VOLUME 73 | ISSUE 4 | OCTOBER - DECEMBER 2022 ISSN 2241-4347

ACTA ORTHOPAEDICA ET TRAUMATOLOGICA HELLENICA

Official Journal of the
HELLENIC ASSOCIATION OF ORTHOPAEDIC SURGERY AND TRAUMATOLOGY
Athens Academy Award 2004

ACTA
ORTHOPAEDICA ET TRAUMATOLOGICA HELLENICA

HELLENIC ASSOCIATION
OF ORTHOPAEDIC SURGERY
AND TRAUMATOLOGY

Published by: ZITA MEDICAL MANAGEMENT S.A.
Omirou 29, Peta Saronikou, Attica, Greece, 190 01,
tel.: +30 22994 40962,
E-mail: info@zita-management.gr

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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.

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CONTENTS

With deep sadness, the Greek Orthopaedic family said goodbye to Professor Georgios Hartofylakidis.

The leading Greek Orthopaedic Surgeon, the distinguished scientist, the tireless teacher.

His contribution to the development of Orthopedics was enormous, his scientific work monumental while his respect and love for the patient, exemplary.

His students and those of us who were by his side, say goodbye to him with respect and gratitude for what he taught us but also for the brilliant example he was for all of us.

His contribution to the development of the Hellenic Association of Orthopaedic Surgery and Traumatology (HAOST) and to the strengthening of its statutory purpose, to improve the level of continuing education of Greek Orthopedics was also decisive.

Furthermore, as HAOST President established the annual Conferences of our Association.

He was also the first President of the College of the Greek Orthopaedic Surgeons during 1983-1988.

The 78th Congress of the Hellenic Association of Orthopaedic Surgery and Traumatology held past October 2022 , was dedicated to his memory.

Thanos Badekas	**Nikolaos Papaioannou**
HAOST President	*Editor in Chief*

The right foot of Joseph Goebbels

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ABSTRACT

Joseph Goebbels is considered to be one of Adolf Hitler's henchmen in this blood-soaked path to the rise and fall of the Third Reich. However, behind this seemingly strong personality, was hiding his humble origins, his inferiority complex due to physical disability and many unfulfilled individual ambitions, along with his great enthusiasm to climb the higher social ranks. Goebbels' role as Minister for Public Enlightening and Propaganda was decisive, both during the rise of the Nazis to power and in the last months before the end of the war, when it was clear that everything was lost. Little documentation exists today of the true nature of Joseph Goebbels' disability. The master of propaganda, who in a short period managed to rule the press, radio, cinema, theater and literature, managed to artificially silence his physical handicap and disorient public opinion in the wrong direction, ensuring its prestige and reputation. Newer research, however, clarifies the lameness in his right foot, classifying it as talipes equinovarus, a congenital deformity of the foot, which he never effectively treated.

KEYWORDS: Joseph Goebbels; clubfoot; talipes equinovarus; limp; lameness; disability.

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Introduction

The Weimar Republic, which took over to rule Germany at the end of the First World War, was unable to solve the large number of problems that had accumulated after the Treaty of Versailles. The humiliation of the German people, disarmament, sanctions, the loss of territory, the socio-economic crises of the 1920s that worsened the already collapsed standard of living, as well as the denial of the expectations that had been achieved, characterized an extremely ominous atmosphere. These were the same reasons, which acted as fertilizer for the flowering of radical tendencies that seemed capable of bringing the hope of change. [1].

National Socialism thus found fertile ground to grow and, from an insignificant party force with revolutionary ideas that at first seemed utopian, succeeded in taking power in Germany within a few years. In his announcements he succeeded in incorporating various social, political and ideological parameters.

After Hitler's failed attempt to seize power in the Munich coup on November 9, 1924, which resulted in his arrest and imprisonment for 5 months, it became apparent that the only credible route was the legitimate parliamentary one. After his release, he regrouped and established a "softer" and more persuasive discourse to appeal to the masses [1-3]. It was at the same time that Goebbels joined the ranks of the party, seduced by Hitler's leadership personality, passion and vision.

Childhood and Adolescence

Paul Joseph Goebbels was born on October 29, 1897 in the independent industrial town of Rheydt, south of Mönchengladbach near Düsseldorf. His parents were Catholics and made sure to instill the faith in their children by raising them in a strict manner. Father Fritz was a foreman in a textile industry and mother Katharina Maria was of Danish descent. Joseph had 5 other siblings: Konrad (1893-1947), Hans (1895-1949), Maria (1896-1896), Elisabeth (1901-1915) and Maria-Katarina (1910-1949), his successor. In 1932, Goebbels published his family tree, in order to dispel any suspicions of Jewish origin.

Little Joseph's health was never excellent. He suffered from frequent respiratory infections, which kept him for long periods away from the play that is identified with the normal development of a child (**Figure 1**). Immediately after his birth, he was in danger of dying from pneumonia, while at the age of 3 he contracted osteomyelitis. There is unconfirmed testimony that the bone infection affected his right foot and caused a form of paralysis (apparently of the peroneal nerve), which explained in some way the limp that characterized his gait. However, another testimony speaks of a congenital deformity of the right foot, which his parents tried to cover up. The truth is that they did everything possible to successfully deal with their young son's physical disability [3].

Figure 1. *Joseph Goebbels with his classmates in 1916.*

Their first move was to react to the prospect of permanent deformity, as the doctors had predicted. They also sought another opinion, resorting to the distinguished scientists of the Medical School of the University of Bonn, which did not correspond to their poor financial situation. They then accepted the solution of applying an orthopedic brace that would support the foot and help the child walk comfortably. Nevertheless, they were persuaded to resort to surgical treatment, after the failure of the brace. Joseph was taken to the operating theater of the Maria Hilf Hospital in Mönchengladbach at the age of 10 to correct his clubfoot, but the operation was a complete failure.

Goebbels's childhood memories, as he recounts them, were full of unpleasant experiences from his classmates and teachers mainly due to his physical disability. The result was that he preferred long hours of isolation, finding refuge in study and reading. Any publication that fell into his hands -a book,

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Figure 2. *The right foot was crooked and the leg shorter than the left.*

Figure 3. *Goebbels emerged as a skilled orator and could rouse the masses who were literally hanging from his lips.*

a newspaper or an encyclopedia- automatically turned into a source of his insatiable reading bulimia. The information he accumulated through this forced contact with knowledge would later prove beneficial to his goals and choices [3].

It is impressive how he managed, in his period of omnipotence, to keep the physical handicap hidden as a state secret. Reporters were specifically instructed to omit the clubfoot of his right foot. This explains his photographing from the waist up in most newspaper snapshots of the time or in cinematographic reportage. Few short videos rescued of Goebbels limping (**Figure 2**).

However, the permanently etched smile on his face in his public appearances, struggled to give a different image to the outside than what was going on inside. He did not take part in the First World War because he was deemed unfit for conscription. This was a godsend for him to study history and philology, first in Bonn and then in Würzburg and Freiburg. His literary ambitions did not find the desired response from publishing houses and newspapers, while he didn’t manage to find work commensurate with his studies, despite obtaining a doctorate at the University of Heidelberg.

The constant and repeated frustrations in his personal life, along with the social and geopolitical circumstances of the time, combined with the constant struggle to compensate for his physical deficit, led the restless Goebbels to seek new ways to stand up and emerge. Attuned to the times (which called for a radical attitude to the humiliating defeat that had preceded it, the weak Weimar Republic and the lurking communist danger), Goebbels early adopted ideologies opposed to the “old principles”.

Minister of Propaganda

Hitler, trusting in Goebbels’ abilities, appointed him head of the newly created Ministry of Propaganda on April 27, 1930. The duties of the new minister were many and significant. He had become competent to preach the principles of the party by any means, manipulating the press, cinema, radio and national education [4]. Goebbels soon emerged as a skilled orator and could rouse the masses who were literally hanging from his lips. Although he never fought in his life, his only weapons were the power of his inspired pen and the spear of his fanatical speech (**Figure 3**).

After Nazis’ unprecedented electoral triumph in

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Figure 4. *Adolf Hitler with his henchmen, Joseph Goebbels and Rudolf Hess.*

Figure 5. *Goebbels inspecting troops, in the last phase of the war.*

1930, Goebbels wrote on September 21 in the party newspaper "Der Angriff": «Overnight we have been transformed from a small and despised group into a leading mass party, and our victory has no precedent in political history. In the past, a party that doubled its percentages celebrated its achievement as a triumph... The broad masses expressed through our movement made a clear and unshakable statement against the Germany of today and in favor of the Germany of tomorrow... It is clear that the desire to rid Germany of the old parties and their ideas no longer belongs only to a small party, but to an entire awakened nation. Our propaganda has liberated this popular will. Now we must put our words into action» [5].

In the same article, the incendiary last paragraph makes an impression: «We stand by the people and fight for Germany. We desire nothing for ourselves, everything for the nation! We will devote all our efforts to the good of the community, striving to regain honor and prosperity for the motherland. We shall stand or fall, following the fate of Germany. Raise the flags!» [5].

In the years of the rise of the Third Reich, the allure that Hitler's personality radiated captivated Goebbels, who believed that the final dominance of National Socialism was due, apart from the massiveness of its social reference, to this very charming personality (**Figure 4**). Striving to deify the image of Hitler, in view of the presidential elections of March 1932, he wrote in an article: «A man who has the power and gifts to build a movement of millions out of a little sect of seven men, a movement which today already includes the largest and best part of the German people, will also find a way to unite the whole nation, freeing it from the terrible political, ideological and social contradictions that divide and harm our people. The greater part of the nation now has a new will to resist. The German people want to rise from blind resignation to a new ideal. This is the work of Adolf Hitler! The masses see him as their last hope. For millions, his name has become the shining symbol of the German will for freedom. Anyone who opposes class struggle and fratricide, anyone who seeks a way out of chaos and confusion, will vote for him!» [3-5].

