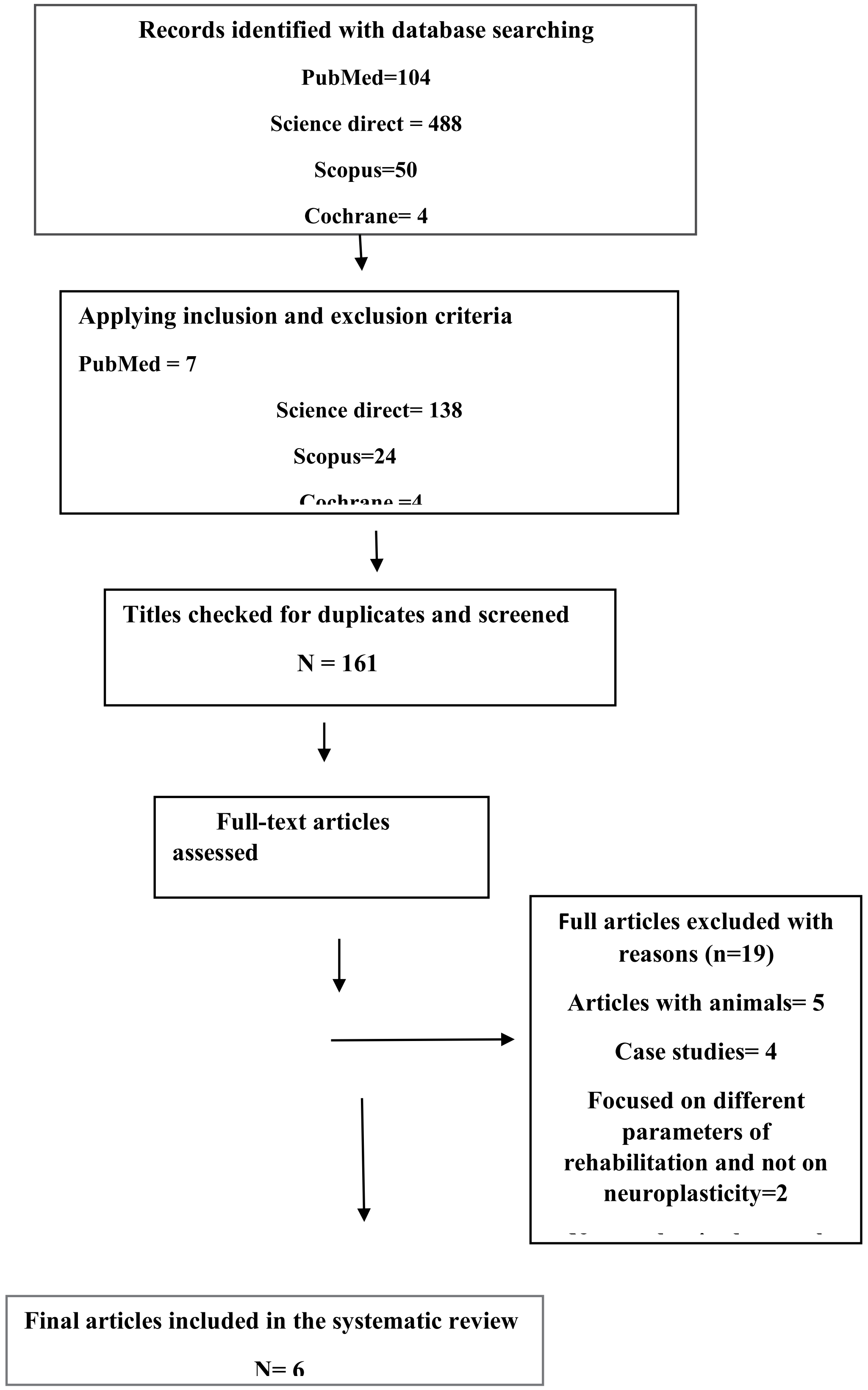
Table. 1 Flowchart



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p< 0.05) and sham-PCMS + exercise (by 17.4±20.1%, p<0.05). Six months later the results persist only in PCMS + exercise group (p<0.05). The findings suggest that PCMS is an effective strategy to facilitate exercise-mediated recovery can help maintain the effects gained in humans with SCI.

In the study of Khan et al,2016 the purpose was to determine whether individuals with SCI showed training-specific spinal plasticity in response to 2 different forms of exercises, endurance training and precision training [14]. In the study, 20 people with SCI participated, between C1-L1 neurological levels. They were randomly assigned to 2 groups and trained according to one type of exercise for two months, followed by two months of rest, and then crossed over to the other exercise regimen for another two months of trainings. As primary outcome measures, they used clonus and cutaneomuscular reflex induced by stimulating the posterior tibial nerve (PTN). The results showed that only Endurance Training induced a significant enhancement of the inhibition in the SOL CMR. Neither form of training changed clonus in a systematic way. The results suggest that intensive training or walking reduce the abnormal reflex excitability seen after SCI and this enhanced inhibition is concurrent with training-induced strengthening of corticospinal input to the motoneurons / interneurons.

The purpose of the study of Navarrete-Opazo et al, 2016 was to compare the effect of a 4-week protocol of intermittent hypoxia (IH) combined with BWSTT (experimental group) versus continuous Normoxia with BWSTT (control group) on eliciting plasticity in the spinal cord and strengthening spared synaptic pathways [15]. The plasticity is expressed as respiratory and somatic functional recovery, that's why they used, as the primary outcome measure, the 10-m walk test (10MWT). As secondary outcome measures, they used the 6-min walk test (6MWT) and the timed up and go (TUG) test. At the study, 35 people with chronic ASIA C and D incomplete SCI participated. The IH group had a greater walking speed than the control group, expressed as a decrease in 10MWT time versus baseline in 5 days (IH: -10.2-3.0 vs. Nx: -1.8-1.7 sec, p = 0.006). In week 2 (IH: -15.5-4.8 vs. Nx: -3.7-3.3 sec, p = 0.04) and week 3 (IH: -17.1 – 5.3 vs. Nx: -7.1 – 2.8 sec, p = 0.03). Not a significant difference in TUG time. There was a greater walking endurance in the IH group compared to the control group on day 5 (IH: 43.1-10.7 vs. Nx: 6.1-3.4 m, p=0.012) and at later time points. Subgroup analysis demonstrated that IH enhances walking speed, endurance, and up and go time in both ASIA C and D subjects, with no statistical differences between ASIA subgroups at all time points (p > 0.05).