On July 9, 1932, Goebbels delivered one of his most iconic speeches, aptly titled "The Storm Is Coming": «I speak as the representative of the largest movement, of millions of people, in German history. I am not here to beg for your vote, your grace, or your pardon. I just want you to be fair. Give your verdict on the past 14 years, on the shame and disgrace they have brought, on our intensifying national, political humiliation. You must decide whether the men and parties responsible for these past 14 years will have the right to participate in the government. We believe that the upliftment of our people will not come from a small clique that does not have strong ties to the people. Only a movement of millions has the active power and ability to change Germany».

Goebbels abhorred the outbreak of war, mainly because of his aversion to the "reactionary" gener-

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Figure 6. *Joseph and Magda Goebbels, with their children in happy moments.*

Figure 7. *Newborn with congenital talipes equinovarus bilaterally.*

als who would inevitably come to the fore again. In the early years of war operations and successes, he remained relatively invisible. His role was almost complete. Nevertheless, he did not hesitate to express his opinion often, regarding the oxymoronic fact of Hitler's double policy, of fighting external enemies at the same time as maintaining peaceful conditions within Germany.

From 1943 onwards, he preached only blood, sweat, tears and pessimism. His essential driving force was no longer his nationalism or fervent patriotism, but his sense of personal fulfillment, the projection of inner chaos (**Figure 5**). He was too dispassionate to become emotionally attached to anything, however ideal it might be. He measured his degree of success by the number of those he could emotionally attach to a cause, just enough to satisfy personal ambitions [5, 6].

He had indeed succeeded in fully mobilizing Germany's potential. He used to shout that "faith can move mountains". But in 1944, although the production of weapons of all kinds reached its zenith, faith alone could perhaps prolong the war, but not change its outcome. In the final phase of the war, when the end was in sight on the bleak horizon, Goebbels played his ultimate propaganda card. "Resistance at all costs" was the headline in his last article, on the last page of the newspaper "Das Reich".

On April 21, the eve of the publication of the article, Goebbels held a final meeting with his subordinates, heads of directorates. Witnesses testified that he began to scream at the German people and their inability to live up to Nazi standards. He was about to leave his stunned audience, when at the door turned back and exclaimed: "But when we leave, the earth will shake". On April 23, he makes a desperate call to the people of Berlin on the radio: «I call on you to fight for your city. Fight with all the means at your disposal, for the sake of your women and children, your mothers and fathers. Your weapons will defend everything we love to this day, and generations to come. Have courage and pride. Be resourceful and skillful... The battle of Berlin must be the signal that will stir up the whole nation» [4, 5].

The day after Hitler and his wife Eva Braun commit suicide, Magda Goebbels kills her children with poison in their sleep, and the pair then go up to the Chancellery garden, where Günther Schwägermann of the SS executes them with a revolver (**Figure 6**). The men of the guard attempt to cremate the bodies. But the gasoline they have is insufficient. The bodies are burned, but they can be identified. In the next few hours, Soviet soldiers will find the bodies of Magda and Joseph Goebbels, identify them and take the relevant photographs [5].

Talipes equinovarus

Regardless of whether the deformity of the right foot was due to osteomyelitis that had affected the growth cartilage and soft tissues, or to a peroneal nerve injury with similar consequences, Goebbels exhibited a characteristic limping throughout his life. The Soviet soldiers who identified his body in the Chancellery garden, described specific deformity in detail. The body was not completely charred and the deformity of the foot was obvious.

It is scientifically incompatible to suggest that Goebbels' foot deformity due to osteomyelitis could resemble the one described by the soldiers or the one we see in the rescued photographs and videos. In this case, clubfoot would be atypical and simpler than a congenital deformity. In case of injury to the peroneal nerve, there would also be a permanent drop foot and weakness for dorsal extension.

In both situations, the problem could be treated surgically with satisfactory results, according to the knowledge of Medicine in Germany at the time. We strongly suspect that the deformity pre-existed and was known from Goebbels's infancy. Of course, infectious or traumatic experiences in his childhood would have given his parents a convincing alibi to absolve themselves of any inherited guilt against a strict society that based its principles on prejudice and stereotypes, while absolving the young Goebbels of the need to give all his life explanations, anything but flattering, about his self-image.

Goebbels' clubfoot, known by the scientific term "congenital talipes equinovarus", is not a rare or unknown foot deformity (**Figure 7**). Nowadays, we know that it occurs in one in every 1,000 births, while it is considered the most common congenital deformity of the skeleton in infancy. The disease is apparently the result of the interaction of many factors acting in the fetal period, in a genetically susceptible foot. The pathogenesis refers to an abnormal morphology of the talus, together with a disturbance of its relations with the other bones of the foot, combined with a progressive shrinkage of the soft tissues on the sole and on the inner side of the foot [7].

Eminent figures in science, politics and art suffered from clubfoot. Emperor Gaius Claudius Germanicus of Rome is the most egregious example. After all, the nickname Claudius indicates the disorder in his gait that characterized him, since in Latin the word means Lame. Lord Gordon Byron, Walter Scott and others suffered from the same disease. Looking back at Hesiod's Theogony, we discover that Hephaestus, Hera's deformed son, for whom he did not need to copulate with Zeus, was thrown into the sea by his own mother in order to destroy him. He was saved from certain drowning by Thetis and the Oceanid Eurynome. Homer ascribes to Hephaestus the epithets of "amfigyieis" and "kyllopodion" (the one who has both legs curved) [8].

The modern therapeutic treatment of talipes equinovarus promises satisfactory to excellent results with minimally invasive operations, as long as the treatment starts early with successive corrective braces and special exercises (Ponseti method). In cases of recurrence of initial deformity in older ages, we now resort to wide surgical ligament release, tendon lengthening, capsular divisions, and/or osteotomies [9, 10]. Nowadays, adults who once suffered from the disease move and work among us, no longer showing functional or aesthetic problems and without showing signs of reduced self-esteem.

The aspect of Individual Psychology

At the beginning of the 20th century, right after Sigmund Freud's publications, the foundations were laid for the principles of individual psychology, in other words the theory of analyzing the individual's personality and the psychotherapy method that derives from it. Alfred Adler, the first to teach this pioneering method, considers the individual as a single whole, on which the physical, psychological and social processes are completed.

In tracing Adler's childhood we discover many features in common with those of Joseph Goebbels. Here we also find physical lameness (rickets and spasms of glottis which often implied the risk of suffocation and death) forcing little Alfred to move with limitations under his mother's protection. Here the feeling of inferiority lurked beneath his efforts to stand out into his environment. Doctors always recommended fresh air to improve his health. This was the reason that explained why he used to play outside the house with the neighborhood children, constantly gaining experience and relentlessly drawing the courage and wider social interest he desired. He himself often claimed that he owed his "man's knowledge" to "his career as a child on the streets".

In 1902, he collaborates with Sigmund Freud as a member of the Vienna Psychoanalytic Society. The collaboration with Freud did not last more than 10 years. The differences between the two psychoanalysts in approaching neuroses were more than obvious. Adler disagreed with Freud because, on the one hand, he considered the role of aggression and social factors important in shaping human behavior, and on the other hand, he questioned the omnipotence of libido. According to Alfred Adler, the personality is formed within the social environment into which the person lives. Soul and body are in absolute interdependence, complement each other, and completed within the individual [11].

In the individual psychology, human behavior is primarily motivated by social drives. Both heredity and environmental influences shape a person's character from a very early age and determine his behavior. The person constantly processes and interprets his experiences, looking for new ones, capable of contributing to the completion of a "life style", unique for each one. Consciousness in individual psychology plays a leading role because it is at the center of the person's personality, in contrast to Freudian theory where the unconscious dominates. Man is conscious of what he says or does, of the points in which he is inferior and of the goals for which it is worth fighting. Therefore, he is able to plan and direct his actions with full self-awareness [12].

In other words, in man there is an innate tendency to impose, but he often runs into his weaknesses, which he perceives from his daily experience. Along with the tendency to impose, a feeling of inferiority develops in the area of the unconscious, which is particularly pronounced in people with physical or other defects. The feeling of inferiority causes a series of unconscious actions aimed at preserving and developing the personality so as to cover real (or imagined) weaknesses. This effort is called "tendency to replenish".

In 1935, while individual psychoanalysis had already taken its course with the creation of educational counseling clinics, Adler introduced a classification that helps to categorize the different personality types, but is not absolute [12]. The "dominant" type (to which we could unreservedly classify the case of Goebbels) shows a high degree of activity to achieve his goals, but shows a deficient sense of sociability, which explains his antisocial behavior [13, 14]. On the contrary, the "receptive" type shows insufficient activity and a disadvantageous feeling of sociability. He expects others to take an interest in him. He loses his independence, does not know his abilities and, when faced with some difficulty, requires help from others. The "avoidant" type is characterized by indecisiveness, while the energy and sense of sociability that possess him are at their nadir. For him, his goal is to escape while keeping a safe distance from his fellow humans. The "socially useful" type is characterized by activity and energy in harmony with the needs of others, so as to prove beneficial to them in practice.

Conclusions

The disability of Joseph Goebbels, as an interesting and controversial clinical case, is today a real challenge for the scientific community. His right clubfoot, although never effectively treated as a physical deficit, apparently acted as a springboard for his social advancement, with substantial political extensions in modern world history. Apart from any theories that may be formulated from time to time, it is of interest to all to constantly process the historical events and analyze the behavior of the protagonists, with the ultimate goals of realizing mistakes and avoiding their repetition in the future.

Conflict of interest
The authors declared no conflicts of interest.

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Markeas NG, Begkas D. The right foot of Joseph Goebbels. *Acta Orthop Trauma Hell* 2022; 73(4): 312-319.

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The Action of Hematopoietic Stem Cells in the Pathophysiological Mechanisms of Spinal Cord Injury

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ABSTRACT

Spinal cord injury (SCI) often leads to catastrophic neurological deficits that dramatically reduce a person's quality of life. Stem cells have attracted particular interest as a potential source for cell regeneration therapy after SCI.

The purpose of this study is to review the action of hematopoietic stem cells (HSCs) in the pathophysiological mechanisms of SCI. 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: ("hematopoietic stem cells" OR "HSCs") AND ("spinal cord injury"). The search included only animal and clinical studies evaluating the action of hematopoietic stem cells in the pathophysiological mechanisms of SCI. Studies published in non-English language, reviews, case reports and study protocols were excluded.

Initially, 39 studies were identified after primary search on Pubmed electronic database. After screening of titles and abstracts, 21 articles were excluded. Among the remaining 18 studies, 9 were rejected as review articles. After checking the references list of the included studies, 13 more studies were added, leaving 22 studies for final analysis. There were 10 clinical studies and 12 animal studies.

The transplanted HSCs may integrate with the host cells in the injured spinal cord tissue, modulating immune and inflammatory reactions. Moreover, they have been associated with axon regeneration and remyelination along with a reduction of glial scar. HSC transplantation has shown promising results in the treatment of SCI, having the potential to repair the injured spinal cord and to enhance functional recovery. However, most studies are experimental and further human studies are needed to fully elucidate the role of HSC in SCI.

KEYWORDS: "spinal cord injury", "hematopoietic stem cells", "transplantation"

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Introduction

Spinal cord injury (SCI) often leads to catastrophic neurological deficits that dramatically reduce a person's quality of life. Surgical fixation and rehabilitation are the only interventions commonly used to improve functional recovery after SCI. Methylprednisolone is the only currently approved pharmaceutical agent and has been used to reduce inflammation in the spinal cord immediately after injury. However, it has limited efficacy and serious side effects, such as gastrointestinal bleeding and increased risk of respiratory infections (1,2). Despite decades of efforts to develop effective methods of management, there is still an urgent need for novel treatment that promotes functional recovery after SCI.

SCI can cause acute damage to the ascending and descending neural pathways and lead to axonotmesis. Immediately after the initial injury, a strong neuroinflammatory response occurs and secondary injury mechanisms are activated in the chronic phases of SCI, leading to cell death and further tissue degeneration. Around the site of injury, cyst formation and growth inhibitory scarring (glial scar) will prevent tissue regeneration (3). For these reasons, stem cells have attracted particular interest as a potential source for cell regeneration therapy after SCI.

Hematopoietic stem cells (HSCs) are a stem cells category, distinguished by a great capacity for self-renewal. They are located in the bone marrow and are responsible for blood formation and the production of all hematopoietic cell lines, such as red blood cells, white blood cells, platelets or lymphocytes. HSCs remain in the marrow at rest and control hemopoiesis by multiplying very rarely, once every 21 weeks. Hematopoietic stem cell progenitors are short-lived hematopoietic cells that produce cell lines for a short period of time (4,5).

Nowadays, HSC transplantation is a modern, established, effective treatment for the treatment of various, severe malignant and genetic hematological diseases. The range of transplantations has expanded dramatically with the use of alternative donors and transplants and as a result, many pediatric patients are treated with the application of this therapeutic procedure. HSCs have been used to treat hematological diseases since 1988, the year of the first successful therapeutic application. Their uses are for the treatment of malignant blood diseases, as well as hereditary hemoglobinopathies and metabolic diseases. In 1988 they were first used to treat aplastic anemia, in 1989 they were used to treat chronic myelogenous leukemia and since 1995 they are considered equivalent to bone marrow stem cells and can have the same therapeutic applications. In 1998 the first autologous HSCs transplantation was performed in a child with a malignant tumor of the nervous system, which even had metastases. In 2007, the first autologous and successful umbilical cord HSCs transplantation was published in a 3-year-old child who developed acute lymphoblastic leukemia and whose family had cryopreserved his stem cells in a private bank (6,7). Today, more than 50.000 HSC transplantations are performed annually worldwide.

There are two types of HSCs transplantations: (a) allogenic in which HSCs are transferred from a healthy individual (donor), genetically compatible or genetically similar, to the patient (recipient); the goal is to replace the patient's abnormal bone marrow with a new, healthy hematopoietic system, (b) autologous in which the HSCs of the patient are removed, collected, processed, frozen, and then, after the administration of chemotherapy, they are thawed and infused. HSCs sources include bone marrow, peripheral blood and umbilical cord blood. CD34 is a marker of human HSCs and human progenitor hematopoietic cells, and all colony-forming activity of human bone marrow cells is found in the CD34+ fraction (8). Studies have shown that HSCs are able to restore hemopoiesis in immunocompromised mice. Their specific ability is based on the CD34+ molecule, which is expressed by these cells. Experiments have also shown that aging HSCs retain their older phenotype after transplantation in young individuals (9).

There are two possible approaches to using stem cells in SCI: Stem cell transplantation at the site of injury and recruitment of neural stem cells of the injured spinal cord (10, 11). The purpose of this study is to review the action of HSCs in the pathophysiological mechanisms of SCI. A literature review was conducted based on the Pubmed internet database, following the PRISMA Guidelines, with the use of the EndNote X3 software (Thompson Reuters) (12). Article titles were searched with the use of the keywords: ("hematopoietic stem cells" OR "HSCs") AND ("spinal cord injury"). The search included only animal and clinical studies evaluating the action of hematopoietic stem cells in the pathophysiological mechanisms of SCI. Studies published in non-English language, reviews, case reports and study protocols were excluded.

Discussion

Initially, 39 studies were identified after primary search on Pubmed electronic database. After screening of titles and abstracts, 21 articles were excluded. Among the remaining 18 studies, 9 were rejected as review articles (figure 1). After checking the references list of the included studies, 13 more studies were added, leaving 22 studies for final analysis. There were 10 clinical studies (13-22) and 12 animal studies (23-34).

Animal Studies

Recently, there is an emerging number of animal studies focusing on the application of HSCs in the treatment of SCI. In 2017, an animal study by Xiong et al analyzed the results of the injection of HSCs into SCI rats and observed that HSCs may enhance the formation of 5-HT (+) fibers and oligodendrocytes in the spinal cord, attenuate astrocyte hyperplasia, and upregulate neurotrophins-3 (NT-3) mediated mitogen-activated protein kinase kinase (MEK-1) expression, thereby improving motor and sensory recovery in SCI rats (25). Koda et al compared the results of HSC and BMSC transplantation in SCI mice. One week following SCI, HSCs, BMSCs or saline were transplanted into the site of SCI. No significant difference was recorded in the motor and sensory scores among studied groups. Injected HSCs and BMSCs survived in the site of injury. Furthermore, injected HSCs expressed a neural lineage marker, whereas BMSCs kept their original phenotype. Authors concluded that HSCs and BMSCs have the capacity to restore the injured spinal cord and to enhance functional recovery of hind limb motor function (23).

In 2004, Zhao et al demonstrated that intraspinal injection of umbilical cord–derived HSCs into the spinal cord improved functional outcome and survival rate in a rat spinal cord hemisection model (28). The same year, Koshizuka et al directly injected HSCs into the spinal cord of mice 1 week after SCI and checked hindlimb motor function once per week for 5 weeks after injection. An important improvement in the functional results of mice transplanted with HSCs was observed in comparison with the control group. Transplanted HSCs were found to survive 5 weeks after injection and expressed specific biomarkers for astrocytes, oligodendrocytes and neural precursors, but not for neurons. Authors concluded that HSCs transplantation is a helpful method for the treatment of SCI (24).

In another animal study including 40 SCI rats, intrathecal transplantation of umbilical cord HSCs was found to improve spinal cord function, when delivered 30 min after experimental SCI (31). Dasari et al showed that umbilical cord HSCs, when injected into the spinal cord 7 days of 52 adult male rats after SCI, survive for at least 2 weeks, differentiate into oligodendrocytes and neurons, and facilitating functional recovery after moderate SCI, with a beneficial effect in the reversal of the behavioral effects of SCI (32). In another experimental study, the same authors observed that umbilical cord HSCs when transplanted in the SCI site 1 week after injury, may inhibit neuronal apoptosis during the repair of injured spinal cord (33).

Nishio et al reported that transplantation of CD34+ umbilical cord–derived HSCs used in SCI rats improved hind-limb motor function, and enhanced the regeneration of spinal cord tissue and axons. Transplanted HSCs disappeared 5 weeks after transplanation (26). Recently, according to Yeng et al, the neuroprotective effects of conditioned medium from cultured human CD34+ cells are similar to those of human CD34+ cells and the conditioned medium was found to augment the neuroprotective effects of estradiol in SCI rats (27). In an experimental comparative study, Cao et al evaluated the results of combined laminectomy with the

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administration of umbilical cord derived CD34(+) cells in SCI rats. Authors concluded that CD34(+) cell transplantation may reverse the SCI-induced spinal cord infarction and apoptosis and hindlimb dysfunction by triggering the production of both vascular endothelial growth factor (VEGF) and glial cell line-derived neurotrophic factor (GDNF) in SCI rats (29). A similar randomized comparative study by Ning et al, observed that transplantation of umbilical cord derived CD34(+) during the acute phase of SCI may enhance the functional recovery better than during the subacute phase after SCI by increasing blood vessel density. Transplanted HSCs were found to survive at least 3 weeks after injection, but did not differentiate into neural cells (30). An animal study by Takahashi et al, found that intraspinal injection of granulocyte colony-stimulating factor (G-CSF) - mobilized peripheral blood derived-CD34(+) cells enhanced angiogenesis, serotonergic fiber regeneration/sparing, and preservation of myelin, resulting in improved hindlimb function after SCI (34).