In the study of Raithatha et al, 2016 the purpose was to investigate the effects on neuroplasticity of pairing transcranial direct stimulation (t-DCS) with LT-RGO in people with chronic, incomplete SCI[16]. The primary outcome measure was manual muscle testing (MMT). Secondary outcome measures included 10MWT, 6MinWT, Timed Up and Go Test (TUG), Berg Balance Scale (BBS), and Spinal Cord Independence Measure III. In the study, 15 people with spinal cord injuries participated, who were randomly separated in 2 groups, LT-RGO+ tDCS and LT-RGO+ sham-tDCS. The active group improved significantly compared to the sham group on the primary outcome measure MMT. The sham tDCS group improved significantly compared to the active tDCS group on 6MinWT and TUG. Between-groups comparison of changes from baseline to 1-month follow-up revealed significantly greater improvements in MMT (right LE) for the active tDCS group. An ANCOVA model used to measure baseline differences showed treatment effect at a 95% confidence interval for MMT (right LE) at both post-intervention and at 1-month follow-up as well as a significant advantage for the sham tDCS group in SCIM-III in 1-month follow-up. This study supports the feasibility of using tDCS in conjunction with a novel LT-RGO protocol that targets corticospinal plasticity to optimize gait recovery for people with SCI.

Conclusion

There is a need to develop physical therapy interventions that can effectively engage spared neural connections to further improve functional recovery in humans with SCI. According to the results of the 6 randomized control trials included in our study, interventions such as massed practice with somatosensory stimulation, Exercise with corticospinal neural stimulation, endurance training, intermittent hypoxia (IH) combined with Body weight supported treadmill training and Paired transcranial direct current stimulation (tDCS) with Locomotor training with a robot-assisted gait orthosis (LT-RGO) can enhance neuroplasticity and induce functional recovery in people with SCI. Therefore, further research needs to be done.

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Activity-based therapy in infants with spinal cord injury, the impact on standing, quality of life and health

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ABSTRACT

Spinal cord-related injury treatment has been massively revamped recently by the principles of neuroplasticity, a fundamental principle of ABT which includes five practices such as: weight-bearing activities, FES, task-specific practice, massed practice, and locomotive training.

This study explores the state of activity-based therapy for different classes of people ranging from adults to infants and its impact on standing, quality of life and health. Herein, activity-based therapies will be explored alongside how they affect the condition of infant spinal cord injury later in life and also where clinicians and researchers should focus to improve protocols at this age.

Keywords: activity- based therapy, spinal cord injury, infants, standing, quality of life

Introduction

In the recent years, there has been an increase in the incidence of spinal cord injuries, the most common causes of which being assault, car accidents, and falls. The resilience of healthcare technology and advances in medical treatment has also increased in tandem with this trend (Behrman et al., 2017)[2]. Ultimately, there has been an increase in life expectancy and quality of life among people living with spinal cord injuries, compared to previous years' outcomes. Indeed, the 21st-century discoveries have paved the way for enhanced healthcare practices, leading to more positive outcomes (Marsh et al., 2011)[10]. Even though contemporary healthcare has seen some ground-shattering breakthroughs, this has not been without some shortcomings. There are secondary risks following SCI including respiratory diseases, which have been reported among the prevalent causes for re-admission of people who have previously suffered from spinal cord injuries. However, such complications can be effectively treated, thus allowing people to lead everyday lives.

Studies have shown diverse results among people who have undergone ABT following spinal cord

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injuries. Behrman et al. provided evidence of the possibilities of substantial recovery upon application of rehabilitative neural stimulation. More studies have elicited promising findings of ABT as it has assisted more patients to stand independently and make voluntary trunk and leg movements. According to Dolbow et al., (2015) [5] Activity-based Restorative Therapy (ABRT) was developed for responding to a diverse range of spinal cord injuries. However, the authors state that the process hinges primarily on SCI rehabilitation. Essentially, ABRT works through stimulation of the areas of proximity to the injury site. It is majorly geared towards addressing issues related to spinal cord paralysis. Other conducted studies relate to perinatal and intrauterine spinal cord injuries (Felter et al., 2019)[6]. Although intrauterine cases are rare, they demonstrate lower chances of survival. ABT in this cases serves a leading role in reducing secondary complications such as ulcers, pain bladder dysfunctions among others. However, SCI at the tender and developmental age can pose problems to the musculoskeletal development, especially without early intervention which may include ABT.

ABT includes stretching and strengthening exercises as well as mental activities (Dolbow et al., 2015) [5]. A better capacity to do day-to-day tasks, less dependence, and an enhanced life quality are some of the goals of the activity-based therapy (ABT) program designed to aid people with SCI.

A German study showed that ABT was associated with significant increases in patients' self-reported functional abilities, quality of life and psychological well-being (Felter et al., 2019) [6]. Several studies have found that ABT improves mobility and stability by strengthening the trunk and improving coordination. In terms of standing, quality of life and health outcomes, ABT's effects can vary widely from one person to another. The benefits of ABT can be influenced in various ways by a variety of factors, including age, gender, the severity of the SCI, and level of activity (Musselman et al., 2018; Behrman et al., 2017)[12][2]. Age-related physical restrictions may prevent older people from experiencing the same benefits from ABT that are achieved in younger patients (Felter et al., 2019)[6]. Accordingly, people who have had more serious spinal cord injuries can need more intense ABT to improve their postural, health status and quality of life. Individuals with SCI have used a wide variety of treatments, such as electro-stimulation and robotic therapy, to improve their health outcomes and their quality of life, in addition to Activity Based Therapy (ABT).The use of these treatments may assist in the improvement of motor control, coordination, and strength. However, it is essential to remember that these treatments are unsuitable replacements for ABT and that, for the best possible outcomes, ABT should be utilized in conjunction with these other therapies.

The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) can be applied to evaluate a person's standing ability, quality of life and health outcomes (Kirshblum et al., 2014; Jones et al., 2012)[9][8]. This registration form provides a complete description of an individual's mobility and functioning level in addition to evaluating the severity of an individual's damage to the spinal cord (SCI). This knowledge can be used to identify appropriate therapies, such as ABT, to ameliorate the negative effects of bad posture, health and quality of life.

To carry out this literature review, a literature search was conducted in the following scientific databases: Google Scholar, Science Direct, Microsoft Academic, PubMed and CINAHL. The key-words (mesh terms) used in the search engines were: "Activity-based Therapy", "spinal cord injury", "ABT in infants", "ABT in children" and "neuroplasticity" in various combinations, with the use of the disjunctive terms AND and OR. The inclusion criteria for the published scientific papers included time of publications, peer review consideration and relevance of the content to the topic. This research utilized a compilation of the available studies related to the study topic. The study began by exploring the article related to activity-based therapy in general, then zeroed in on one more specific detail about the topic by adjusting the keywords, such as the inclusion of infants and children to the stated search words, to identify the most relevant studies (Chen & Xiao, 2016) [4]. Moreover, time factors were applied in filtering the studies by selecting the acceptable threshold age of the target articles. The articles which have been published within the last ten years were the most preferred and were selected on the ground they contain updated data and current statistics and figures related to the study topic (Arici et al., 2019) [1]. In parallel, this study applied peer-reviewed articles and the ones found in credible online databases . Similarly, at least 15 articles were used in the study to provide a broad basis for comparing facts and findings from different sources hence minimizing the chances of errors and bias. Ultimately, this study was conducted with close attention to the required ACTA standards.

Discussion

Activity-Based Therapy Impact on Children with Spinal Cord Injury

Children with spinal cord injuries benefit from physical therapy in the form of activity-based therapy to improve their health and quality of life. It's predicated on the idea that people can recover lost abilities by engaging in targeted exercises (Felter et al., 2019) [6]. Therapy that places an emphasis on movement may incorporate exercises such as standing, walking, swimming, or cycling.

More and more studies have been done in recent years on the outcomes of activity-based therapy for children with spinal cord injuries. These therapies have been shown to enhance postural quality of life and health outcomes for children with SCI (Kirshblum et al., 2014)[9]. Children with spinal cord injuries can improve their motor control, strength, and mobility with the help of intensive activity-based therapy. The findings of the studies prove this. Children with spinal cord injuries made significant progress in their ability to walk, run, and use their hands through activity-based rehabilitation.

The International Spinal Cord Injury Association establishes guidelines and provides a way to record the extent of spinal cord injuries (Kirshblum et al., 2014)[9]. It is used to assess the severity and prognosis of SCI. Several scientific investigations have demonstrated that the ISNCSCI is an accurate method for rating the severity of spinal cord injuries in young people. Several forms of physical therapy are employed to enhance the ability of standing, quality of life and health outcomes for children with spinal cord injuries, in addition to activity-based rehabilitation . All of these approaches involve some form of physical therapy with the goal of improving patient's range of motion, muscular strength, and coordination (Kirshblum et al., 2014)[9]. A child's range of motion, balance, and coordination can all benefit from water therapy following SCI.

Standing, quality of life and health outcomes for children with spinal cord injuries can be significantly improved with the use of activity-based treatment. Used in conjunction with other physical therapy methods (including stretching, and balance training), it can help patients recover from injuries and regain mobility and strength (Harkeman et al., 2012; van Hedel & Dietz, 2010)[7][14]. The International Standards for Neurological Classification of Spinal Cord Injury has been proven useful in numerous research efforts for assessing serious SCIs. (Kirshblum et al., 2014)[9]. Children with SCI can benefit from activity-based therapy with or without orthostatics, in terms of both standing, quality of life and health outcomes.

The Effect of ABT on Babies With SCI

Infants (6-24month) with SCI can benefit considerably from activity-based therapy in terms of standing, quality of life and health outcomes. From 0 year old to 6 months, there are no protocols for ABT. at this tender age. At the age of 6 months, an uninjured infant can begin to stand upright with assistance. If the injury occurs during the first 6 months, the goal must be to maintain the extensibility of the soft tissues by the therapists and the parents, so that as the baby grows, it is not limited by secondary comorbidity issues. Meng et al. (2015)[11] found that robots-assisted variants of ABT can be deployed in assisting in the rehabilitation of the lower limbs.

The primary objective of movement therapy is to encourage as much physical movement as possible. The goal is to help patients regain their physical ability as much as the damage level allows. However, Meng et al. (2015)[11] observed that the point that most of the currently available interventions hinge on the therapists' experience and subjective judgement is a serious hindrances to the realization of strong SCI, as there is not an established intervention manual. Simple exercises, climbing stairs, getting up from a seated position, and extending arms and hands, can help mobility and strength.

Infants with SCI benefit from ABT, since it has been found to enhance life quality and health outcomes.

The patient's mobility, coordination, and stability can all benefit from activity-based therapy. Hence, their quality of life will improve since they will be able to take part in more of their regular activities by using strategies which conquer in the treatment program. Activity-based rehabilitation can help lessen the intensity of post-spinal-cord-injury complications like stiffness and muscle atrophy.

As a result of ABT, changes might be shown in ISNCSCI in incomplete. The ISNCSCI classifies patients into different categories based on their overall state of physical, mental, and cognitive health (Felter et al., 2019)[6]. The motor skills of patients who engage in activity-based therapy may improve, leading to a higher ISNCSCI classification. Those who are mindful of their posture may experience positive changes to their health and well-being.

Hence, more evidence are needed for benefits of infants with SCI from activity-based therapy to improve their standing ability, quality of life and health outcomes. Patients who take part in activity-based therapy have a higher ISNCSCI classification, report less pain, and have improved mobility, balance, and coordination Behrman et al. (2017) [2]. Hence, healthcare practitioners should consider the perceptible importance of ABT when treating newborns with SCI.

Neuroplasticity in Babies

The potential of neuroplasticity to aid those who have suffered neurological impairment has been the subject of increased research in recent years. Because of their greater neuroplasticity and recovery potential after severe neurological impairment, babies and children are of particular interest (Brazg et al., 2017) [3]. The potential of activity-based restorative therapy to aid recovery from spinal cord damage in newborns, children, and adults is the primary focus of the publications presented.