Clinical studies

In a prospective study, published in 2012, Frolov and Bryukhovetskiy transplanted intrathecally CD34+ HSCs in 20 chronic SCI patients and used regular neurophysiologic examination for at least 1 year to assess neurological recovery. In 3 patients the initially absent short-latency somatosensory evoked potentials were restored. In 4 patients, the N20P23 interpeak amplitude elicited by median nerve stimulation was increased. In 2 patients, the P38 latency in somatosensory evoked potentials elicited by tibial nerve stimulation was decreased. In 3 patients, the motor evoked potentials appeared. Authors commented that the mixed results of HSCs transplantation are due to the variety of spinal cord lesions and the different pathways involved. The results of the study demonstrate the ability of HSCs to install and spread within the spinal cord, participating in the neurological recovery process (16).

An Iraqian study published in 2012 enrolled 277 SCI patients. Peripheral blood-derived HSCs were injected into the spinal cord, 1-4 times within 6-8 weeks. 56.7% of patients showed no neurological improvement, while the rest of the patients (43.3%) experienced clinical improvement after 4 weeks. Transient backache was recorded in 90% of cases (17). Thakkar et al, in 2016, in a prospective single arm open-labeled clinical trial, evaluated the therapeutic combined infusion of HSCs and autologous adipose tissue-derived mesenchymal stem cell differentiated neuronal cells in the spinal cord of 10 SCI patients. After a 3-year follow-up, variable clinical improvements were observed. All patients mentioned subjective crude pain sensation at 15 days after treatment. Sixty per cent of patients reported crude touch sensation 30 days after treatment, followed by fine touch sensation and deep pain sensation 3 months after treatment up to 3-4 levels below SCI. At 3 months after infusion, all patients could stand with aid, with a gradual increase of the duration of standing. At 8 months, 80% of patients could walk for at least 1 hour without help. At 3-years follow-up, in half of the patients, the control of bladder and bowel was significantly improved. No complications or side effects were observed (18).

Al-Zoubi et al, in a prospective cohort study, evaluated the efficacy of transplantation of CD34+ HSCs in the spinal canal of 19 patients with complete thoracic SCI. At a 5-year follow-up, 7 patients had improvement in segmental sensation, 2 patients had improvement in motor function, showing improved strength of abdominal and hip muscles, allowing them to walk with aids. No side effects were recorded (19). In 2015, Bryukhovetskiy et al conducted an open parallel controlled trial including 202 SCI patients and 20 matched controls. A combination of HSCs and hematopoietic progenitor cells was administered intrathecally every 3 months for 3-5 years. At the 3 years follow-up, the efficacy of the combined transplantation was 57.4%. No clinical improvement was observed in 42.6% of cases. Half of the patients experienced a degree of motor recovery, initiated after the first transplantation. In 47.7% of patients, bladder function was improved. Improvement of neurological symptoms was observed in 56.9% of cases. No complications or severe side effects were recorded. Authors concluded that the method is safe, effective and considerably improves the life quality of SCI patients (14).

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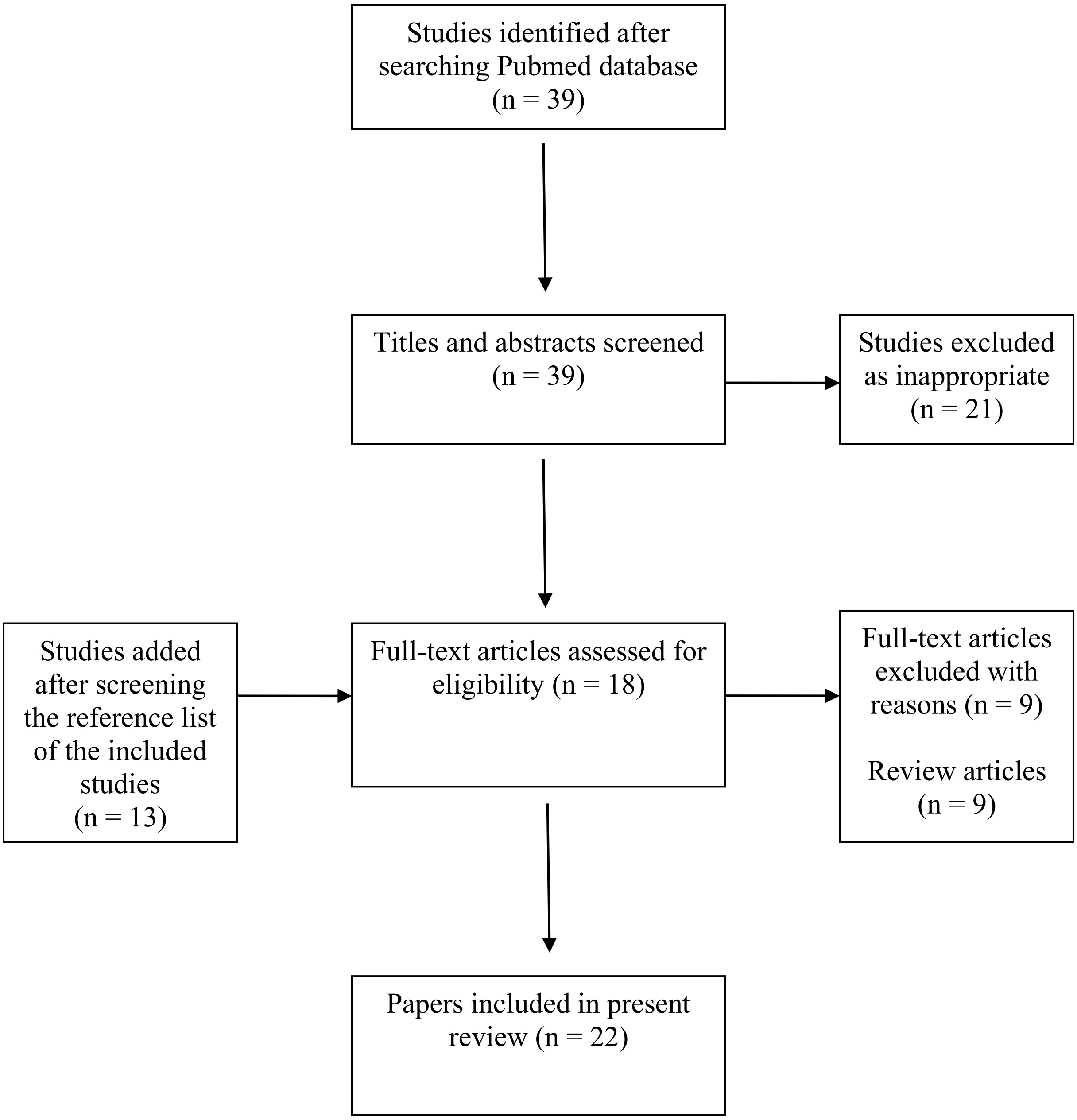

Figure 1. *Study flowchart*

In 2017, Ammar et al published a study including 4 SCI patients that underwent reconstruction of the spinal cord using a combination of autologous HSCs and platelet-rich protein (PRP) that served as a scaffold for the HSCs. Postoperatively, patients were checked clinically with regular electromyograms and MRIs. After a 2-3 years follow-up, one patient demonstrated motor and objective sensory improvement, two others reported subjective sensory improvement, and the fourth patient remained without any improvement. No complications or clinical deterioration was recorded. All the insert-

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ed biological scaffolds remained intact, as shown in MRI studies (13). Another study by Deda et al assessed 9 patients with chronic (more than 6 months) complete SCI, ASIA grade A, who were treated with autologous bone marrow-derived HSCs transplantation, during laminectomy. With a 3-weeks follow-up, all patients experienced motor and sensory improvement (ASIA grade B or C). No complications or severe side effects were recorded (15). A prospective, non-randomized clinical study examined the effect of CD34+ cells infusion on 39 patients (28 males and 11 females) with complete cervical and thoracic SCI. After a - 2.5 years follow-up, neurophysiologic examination revealed that 67% of the patients showed recovery of somatosensory evoked potentials in response to peripheral stimuli. This finding may be explained by the HSC-induced formation of new synapses between neurons or by new myelination of glial cells. The rate of complications was 10.2% including one case of pneumothorax and 3 allergic reactions (21). In another case series by Geffner et al, CD34+ cells were administered in 8 SCI patients either into the spinal cord or intravenously. Authors observed morphological changes in spinal cord, as depicted in MRI studies. CD34+ cells transplantation improved the quality of life of all patients, without any severe adverse events (20). Callera and de Melo, in a comparative study, found that autologous bone marrow CD34+ cells labeled with magnetic nanoparticles that were injected into the spinal cord migrated into the injured site in 16 patients with chronic SCI (22) .

The exact mechanism of functional recovery enhancement induced by HSC transplantation has not yet been clarified. HSCs may secrete neurotrophic growth factors, such as angiopoietin-1, which can enhance restoration of the spinal cord and improve functional outcome. (35,36). The transplanted HSCs may integrate with the host cells in the injured spinal cord tissue, modulating immune and inflammatory reactions. Moreover, they have been associated with axon regeneration and remyelination along with a reduction of glial scar (37).