Articles discussing transdisciplinary, intense, activity-based treatment for intrauterine spinal cord infants are particularly intriguing. Examining the case of a 3-month-old baby who was successfully treated after suffering a spinal cord injury at birth, it is clear that electrical stimulation was used in conjunction with physical and occupational therapy to assist the infant in regaining mobility (Quel et al., 2017)[13]. This case study's optimistic findings provide preliminary evidence that activity-based restorative therapy may be beneficial for newborns with SCI.

Restorative therapies involving physical exercise are viewed in terms of their potential to aid in rehabilitating people with SCI. These articles highlight the significance of applying international criteria for the neurological categorization of SCI foradolescents and children and the requirement for trustworthy data (Winstein et al., 2014)[16]. They also talk about how neurological damage affects how SCI kids move around when standing up. Evidence from this research suggests that activity-based restorative therapy may help patients with spinal cord injuries regain some movement.

Much work is needed, but activity-based restorative therapies have shown promise in helping children and adults recover from spinal cord injuries. The need for accurate evaluation methods for youngsters is a serious obstacle. Moreover, there is difficulty in coming up with solutions that are both harmless and productive for kids (Felter et al., 2019; Winstein & Kay, 2015)[6][15]. Finally, minimizing potential adverse outcomes is difficult while keeping therapies positive for newborns and young children.

Notwithstanding these obstacles, activity-based restorative therapies have shown promise in facilitating healing in newborns, children, and adults with spinal cord injuries. This review's articles shed light on the promise of activity-based therapies for facilitating recovery and the obstacles that must be overcome to realize that promise (Felter et al., 2019)[6]. SCI recovery in newborns, children, and adults may benefit from activity-based restorative therapies in the future if current research and development efforts are successful.

Conclusion

Compendiously, regardless of age, people with SCI can benefit significantly from activity-based rehabilitation in standing, quality of life and health outcomes. Activity-based therapy has been shown to benefit children and adults with SCI by enhancing their mobility, strength, and coordination hence can be a key driver in the unlocking of less pain and improved life quality. In addition to helping patients achieve a higher classification on the ISNCSCI, activity-based therapy can lessen the likelihood of secondary disorders developing. In addition, infants with spinal cord injuries benefit from activity-based therapy. The current experimental developments in activity-based therapy and activity-based restorative therapy harbour the promise of more robust discoveries which can allow the restoration of standing and walking abilities among the affected people. From the available evidence sourced from recent studies, it has been unravelled that mobility, motor control and strength can be restored with the aid of intensive ABT interventions.

Despite the ground-breaking breakthroughs which have been revealed so far, most of them are majorly at the experimental stage; hence ABT is yet to be integrated into mainstream intervention approaches. Further study and development are needed, but activity-based restorative therapies show promise for helping people of all ages recover from spinal cord injuries. The quality of life of people with SCI can be enhanced through activity-based therapy, which may also lead to more independence and mobility. However, in order to respond effectively to the SCI issues of every patient, there is a need for a customized approach that resonates with the unique nature of the individual challenges of the involved people. Likewise, it is recommended that proper and more overriding SCI measures be integrated with traditional mechanisms such as stretching and chiropractor-oriented intervention to increase the chances of more positive outcomes, even though this requires more scientific interventions. As a result, more research is beckoning to unlock the full potential of the ABT field.

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Physiotherapeutic methods for promoting neuroplasticity in patients with multiple sclerosis.

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ABSTRACT

Multiple sclerosis (MS) is a disease of the central nervous system of autoimmune origin, characterized by inflammation, demyelination, gliosis (fibrous proliferation of the glial cells in the affected area) and finally, destruction of the neural cells (neural loss). Non pharmacological interventions for patients with MS focus primarily on physical and psychological rehabilitation.

Neuroplasticity can be defined as the ability of the brain to change, remodel and reorganize itself to obtain the ability to adapt to new situations. Although the concept of neuroplasticity is quite novel, it is one of the most important discoveries in neuroscience. The aim of the present scoping was to investigate and present the recent literature data regarding physiotherapeutic and other methods for promoting neuroplasticity in patients with multiple sclerosis.

In total, 102 relevant scientific papers (reviews, systematic reviews and original trials), published after 2010 were analyzed. The findings of the review are encouraging - a number of physiotherapeutic methods (such as therapeutic exercise or neurophysiological rehabilitation techniques, for example) appear to be effective in promoting neuroplasticity in patients with MS; on the other hand, the findings of newer and increasingly popular methods such as, for example, robotic – assisted rehabilitation are not clear.

However, as the relevant research is based on small and not always high quality clinical studies, it is clear that additional research is needed, with randomized controlled trials of sufficient statistical power in order to extract more solid scientific data.

Key – words: Multiple sclerosis, Neuroplasticity, Physiotherapy, Rehabilitation

Introduction

Multiple sclerosis (MS) is a disease of the central nervous system of autoimmune origin, characterized by inflammation, demyelination, gliosis (fibrous proliferation of the glial cells in the affected area) and finally, destruction of the neural cells (neural loss) [1]. Although, to date, the aetiology has not been clearly established, three main factors are thought to be involved in its pathophysiology: genetic factors, factors related to the environment and finally immune factors [2]. However, now the most likely etiology of the disease is considered a disimmunity mechanism caused by an autoimmune attack to the patient's central nervous system. A leading role in this process seems to be played by the CD4-positive (CD4+) lymphocytes; Th1 and Th17 effector cells are activated by an unknown antigenic trigger, causing the immune attack through cross-reactivity [3]. This is the "Outside-In" model, whereas, according to the "Inside-Out" model, an intrinsic abnormality of the central nervous system is the main factor triggering the inflammatory-mediated neural tissue damage [3].

It is estimated that more than 2.5 million patients worldwide currently suffer from the disease, with the vast majority of them being women (male to female ratio 3/1). The disease occurs for the first time primarily in the 20-40 age groups, although it can affect any age (typically, in 10% of cases it occurs early, before the age of 18) [4]. The three main features of MS are: (a) the formation of lesions in the central nervous system (also called plaques), (b) inflammation and (c) destruction of neurons' myelin sheath. These features interact in a complex way that is not yet fully understood, causing the breakdown of nerve tissue and this in turn causes the signs and symptoms of the disease [4].

Depending on the clinical course of the disease, MS is divided into seven main categories (groups) [5]: (a) relapsing – remitting (RR) group (70% - 80% of the patients), which is characterized by a relapsing course, (b) primary progressive (PP) group (15% - 20% of the patients), with a gradual and continuous deterioration of the clinical picture of the patient, but without the presence of corresponding relapses, (c) secondary progressive (SP) group, with slower and more gradual deterioration in comparison to the patients belonging to the primary progressive group, (d) progressive-relapsing (PR) group (5% of the patients), in whom there is a gradual worsening of the disease with intermittent periods of relapses, (e) clinical isolated syndrome (CIS), characterized by the occurrence of a single episode of central nervous system inflammation accompanied by demyelination, (f) fulminant disease, with severe symptomatology and rapid progression leading very quickly to a high degree of disability of the patient and finally and (g) benign disease, with mold symptomatology, rare relapses, causing mild disability to the patients.

As is evident from the above, the vast majority of MS patients belong to the relapsing-remitting category, in whom the relapses that occur gradually recover after weeks or even months, even without treatment; over time, however, the residual symptoms that remained after the relapses of the disease that did not fully subside accumulate, gradually increasing the patient's functional discomfort and disability [5]. The treatment of the disease and especially of the relapsing-remitting group is based on the administration of a number of drugs that have the potential to modify the course of the disease: these include, among others, glatiramer acetate, interferon-beta preparations, natalizumab, fingolimod, mitoxandrone and dimethyl fumarate.

Non-pharmacological interventions for MS focus primarily on physical and psychological rehabilitation. Non pharmacological-cognitive treatment involves aerobic training and exercise, interventions which aim to improve the quality of the patients' sleep, and neuropsychological rehabilitation, aiming aims both to improve cognitive disorders, and to increase patients' awareness of the deficits they have in performing activities of daily living [6]. Finally, among the innovative treatments applied in recent years are whole body cryostimulation [7], brain stimulation techniques such as the transcranial magnetic stimulation (TEMS) and the transcranial direct current stimulation (tDCS) [8] and even computer-based training programs [9]. The specific therapeutic methods aim, among other things, to improve the clinical picture of the patient through the stimulation of the plasticity of the central nervous system [6].

Neuroplasticity can be defined as the ability of the brain to change, remodel and reorganize itself in order to obtain the ability to adapt to new situations [10]. Although the concept of neuroplasticity is quite novel, it is one of the most important discoveries in neuroscience; the fact is that neural networks are not fixed, but their structure and function changes throughout the life at different levels such as: molecular structures, changes in gene structure, changes in gene expression and behavior depending on our experiences.

It was about 130 years ago when William James was

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the first scientist who introduced the theory of neuroplasticity in his "Principles of Psychology", were he proposed that the human brain is capable of continuous functional changes [11]. The term "neuroplasticity" was introduced for the first time in 1948, by Jerzy Konorski, a Polish neuroscientist; he proposed the theory that neurons that have been activated by a nearby active neural circuit change and integrate into that circuit [12]. Donald Hebb, a Canadian psychologist introduced "Hebb's rule", describing that any synchronized activity of two neurons can lead to the strengthening of their synaptic connections [13].

All these scientists had to fight against an academic society that did not accept the existence of neuroplasticity of the brain in adults, except in the developmental phase. Eric Kandel, who won the Nobel prize in Medicine in 2000 for his work on the neuroplasticity of the central nervous system stated that neuroplasticity has marked the last decade of the previous century (1990 – 2000), the "Decade of brain". His research in this area had begun as early as 1970, when he observed that in the simple brain of the marine snails, the chemical signals produced during the learning process resulted in definite changes of the structure of the neural synapses where these signals originated and terminated [14].

Two are the main types of neuroplasticity: (a) functional neuroplasticity, which is determined by the functions of memory and learning; it seems that during both of those functions of the human brain, permanent changes are established in the neuronal synapses, due to various intracellular biochemical processes [15] and (b) structural neuroplasticity, or synaptic plasticity, produced by complex changes in the intracellular synthesis of various proteins along with permanent changes in the number of the synaptic neurotransmitters [16].

The extensive and multilevel scientific research in the field of neuroplasticity that has been carried out over the past few decades has concluded that the human brain evolves and changes throughout an individual's lifetime; according to Demarin and Morovic (2014) [14], the great challenge for neuroscientists is to find and define the various neural pathways (both the major and the minor ones) who have the ability to support neuroplasticity of the compensatory circuits of the neural system. Although significantly damaged nerve cells do not have great regenerative capacity, there is now evidence that even after adulthood, neurons have the potential for varying degrees of circuit regeneration especially in those cases in which the significant barrier of the glial tissue can be narrowed, modified or even eliminated [17].

The aim of the present paper was to investigate and present the recent literature data regarding physiotherapeutic and other methods for promoting neuroplasticity in patients with multiple sclerosis. In order to achieve this objective, the tool of scoping literature review was chosen. Scoping review is a research method that follows a systematic way of approach, in order to capture, in the most possible comprehensive way, the scientific knowledge on a specific topic, identifying and recording the basic concepts, theories, sources of knowledge and, finally, the gaps that still exist [18]; it allows the researcher greater flexibility compared to systematic literature review and meta-analysis, as it is possible to present and interpret a wide range of published studies that address the research question, which have been conducted with different methods [19].

In order to carry out this literature review, a literature search was conducted in the following scientific databases: PubMed/NCBI, Cochrane Library of Systematic Reviews, Scopus, Nature and Science Direct. The key-words (mesh terms) used in the search engines of those databases were: *Mutliple sclerosis, MS, Neuroplasticity, Neuromodulation, Physiotherapy, Treatment methods,* in various combinations between them and with the use of the disjunctive terms AND and OR. The inclusion criteria for the published scientific papers were the following: (a) original clinical trials (randomized and non-randomized controlled studies and case series), narrative reviews as well as systematic reviews / meta-analyses of the literature, (b) publication date was later than 2010, (c) the language of publication is English and the full text of the article could be retrieved, (d) original trials, both clinical (in vivo) and experimental (in vivo), involving individuals of all ages and animals as well (in the experimental trials).