HSC transplantation has several advantages. They can be easily obtained from bone marrow from animals and humans. HSCs can be transplanted without cultivation as optimal timing for HSC transplantation in SCI is limited to the first 1–2 weeks after SCI (38,39). The disadvantages include a difficulty in acquiring an adequate number of HSCs, as they constitute less than 1% of bone marrow cells in the adult human, and ex-vivo expansion of HSCs has not yet been established. Alternatively, umbilical cord blood may be used as a source of HSCs. These HSCs can be used for cell therapy for SCI, as they are abundant, immature, with low rate of immunologic rejection and with a potential application for treatment of central nervous system diseases (40).

Conclusions

HSC transplantation has shown promising results in the treatment of SCI, having the potential to repair the injured spinal cord and to enhance functional recovery. However, most studies are experimental and the clinical application of HSC transplantation in SCI needs further high-quality clinical trials. It seems that the combination of HSC transplantation with tissue engineering scaffolds, local drug administration and postoperative physical and occupational therapy may help SCI patients regain their normal life. Further human studies are needed to fully elucidate the role of HSC in SCI.

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Autologous osteochondral grafts for the treatment of focal chondral lesions of the femoral head: an experimental study in rabbits

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ABSTRACT

The use of autologous osteochondral graft is a useful method for the treatment of cartilaginous lesions. In our study we compared the results of autologous osteochondral graft and simple drilling in cartilaginous lesions in rabbits. The graft was taken from the lateral femoral condyle and put in the hip joint. We evaluated the histological quality of the femoral head 24 weeks after the usage of the graft or the simple drilling for the treatment of the osteochondral defect. Autologous osteochondral graft had excellent results, with high quality new articular surface in comparison with the results of drilling. However, the usage of autologous osteochondral is far more difficult than drilling the osteochondral defect.

Keywords: Articular cartilage; Chondral lesions; Osteochondral grafts; Autologous; Rabbits.

Introduction

The usual response of physiological cartilage to defect formation of either traumatic or degenerative origin is restoration with lower quality tissue. The physiological and mechanical properties of the new tissue differ to those of articular cartilage resulting to a function alteration of the articular surfaces of the joint. Chondrocytes of the environment surrounding the defect, possess the ability of migration but are not capable of multiplication and production of macromolecules necessary for the synthesis of an organized basic network of normal hyaline cartilage.

Reconstruction of the articular surface and defect coverage is necessary in order to avoid the development of osteoarthritis of the joint. Autologous osteochondral transplantation is widely used for the treatment of chondral and osteochondral defects of the knee and ankle joint. Clinical and radiological results show that autologous osteochondral transplantation

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Figure 1: *Osteochondral graft 24 weeks after transplantation.*

Figure 2: *Photograph of the cartilage 24 weeks after subchondral drilling.*

is a method that offers reconstruction of the articular surface with mature autologous hyaline cartilage.[1-4] The application of this method on focal chondral pathology of the femoral head of the hip joint, has initially been described by Hangody et al.[2] but no report has been provided for the clinical or radiological outcome of the articular surface of the treated hip joints. On experimental level, to our knowledge, there is lack of literature reporting the usage of this specific method in the hip joints of animal models. Questions concerning the quality of the transplanted tissue, the coverage of the chondral defect, the integration of the transplant and the function of the joint are left open. This study is an effort from our side to give an answer to these questions and to provide the autologous osteochondral transplantation as a safe and effective method for extended cartilaginous lesions.

Materials and methods

After performing the experimental procedure in 3 pilot animals, 12 rabbits were used for the experimental study. They were divided into 2 different groups (A and B). All animals were driven to euthanasia 24 weeks after the transplantation. Group A (C, G, H, J, K, and L) animals underwent autologous osteochondral transplantation of an iatrogenic produced osteochondral defect of 2,7mm diameter and 2mm depth. Group B (A, B, D, E, F, and I) underwent subchondral drilling of an iatrogenically produced defect of 2.7 mm diameter and 2 mm depth. More specifically, the surgical technique included sedation through 1-1.5 mg sodium phenobarbital injection. After thorough aseptic cleaning of the hip joint area, skin and soft tissues were prepared until the hip joint capsule was reached. The anterolateral part of the joint capsule was penetrated and opened in a direction parallel to the femoral neck offering vision to the craniolateral portion of the femoral head with the hip positioned in extreme internal rotation. An iatrogenic lesion of the craniolateral portion was created through manual drilling of the femoral head into a depth of 5 mm with a drill, aiming to avoid thermal destruction of the surrounding cartilage. The diameter of the drill was 2.5 mm.

In the autologous osteochondral transplantation group the ipsilateral knee joint underwent aseptic cleaning and preparation as well. A lateral parapatellar arthrotomy was performed and a 2.7 mm in diameter and 5mm in length osteochondral graft was taken from the lateral femoral condyle. The incision was sutured and the knee joint was closed in layers. The osteochondral graft was transplanted into the prepared site of the femoral head with care to bring it to the same level as the surrounding cartilage. The joint was irrigated and closed in layers. In the subchondral drilling group the iatrogenic

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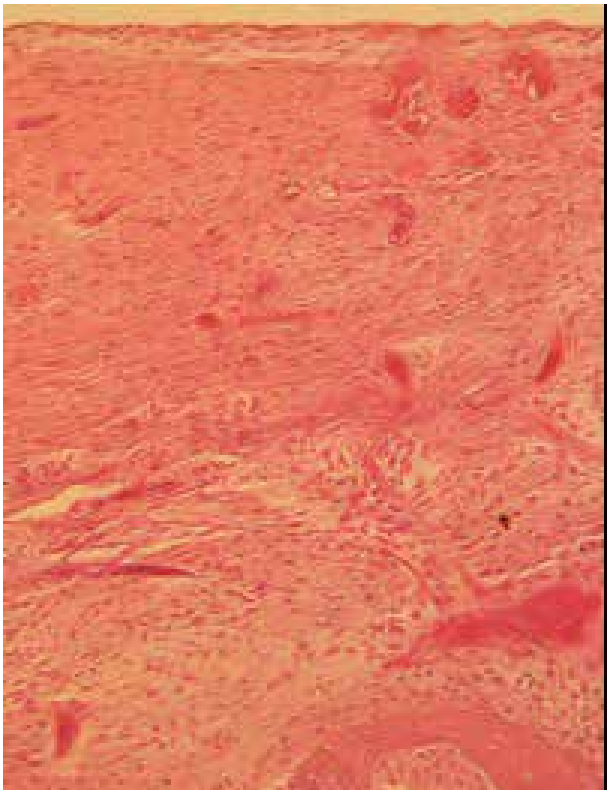

Figure 3: *Histological section 24 weeks after subchondral drilling shows fibrous and fibrocartilaginous tissue with multiple vessels.*

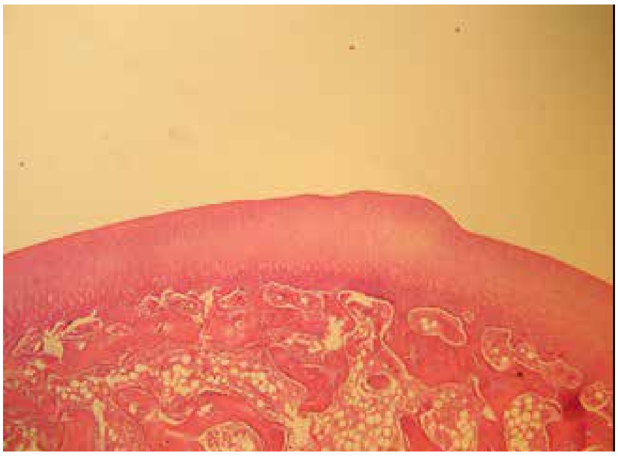

Figure 4: *Histological section 24 weeks after osteochondral grafting shows hyaline cartilage on the top and subchondral bone without any significant changes.*

lesion was left without further treatment. Immediate full weight bearing, without any restrictions of range of motion was allowed. After euthanasia of the animals, the proximal part of the femur was dissected and cleaned from the surrounding soft tissues and was contained in formaldehyde for 24 hours. The dissected parts underwent demineralization. Pieces of 0.3 – 0.4 cm thickness were taken and were positioned into special cassettes and were subjected to dehydration with dilutions of ethylic alcohol 50%, 70%, 96% and 100% as well as xylol where the cassettes were inserted for 45 minutes periodically. Paraffin embedment followed for 120 minutes at a temperature of 62^{o} C. After that the pieces were shut into paraffin cubes and were cut into histological slices with thickness of 5 μ. These slices were painted with hematoxylin /eosin. The results were classified according to the classification system of the International Cartilage Research Society (ICRS).[2] This classification system controls and evaluates 6 important histological parameters. 1) normal appearance of the reconstructed articular surface, 2) quality of matrix, 3) chondrocyte distribution, 4) chondrocyte viability, 5) quality of subchondral bone and finally 6) the nature and site of chondral calcification zone. These parameters are rated with 3 for an excellent result and 0 for failure.

All variables were represented by the number of patients (N), mean value (mean), standard deviation (SD) and median value. Comparisons of variables between the 2 groups were performed with the Mann-Whitney test. All tests were two-sided with 95% significance level. Statistical analysis was done using the statistical package SPSS v. 12.00 (Statistical Package for the Social Sciences).