On the other hand, case reports and studies in which MS was not among the pathological conditions of the central nervous system studied were excluded.

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Figure 1 presents the flow-chart of the scoping literature review, according to the principles of PRISMA [20]. In the following sections the findings of the literature review will be presented in detail.

Discussion

Initially, 1712 studies were identified after initial search on Pubmed internet database. After screening of titles and abstracts, (figure 1), 138 studies were included for final analysis in the present review.

The key factors that will determine the outcome of patients with MS are undoubtedly inflammatory demyelination along with axonal loss; the possibility of functional rehabilitation of these patients therefore depends primarily on the successful and at the same time sustainable repair of the damage that has already been caused, through the regression of inflammation, remyelination, and finally, the neuronal circuit functional reorganization [21,22]. According to Ksiazek-Winiarek et al., (2015) [2], the most likely molecular mechanisms that promote neuroplasticity in patients with MS are the following:

- *Brain derived neurotrophic factor (BDNF),* whose role is particularly important in the process of creating new and healthy nerve synapses,
- *Interleukine 1β,* whose role is important in the inflammatory processes of the CNS that develop in the context of MS,
- *Amyloid-β_{1-42},* which also has a key role in the acute inflammatory process in the synaptic area,
- *Platelet-Derived Growth Factor (PDGF),* participating in the remission stages of the disease and finally,
- *Cannabidoid Type 1 Receptors (CB1Rs),* who are responsible for the reduction of the excessive glutamate-mediated excitation of the neuronal synapses [23].

In the following sections, the data of recently published original studies will be summarized in relation to specific physiotherapeutic methods that have the potential to promote neuroplasticity in patients with MS.

The role of exercise

Aerobic exercise seems to play an important role for the induction of neuroplasticity of the motor cortex. Garnier et al., (2017) [24], showed, in 12 healthy volunteers, that just submaximal (60% of the maximum heart rate) treadmill exercise increased the corticospinal excitability in just 30 minutes. Moti et al., (2017) [25], in a narrative literature review, showed that regular exercise may have positive effects in patients with MS in their balance, cognition, fatigue, depressive symptomatology, quality of life, quality of sleep, metabolic and cardiovascular co morbidities; moreover, the authors concluded that regular exercise might promote neuroplasticity on this particular group of patients. It seems that regular exercise and physical activity is essential in all patients with immune system diseases (including patients with MS) and treating physicians should recommend them daily regular exercise [26].

Feis et al., (2019) [27], in a randomized controlled study showed that just 12 weeks of regular exercise (three times per week) in terms of community-located jogging, improved, along with the aerobic capacity and the quality of life, the patients' visuospatial memory and pallidum volume. In another interesting prospective preliminary study the same year, on 12 patients with MS, Hoque et al., [28], showed that downslope walking, an eccentric exercise, promoted neuroplasticity (spinal excitability and walking function) of the patients. Stellmann et al., (2020) [29], in a randomized controlled study (57 patients with multiple MS) showed that just after three months of moderate-intensity exercise, there was an obvious increase of the functional connectivity of the brain hubs, which tried to compensate for the loss of the structural connectivity of the MS patients; this is therefore, according to the authors, a clear proof of the exercise-induced neuroplasticity in patients with MS, on the biological level. Furthermore, it appears that at a second stage, increased functional connectivity results in adaptive remyelination and oligodendrogenesis [30].

Chaves et al., (2020) [31], in a prospective pilot case series involving 10 patients with MS, who needed assistive ambulatory devices in order to carry out the activities of their daily living, showed that aerobic exercise (40 minutes walking using body weight, less than 10%, support), resulted in shorter length of the cortical silent period and increased motor evoked potential amplitudes. The main conclusion of the authors was that even in the group of MS patients who have a significant impairment of their mobility and functional capacity, the ability of neuroplasticity is preserved through systematic aerobic exercise; a further conclusion of the study was that patients' lower fitness levels and higher body fat levels were associated with limited exercise-induced enhancement of corticospinal excitability which is a specific biomarker of neuroplasticity [32]. Both the treating physicians and the patients' therapists should encourage systematic exercise and physical activity, through which not only the body, but also the CNS is trained [31].

In the same year, Devasahayam et al [33], in a prospective study including 10 patients with MS, showed that moderate to vigorous aerobic exercise (up to 65% of the maximum heart rate, 10 weeks for three sessions per week), in a room cooled to 16^{o}C, improved fitness, walking speed and ability and quality of life; moreover, a statistical significant decrease in the value of serum IL-6 was noted, along with an increase in the value of brain-derived neurotrophic factor, which, as already reported, are important biomarkers indicative of the progression of neuroplasticity in MS patients [2].

Over the past few decades, Tai chi has gained increasing popularity as a therapeutic exercise method for treating a range of nervous system conditions including MS [34]. Liu et al., (2021) [35], in the context of a systematic review (24 in total, original papers) of the literature in relation to the effectiveness of this therapeutic method in the process of neuro-rehabilitation, concluded that (a) a number of proinflammatory biomarkers are reduced (IL-1,6,10,12, TNF, CRP), (b) a number of anti-inflammatory cytokines are increased (IL-10,13), (c) various oxidative factors are decreased (protein carbonylation, plasma 8-isoprostane and malondialdehyde) and (d) various neurotrophic factors are increased (BDNF, N-Acetylasperate). It is obvious that the Tai chi therapeutic method can offer multiple benefits in the process of neuro-rehabilitation, promoting neuroplasticity in patients with MS [35].

From all of the above mentioned, the significant effect of systemic physical activity and exercise on the promotion of neuroplasticity in patients with MS has been presented. These are findings which are broadly in line with the corresponding findings of the recently published systematic literature review by Sandroff et al., (2020) [36] regarding exercise training as a neuro-plasticiy-inducing therapeutic method in patients with MS; the authors of the review stated that although this field of research is still in its infancy, with the few relevant studies involving only a small number of patients -only 10 original papers were included in the systematic literature review, most of them pilot studies, with a small number of participants -, the first, isolated results seem promising. It seems that there is indeed a tentative statement that exercise training has the potential to induce neuroplasticity in this particular group of patients [36] .

In another systematic literature review, Tavazzi et al., (2021) [37], investigated the efficacy of motor rehabilitation on the neuroplasticity, based on MRI markers of structural and in patients with MS; after analyzing 15 relevant original papers, they concluded that, although the small participants' numbers and the heterogeneity of the data, definite positive adaptive brain changes have been recorded, with are combined with a significant improvement in the clinical picture of patients. It is obvious that the MRI markers of functional and structural brain connectivity (such as the diffusion tensor imaging or the task-related and resting-state fMRI, should be introduced in daily clinical practice in order to accurately asset the neuroplasticity achieved in the context of motor training of MS patients and thereby to introduce or modify the rehabilitation protocols of the disease accordingly [37].

The role of robotic – assisted rehabilitation

One of the relatively most recent new therapeutic options in the arsenal of rehabilitation for a range of central nervous system injuries and pathologies, including MS, which began to be widely used in the 1990s is robotic – assisted physiotherapy. The use of specialized robotic devices enables the patient to achieve functional mobilization and ambulation, which is a very important element in all stages of rehabilitation [38]. The first published literature reviews did not clarify whether robotic – assisted gait training and body - weight supported treadmill training with the initially used rehabilitation robotic devices (especially the Lokomat device), were superior to the traditional physicotherapeutic approaches [39].

Straudi et al., (2017) [40], published the research protocol of a randomized controlled study involving 98 patients with progressive MS (the RAGTIME study), in order to compare the effectiveness of conventional physiotherapy versus robot – assisted gait training in this group of patients; among the outcome measures of the study were instrumental and circulating laboratory markers which were directly related to the promotion of neuroplasticity, such as the cortical activation, pro and anti-inflammatory cytokines and chemokines, coagulation, growth and neurotrophic factors. The results of the study published three years later [41], did not prove the superiority of robot-assisted gait training over the traditional intensive overground walking rehabilitation protocols in any of the study's outcome measures, including the neuroplasticity markers.

In one of the most recently published relevant papers, Adrowis et al., (2020) [42] conducted a pilot randomized controlled study, in 10 patients with MS in order to evaluate the effectiveness of the robotic exoskeleton REAER (Ekso-GT, Ekso Bionics, Inc) in the rehabilitation process of those patients; among to the outcome measures of the study was the brain connectivity (thalamocortical resting-state functional connectivity - RSFC), as it was measured by fMRI. The results of this small pilot study showed that there was a definite improvement of the thalamocortical RSFC, along with the patients' functional mobility, whereas no differences were found in relation to the patients' walking endurance. According to the authors, the improvements recorded on the MS patients' functional mobility were most probable due to integrative and adaptive central nervous system plasticity.

From all the above it is evident that scientific research in the field of robotic rehabilitation of MS patients, especially in the field of neuroplasticity, is still at a very early stage. The encouraging results of some pilot clinical studies [42], make it necessary to immediately design and conduct high quality randomized controlled studies with a large number of participants, in order to draw clearer conclusions.

The role of various other physiotherapeutic methods

Apart from rehabilitation programmes based on therapeutic exercise and robot-assisted rehabilitation, some studies have been published in recent years investigating the promotion of neuroplasticity after different types of physiotherapeutic interventions in patients with MS. In a narrative literature review, Flatchenecker (2015) [43], concluded that a number of physiotherapeutic interventions based on the neurophysiological principles (such as the proprioceptive neuromuscular stimulation, Vojta, Bobath, or even the newer constraint – induced movement therapy), have the ability to produce plastic changes to the MS patients' central nervous system, which over time are likely to have significant clinical benefits.

High – intensity rehabilitative task-oriented circuit training (TOCT) is one of those interventions, which aim to promote neuroplasticity through a number of exercises and tasks, which combine repetition, intensity and specificity. Straudi et al., (2014) [44], in one of the first relevant published randomized controlled trials, showed that after three months of a home-based TOCT exercise program the patients of the intervention group had a statistical significant improvement in their walking ability and their health – related quality of life.

Action observation training (AOT), is a relatively new physiotherapeutic intervention, whose use is aimed at improving the function of the upper limbs of patients with various neurological pathologic conditions, including MS [45]; Rocca et al., (2019) [46], in a preliminary randomized controlled study (41 patients suffering from MS and 46 healthy control participants), after a two week's AOT, found out with the use of functional MRI scans, definite effects in the frontal – temporal area of their brain, with no modifications of their white matter. At the same time, the clinical improvement recorded in the mobility of patients in the intervention group was directly correlated with the functional and volumetric MRI changes produced [46]. In the same year, Bonzano et al., [47], using an upper limb task – oriented motor training program in 30 patients with MS, showed that the patients in the intervention group had a more normal brain activation, with the activation clusters located mainly in the areas of the right cerebellum and the left hemisphere; those findings, based on functional MRI imaging, according to the authors show that this particular voluntary task – oriented exercises produces plastic changes to the MS patients' central nervous system towards a definitely more health pattern.

Avgerou M.D.et al. Physiotherapeutic methods for promoting neuroplasticity in patients with multiple sclerosis