Results

The articular cartilage of animals sacrificed 24 weeks after the osteochondral transplantation showed a smooth and subwhite surface with 0.05 cm of thickness (Figure 1). Animals sacrificed 24 weeks after subchondral drilling showed an irregular surface with a diameter of 0.3 cm at the treated site. The surrounding cartilage was white and grey (Figure 2). Histological examination of specimens from the six rabbits sacrificed 24 weeks after subchondral drilling showed an irregular articular surface. The defect was covered by fibrous tissue in 2 animals, by fibrocartilaginous tissue in one ani-

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TABLE 1.

ICRS visual histological assessment score of animals treated with subchondral drilling 24 weeks later (Group B).

Subchondral drilling	A	B	D	E	F	I
Articular surface	3	3	0	3	0	0
Martix	2	2	0	2	1	0
Cell orientation	0	0	0	0	1	0
Cell viability	3	3	3	3	3	3
Subchondral bone	2	2	2	2	2	2
Cartilage mineralization	3	2	0	3	0	0

TABLE 2.

ICRS visual histological assessment score of animals treated with osteochondral grafts 6 weeks later (Group A).

Osteochondral grafts	C	G	H	J	K	L
Articular surface	3	3	3	3	3	3
Matrix	3	3	2	3	3	3
Cell distribution	2	2	2	2	2	2
Cell population viability	3	3	3	3	3	3
Subchondral bone	2	3	2	3	3	3
Cartilage mineralization	3	3	2	3	3	3

mal and in the remaining 3 animals by combined hyaline cartilage and fibrocartilage. The tissue of all specimens consisted of viable cells arranged clusters in 3 animals. In 2 animals they are arranged in clusters only. Subchondral bone showed increased remodeling in 4 animals. In 1 animal the subchondral bone underwent necrosis and fibrous tissue formation. In 3 animals we observed normal cartilage calcification. None of the joints treated with subchondral drilling showed full restoration of the articular surface with hyaline cartilage or normal subchondral bone (Figure 3, Table 1). Histological examination of specimens from 6 rabbits sacrificed 24 weeks after osteochondral graft transplantation showed smooth articular surface in all animals consisting of mature viable chondrocytes with column and cluster distribution. In 5 of the 6 animals the cartilage covering the operated site has the appearance of hyaline cartilage, and in one animal the appearance of hyaline cartilage and fibrocartilaginous tissue was observed. The subchondral bone in 4 animals showed no significant changes. In 2 animals the subchondral bone showed increased remodeling. Normal calcification of the cartilage was detected in 5 animals (Figure 4, Table 2).

Statistical analysis showed a statistically significant difference for all variables: articular surface ($p= 0.049$), matrix ($p= 0.003$), cell distribution ($p< 0.0005$), subchondral bone ($p= 0.010$), cartilage mineralization ($p= 0.000$), except for cell population viability between the 2 groups. Additionally, no histological evidence of osteonecrosis of the femoral head in any of the animals was observed (Table 3).

Discussion

Autologous osteochondral transplantation is being

TABLE 3.

Comparison of the mean values of each parameter of the ICRS visual histological score

	Group	N	Mean	SD	p-value
Articular surface	GROUP B	6	**1.50**	1.64	**0.049**
	GROUP A	6	**3.00**	0.00	
Matrix	GROUP B	6	**1.17**	0.98	**0.003**
	GROUP A	6	**2.83**	0.41	
Cell distribution	GROUP B	6	**0.17**	0.41	**< 0.0005**
	GROUP A	6	**2.00**	0.00	
Cell population viability	GROUP B	6	**3.00**	0.00	**1.000**
	GROUP A	6	**3.00**	0.00	
Subchondral bone	GROUP B	6	**2.00**	0.00	**0.010**
	GROUP A	6	**2.67**	0.52	
Cartilage mineralization	GROUP B	6	**1.33**	1.51	**0.040**
	GROUP A	6	**2.83**	0.41	

applied in the treatment of chondral as well as osteochondral defects of the knee and the ankle joint. Good clinical as well as radiological reports showed that it is a method offering successful reconstruction of the articular surface with grafts consisting of bone and hyaline cartilage.[1-4,5] The application of this method of treatment in the hip joint has been initially reported by Hangody et al.[2] nevertheless without any published reference on the clinical or radiological follow up of their results. This leaves questions concerning the histological quality of the tissue covering the chondral defect, the congruity of the newly formed articular surface or the integration of the graft into the transplanted site of the specific joint, open for answers. This experimental study aimed to investigate histologically the results of the reconstruction of the articular surface of the hip joint through the application of subchondral drilling and autologous osteochondral transplantation, in case of an osteochondral lesion of the femoral head. The most vulnerable and important part of the articular surface of the hip joint is the craniolateral weight bearing area of the femoral head. This area receives the main part of weight bearing forces when the animal is standing as well as walking.

In order to achieve a realistic simulation of the reconstructed area under weight bearing forces, the autologous osteochondral grafting as well as the drilling were performed at the proximal, lateral quarter of the femoral head, based on the hypothesis that it is an area of increased loading pressure. The animals were free to full range of motion and full weight bearing of the hip joint. One major concern of the study was the influence of the dissection and the extreme position of internal rotation of the hip joint on the vascular supply of the femoral head. Since there was no evidence of osteonecrosis of the femoral head an assumption can be made that the vascular supply of the joint capsule compensates well the single lateral incision as well as the internal rotation without any negative influence on the osseous structure of the femoral head. Macroscopically as well as microscopically the osteochondral defect treated with autologous osteochondral transplantation was fully covered from tissue showing definite difference to the tissue produced after subchondral drilling. In order to compare the histological results of the two treatment methods we used the International Cartilage Research Society Scoring system. This system allows histological estimation of the quality of the newly formed tissue. Clear superiority of the score of the group treated with autologous osteochondral transplantation was shown in comparison to the group treated with subchondral drilling after a period of 12 weeks. The comparative analysis of the parameters observed in the histologic outcomes of each method justifies the results. More specifically, the articular surface of all the rabbits belonging to the group of autologous osteochondral transplantation was smooth becoming a high histological average ICRS score 3 (excellent). On the other hand the subchondral drilling group showed in 3 out of 6 animals an irregular articular surface, result of the uncontrolled action of the multipotential mesenchymatic cell gatherings of the blood clot produced at the defect site. The histological score was very low in these cases and influenced in a negative way the overall histological outcome although the rest 3 animals showed a smooth articular surface. The average of the histological scores of this group parameter was 1 (poor). The histological assessment of the matrix in the autologous transplantation group showed the existence of tissue of equal quality with the articular surface of a normal joint since hyaline cartilage was observed in 5 out of 6 animals and fibrocartilage in 1 animal a very good result since the primary goal of such procedures was accomplished. The average of the histological scores of this group parameter is the number 2.8 (excellent). On the other hand the subchondral drilling group showed existence of mixed hyaline and fibrocartilage tissue as well as fibrocartilage in 4 out of 6 rabbits. Histological investigation of the rest 2 animals showed fibrous tissue. The average of the histological scores of this group is the number 1.2 (poor). This observation agrees with the reports of De Palma and Mitchel according to which the procedure of cartilage defect reconstruction does not end up into a rebuilding of normal cartilage. Instead of normal cartilage the defects fill up with a mesenchymal type of tissue converting into fibrocartilage. It is well known that this type of tissue is less resilient to stress forces leading finally to degenerative changes of the joints.

Another important difference was observed in the distribution of the cells, an important structural component of normal cartilage. The presence of chondrocytes is a fact in the tissue produced by subchondral drilling as well in the cartilage of the osteochondral grafts.[6-8] The main parameter that characterizes normal hyaline cartilage concerns the distribution of those cells inside the matrix which produce the 4 zones of the chondral tissue. In all osteochondral grafts the cells were well distributed in columns or columnar-clusters and the average score of this parameter was 2. On the other hand the subchondral drilling group showed individual or disorganized cells in 5 out of 6 specimens and clusters in 1 specimen. The average score of this parameter was 0.2.

No difference was observed in the viability of the cells of both groups since all cells were viable and contributed in the reconstruction and remodeling of the treated area. The average score of this parameter was 3 for both groups. The subchondral bone in the group treated with autologous osteochondral grafts was histologically predominantly normal with an average score of 2.8 showing good integration of the grafts without any resorption of the osseous part. The group treated with subchondral drilling showed evidence of increased remodeling with an average score of 2.

Cartilage mineralization was normal in all the specimens of the graft group with a scoring average of 3. In the subchondral drilling group 3/6 specimens showed abnormal /inappropriate location. The results concerning all the histological parameters of subchondral bone and cartilage mineralization show the advantage of the osteochondral graft which provides mature, organized tissue to the defect site in comparison to the subchondral drilling which relies on the random rebuilding of the tissues.[9,10]

Conclusion

Autologous osteochondral transplantation in the treatment of an osteochondral defect of the femoral head provides superior results concerning the quality of the new articular surface tissue as well as structure. The results reward the demanding technique and the difficulty in the effort of implantation of the graft in comparison to the easiness of subchondral drilling which lacks the advantage of the ready to use structural and histological properties of the graft providing inferior histological results.

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REVIEW
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Hip Sonography for Developmental Dysplasia of the Hip: The Graf Method

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ABSTRACT

Developmental Dysplasia of the Hip (DDH) is one of the most common musculoskeletal disorders for children. Multiple risk factors as female sex, positive family history, breech positioning in utero are blamed for the presentation of this entity. The hip joint of the infant is affected and more specifically, the acetabulum remains shallow and the femoral head grows in a wrong position. Until 1980 the diagnosis was based on clinical examination (Barlow and Ortolani maneuvers) and radiological imaging. The diagnosis was not certain and many cases remained undiagnosed until childhood or adolescence. In 1980 Prof. Reinhard Graf presented his ultrasonographic method for the examination of the infant hip joint. This method evaluates the bony and cartilaginous coverage of the femoral head by the acetabulum in the infantile joint by measuring α-angle and β-angle. Using and valuating these measurements the hip joint is later on classified by Graf classification (Types I-IV) and each type corresponds to a specific treatment option. Graf method is the most used ultrasonographic examination in many European countries and has contributed to the reduction of neglected DDH cases and decreased the number of complex pelvic operations that children with dysplastic hips should undergo to be cured.