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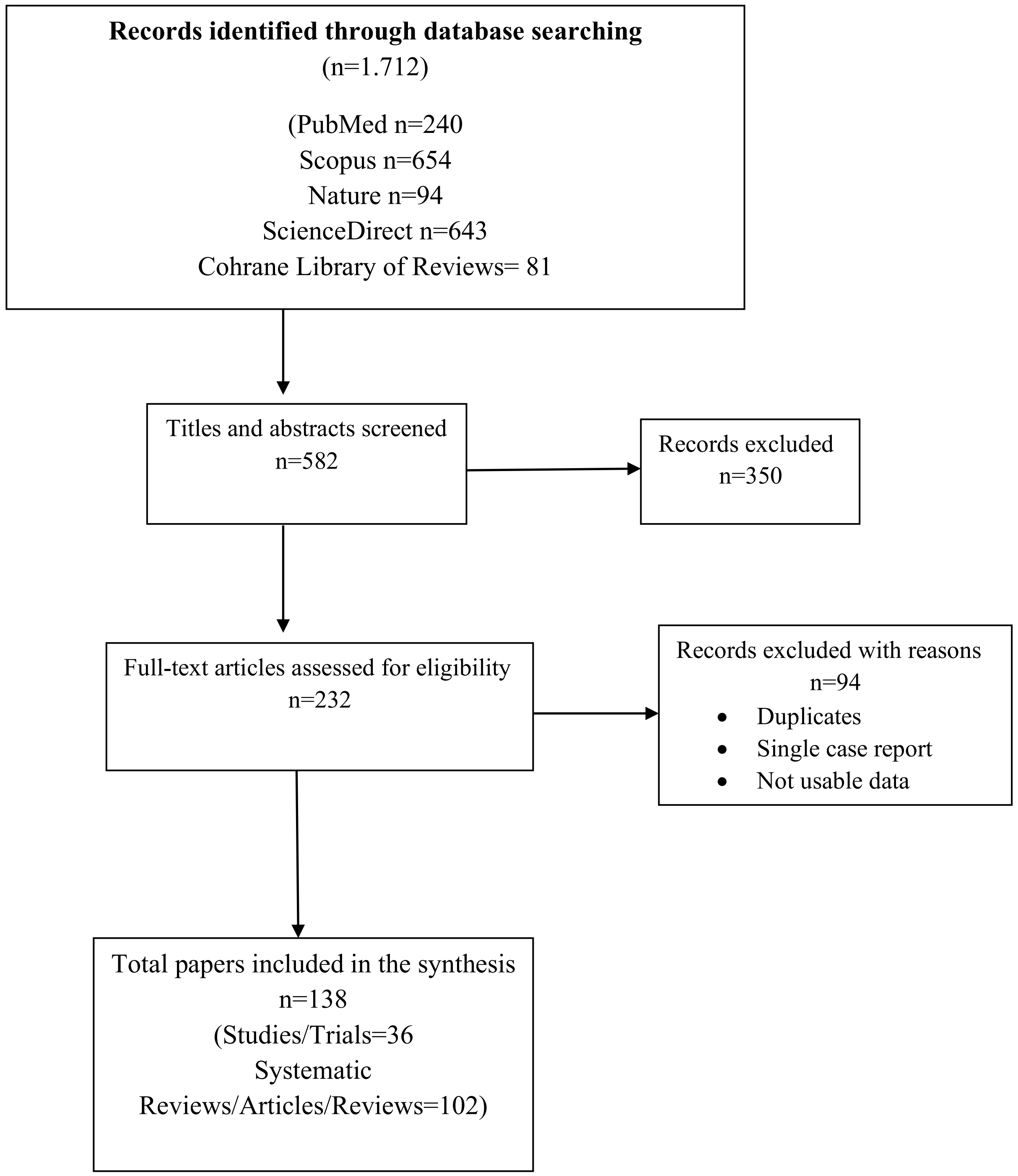

Figure 1: The PRISMA flowchart of the present scoping literature review

One of the early symptoms of the disease, which significantly aggravates the clinical picture of the patients, is weakness of the respiratory muscles. Exercise has the ability to strengthen those specific muscle groups, improving the patients' respiratory function while at the same time promoting neuroplastic changes [48]. Huang et al, (2020) [49], showed that a 10 week's respiratory training using the Threshold Inspiratory Muscle Trainer method (IMT), produces statistical significant improvements in the inspiratory muscle strength in 36 non – ambulatory patients, being in advanced stages of MS; according to the authors, the specific overload principles of the method induce the neuroplasticity which in turn produces the favourable clinical outcomes.

The Assistive Device Selection, Training and Education Program (ADSTEP) is a multicomponent, progressive program of task – oriented walking aid selection [50]; Fling et al., (2019) [51], in a pilot study in 14 patients with MS who have already been using walking aids, showed, with the aid of functional MRI, that after just six weeks of ADSTEP, there was an increased functional connectivity between supplementary motor areas and both the putamen and the primary somatosensory cortices. These are, according to the authors, findings that clearly demonstrate that this specific way of rehabilitation and gait training of MS patients leads to specific modifications of central nervous system plasticity, with positive effects on the clinical progression of patients.

The Exergames therapeutic intervention (with the specific term coming from the combination of the words "exercise" and "games"), consists of exercising the whole body through the use of commercially available video games [52]. Prosperini et al., (2021) [53], published a systematic literature review and meta-analysis regarding the efficacy of the Exergames in balance dysfunction on patients suffering from various neurologic pathologies, including MS. The authors consider that among the mechanisms that explain the effectiveness of the method is the produced increasing efficiency of the attentional and executive brain networks, characteristic elements indicating plastic changes of the patients' central nervous system; furthermore, it was found that the effectiveness of the method depended mainly on the frequency of the Exergames exercise sessions and not so much on their duration or intensity.

Conclusion

Over the last two decades, the scientific community's knowledge on the plasticity of the central nervous system has increased significantly and continues to evolve to this day. It has become apparent that the long-held notion that the human brain is an organ which, after its initial rapid development, then gradually degenerates is not correct. On the contrary, in the healthy brain there are a number of complex mechanisms, collectively known as neuroplasticity, which attempt to resist the specific process of degeneration while at the same time adapting to the constantly changing conditions of the internal and external environment. Of course, this process is significantly altered, for the worse, in cases of severe acute and chronic diseases of the central nervous system, which significantly disturb all its physiological functions. Nevertheless, it seems that the function of neuroplasticity is maintained, in various degrees each time,trying to improve as much as possible the function of the brain.

This scoping literature review presented recent research data on the effectiveness of a range of physiotherapeutic methods in promoting neuroplasticity in patients with MS. The findings of the review are encouraging - a number of physiotherapeutic methods (such as therapeutic exercise or neurophysiological rehabilitation techniques, for example) appear to be effective in the associated field; on the other hand, the findings of newer and increasingly popular methods such as, for example, robotic – assisted rehabilitation are not clear. However, as the relevant research is based on small and not always high-quality clinical studies, it is clear that additional research is needed, with randomized controlled trials of sufficient statistical power in order to extract more solid scientific data.

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