KEYWORDS: Developmental Dysplasia of the Hip (DDH), Graf method, hip ultrasonography, preventive screening

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Introduction

Developmental Dysplasia of the Hip (DDH) is a common musculoskeletal disorder for children, with a median prevalence of 0.1–2 per 1,000 infants.[1] According to the World Health Organization (WHO) 10%-15% of patients with hip replacement under the age of 50 have positive clinical history of infant hip dysplasia.[2]Developmental dysplasia of the hip (DDH) describes the malformation of hip joints in newborns. This disorder contains a wide spectrum of conditions from acetabular dysplasia, to severe dysplasia with dislocation and possible irreducible hip dislocation with proximal femoral displacement.[3] DDH defines congenital malformation, other perturbations during development process and describes the combined etiology of the disease, with genetic and developmental causes to be responsible for the disorder.[4-6] In some cases when DDH is misdiagnosed, symptoms may appear in adolescence and cause severe degenerative joint disease in early adulthood.6 Different risk factors as family history, breech positioning in utero, being the first-born child, oligohydramnios, female sex, and deformities (postural or structural) of the foot and torticollis have been reported. Historically, Dupuytren described with accuracy this condition based on anatomy, pathology and clinical presentation in 1820s.[7] The diagnosis of DDH was based in clinical examination (Barlow and Ortolani tests), in clinical presentation, radiographs and in 1980, Prof. Reinhard Graf presented his ultrasonographic technique that nowadays dominates as the easiest and most useful screening ultrasound technique.[8] Graf method evaluates the quality of the infantile hip joint, and more specifically, the bony and cartilaginous coverage of the femoral head from the acetabulum by counting specific angles (angle α and angle β).[9] The significance of Graf method is that according to description and these measurements, there is a specific classification (types I to IV) for the DDH that is a guide for the selection of the optimal treatment option. (**Table 1**) Graf method for screening infantile hips has been adopted by the healthcare systems in many European countries as Germany, Austria and Switzerland leading to an important decrease of neglected cases of DDH and to a reduce of open reductions and osteotomies.[10]

Developmental Dysplasia of the Hip (DDH)

The mean incidence of DDH in children without associated risk factors is 11.5/1000 live births according meta-analyses protocols and varies from 0,06/1000 in Africans to 76.1/1000 in Native Americans and Laplanders. DDH appears more frequently in females (19/1000) than males (4.1/1000) and when there is positive family history the risk is 1.7 times higher.[11] DDH is more common in the left hip (64%) than in the right hip (36%) and is usually unilateral (63%).[12] Breech presentation of the infant is connected with high incidence of DDH (7.1% to 40%).[13] Recent methods have proven that feti that are in breech position in utero life have lower incidence of DDH when delivered with Caesarean section, but as expected, higher incidence than children born in vertex position.[14] Family also increases the possibility of DDH presentation.[15] Statistically significant correlations have been found among first-, second-, third-degree relatives and also among siblings, uncles/aunts and cousins.[16,17] Additionally, firstborn children have higher incidence of DDH. Other disorders that are related to DDH are hormonal diseases of the infants (increase in urinary excretion of conjugated estrogen and 17 β-estradiol) and oligohydramnio.[18] Literature is not clear about the role of swaddling, but it seems that populations worldwide that use swaddling for the newborns show higher incidence of DDH.[19,20] Genetics are recently being studied for possible connection with DDH. Until now, different studies have shown correlation between the presence of Human Leucocyte Antigens (HLA A1 and HLA DR4) and DDH and the existence of an autosomal dominant genetic mechanism and a two-gene system of genes (dominant for joint laxity and polygenic for acetabular dysplasia) that is accepted by scientific community.[21,22] Risk factors developed during pregnancy are hypothyroidism or phenylketonuria of the mother, taking progesterone in the 1st trimester for any reason and older parental age.[23-25]

Abnormalities in bones and soft tissues of the hip joint are usual in patients with DDH. The normal

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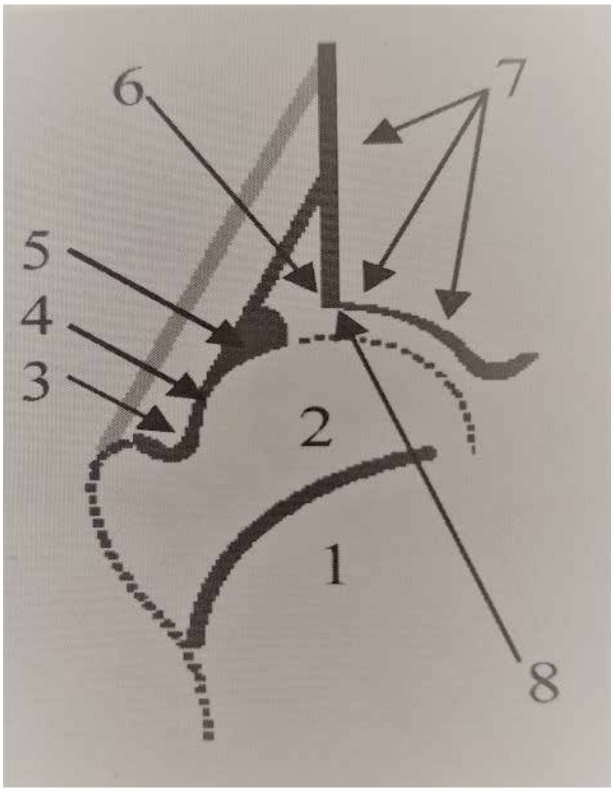

Figure 1: *Infant hip joint anatomical structures: 1. Chondro-osseous border, 2.Femoral head, 3 Synovial fold, 4. Joint capsule, 5. Labrum, 6. Hyaline cartilage, 7. Acetabulum (bone) , 8. Bony rim*

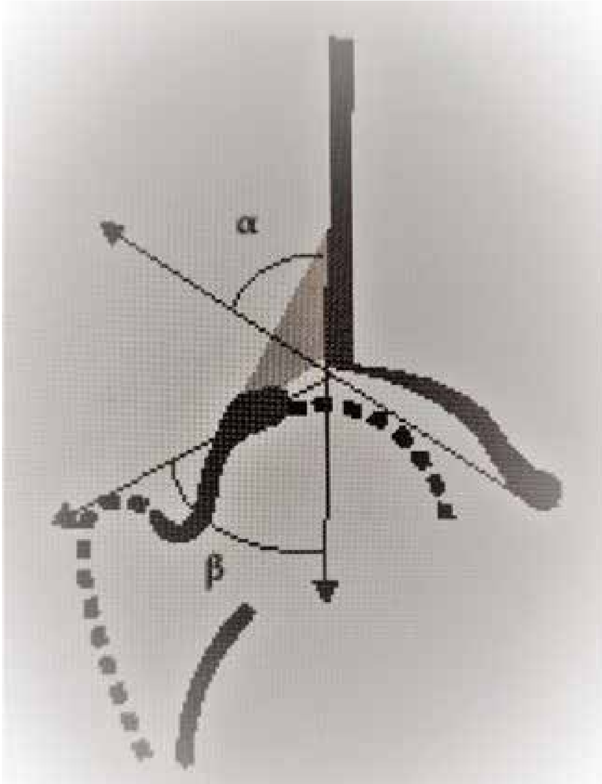

Figure 2: *Angles a and β in Graf ultrasonography method*

hip joint has a ball-socket shape with deep acetabulum in utero life, that becomes shallow at birth and as the newborn develops, becomes deeper and finally covers totally the femoral head. In DDH, the acetabulum remains shallow and the femoral head grows in non-anatomical position. The acetabular index enables to evaluate the coverage of femoral head by acetabulum. The normal range is 3° to 13° and above 13°, there is suspicion of DDH presentation.[26] If the femoral head is positioned out of the acetabulum, the epiphysis develops slowly, the femoral head is flattening and aseptic necrosis is not unusual. In these cases, the labrum of acetabulum becomes hypertrophic, leading to the creation of a secondary "false" acetabulum posteriorly and superiorly of the original one. Even more, a case of double femoral head in DDH patient has been reported as a complication. The femoral neck becomes thick and short and the anteversion of the femoral head changes. As a result, the architecture of the joint is disturbed. Soft tissues of the hip joint also get affected in DDH patients. The articular capsule is thicker in newborns with this disorder and often appears being stuck on the superior and posterior aspect of the acetabulum.[27] The glenoid labrum that is part of acetabular labrum, positioned posterosuperiorly is usually attached at the femoral head and the articular capsule in one side and the cardilaginous part of the roof in the other and along with the hyaline cartilage of the acetabular roof (the epiphyseal plate that deepens the acetabulum) block the reduction of the femoral head.[28,29] It is also described that the acetabulum of DDH patients fills with fat, the empty space is occupied and the closed reduction becomes impossible in neglected cases.[30] The iliopsoas tendon comes in front of the articular capsule, also diminishing the possibility of reduction. When DDH is unilateral, the pelvic inclines and the spinal

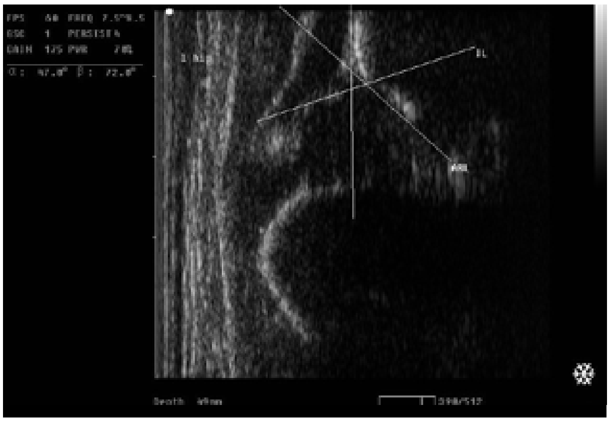

Figure 3: *Sonographic image of infant with a-angle = 47o and β-angle = 72o, type IIc in Graf classification*

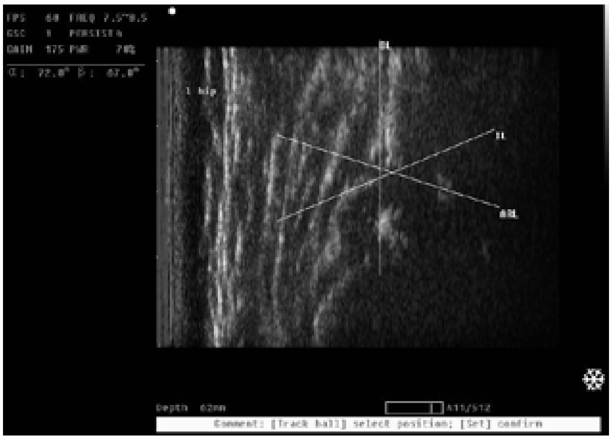

Figure 4: *Sonographic image of infant with a-angle = 72o and β-angle = 67o, type Ib in Graf classification*

curve changes. Furthermore, the abductors of the hip thicken as age of the patient increases, leading to length asymmetry of the lower extremities and hip joint instability.[31] In cases of bilateral DDH the vertical spinal balance changes (increased lumbar lordosis and hip kyphosis), waddling gait is developed.[30] Histologic examination of DDH joints has shown that the articular capsule contains bundles of collagen fibers, thicker than in normal cases, with irregularly distributed fibroblasts internally and also Increased number of elastic fibers, together with chondrocytes of irregular shape. The labrum is inclined to adhere the perichondrium of the outer ilium or the femoral head and shows fibrous metaplasia. The perichondium and the bone around the cartilage is usually normal, but the histology of the acetabulum changes as the growth plates of, ischial, pubic and especially of iliac bones are affected. The ligaments of the hip joint contain randomly arranged collagen bundles and elastic fibers. The vessels of these zones are thick and dilated. The acetabulum becomes anteverted and less vertically inclined and the femoral neck-shaft angle is usually normal or slightly valgus. The delay of growth of femoral head leads to small and spherical shape, or flattened shape in cases of high dislocation. When early closed reduction is successful, the femoral head grows normally.[32]

DDH contains a wide spectrum of hip disorders, from dysplasia (shallow and undeveloped acetabulum) to the teratologic hip.[33] The physical examination is crucial to recognize DDH indications. The most useful tests for the neonatal hip are the Ortolani and Barlow maneuvers. Positive results in these tests are strong indications of luxation of the hip.[34] Furthermore, Galeazzi sign is often used used between 3 and 6 months (with the child in supine position and with the knees and hips in flexion, the examiner notices if the extremities have the same length). Bilateral DDH is more difficult to diagnose without radiological imaging. The median walking age of children with DDH does not differ significantly from healthy children and during growth the patient may develop Trendelenburg sign (opposite side of pelvis dips during one legged stance).[35] Nowadays, DDH is diagnosed with ultrasonographic examination and is usually treated conservatively in infant age. In rare neglected cases, DDH leads to a progressive disorder that badly affects the every-day routine and life of an adolescent and an adult. The physicians must be suspicious for the presentation of the disorder and to suggest hip sonography with Graf method for every newborn as a screening method.

Although physical examination is very important, imaging of the infantile hip is appropriate, not only when there is the suspicion of DDH existence, but for all the newborn infants, because the usual tests (Barlow and Ortolani maneuvers) are not absolutely accurate.[36] Ultrasonograhy is the most useful option for the diagnosis of DDH. In 1980, Prof. Graf

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TABLE 1.

Graf classification

Type	Description	Bony Roof	Bony Rim	Cartilage Roof	α- angle (deg.)	β-angle (deg.)	Subtype
I	Mature hip	Good	Angular/ blunt	Covers the femoral head	≥ 60		Ia: β ≤ 55º Ib: β > 55º
IIa	Physiologically immature (< 3 months)	Deficient	Rounded	Covers the femoral head	50-59		IIa+ : α = 55o-59º IIα- : α = 50o-54º (at 6 weeks of age)
IIb	Delay of ossification (> 3 months)	Deficient	Rounded	Covers the femoral head	50-59		
IIc	Critical hip	Severely deficient	Rounded to flattened	Covers the femoral head	43-49	<77	Stable (β < 77º) or unstable (β > 77º) under pressure
D	Decentring hip	Severely deficient	Rounded to flattened	Displaced	43-49	>77	
III	Dislocated hip	Poor	Flattened	Pressed upward, perichondrium slopes cranially	< 43	>77	IIIa: hypoechoic cartilage acetabular roof IIIb: hyperechoic acetabular roof
IV	Dislocated hip	Poor	Flattened	Pressed downward, perichondrium dips caudally	< 43		

presented his technique to study and evaluate infantile hips for the possibility of DDH presentation. He suggested that ultrasonography study should be included as screening test in all newborns, regardless of any risk factor presence. Nowadays, hip sonography with the Graf method is included in mandatory screening examination of the newborns in Germany, Austria, Switzerland, Czech Republic, and in other European countries.[37] Additionally, other sonographic techniques have also been developed (e.g., the Harcke, Terjesen, and Suzuki methods), but the Graf method has dominated because of its standarized examination technique and of its high sensitivity and specificity.[38] Anatomy of the infantile hip is important for the Graf technique. The distal femur consists of hyaline cartilage (femoral head part of the neck and the trochanter) and between the cartilage and the osseous parts, there is the chondroosseous border, which guides the identification of the other anatomical structures during hip sonography. The femoral head has oval shape and the nucleus (ossification center) is seen in ultrasonographic examination 4–8 weeks earlier than in radiographs. The synovial fold penetrates the femoral neck .The joint capsule includes the femoral head with cranial direction to the rectus femoris muscle. Medially of the capsule is located the labrum of the acetabulum, which has triangular shape and is connected to the acetabular cartilaginous roof and is needed to be identified in order to have a proper ultrasound examination. Finally, the bony rim of the acetabulum is a very significant anatomical structure that distinguishes the osseous and cartilaginous parts of the acetabulum and gives us information about the coverage of the femoral head by osseous acetabulum. In ultrasonographic examination it is the spot where concavity switches to convexity in acetabulum.[39] In order to have accurate ultrasonographic examination, the physician must recognize all the following anatomical structures (**Fig. 1**): chondrooseous border, femoral head, synovial fold, joint capsule, labrum, hyaline cartilage, acetabulum (bone), and bony rim (concavity to convexity). In the evolution of the human species, the posterior osseous part of the acetabulum is more developed than the other parts because of the bipedal gait and the standing position, but the middle part is the more significant, because is the location where the load is transported from the corps to the lower limbs. For this reason, we select sections of the middle acetabulum to evaluate the joint in hip sonography of infant hip.[40] Radiography is useful for the study of DDH at the age of 4–6 months or more, when the ossification center of the femoral head appears and can be recorded in radiograph. Anteroposterior and frog position radiographs are to show possible reduction. In radiographs, the most useful signs are the Shenton line and the acetabular index. Radiography is also useful for the follow-up of infants to be treated with Frejka pillow and Pavlik harness and for the intraoperative imaging of the reduction when hip spica is put.[41] CT scan and MRI are widely used for the diagnosis of DDH. CT is mainly in adolescent and young adults as part of preoperative plan, before operations including pelvic and femoral osteotomies. MRI is impossible to be performed for neonates because it requires 30 minutes of isolation in the machine and is rarely used in adolescent and young adults to note labral abnormalities.[42]

The Graf Method

Graf method for the diagnosis of DDH in infants is the gold standard of hip sonography and has dominated on other ultrasonographic techniques because of its high sensitivity, specificity and relationship with a specific classification, which guides the physician to select the optimal treatment option.[43] Physicians who perform ultrasonographic examination should have deep knowledge of the anatomic area. As already, mentioned, for an accurate examination the examiner has to be able to see and recognize all the following structures: chondrooseous border, femoral head, synovial fold, joint capsule, labrum, hyaline cartilage, acetabular bony roof, bonny rim (concavity to convexity). In ultrasonographic examination with Graf method for the infant hip, the physician has to be able to find and signal the exact spot where concavity switches to convexity in acetabulum.[39] The second part of sonographic examination is the usability check. More specifically, during the examination the hip joint has to be depicted in a standardized plane. The lower limb of iliac bone is more or less the center of the acetabulum, next to the triradiate cartilage and it has to be visible during the examination to make it valid.[44] The examiner puts the ultrasound transducer in the coronal plane and moves backwards and forwards to illustrate the lower limb as big and clear as possible. Then he freezes the image and checks the plane. He rotates the transducer appropriately and repeats the forward-backwards movement. This process is repeated until lower limb and correct plane are both visible. For the accurate evaluation and classification of the infant hip joint with sonographic examination, Prof. Reinhard Graf described angles α an β, that are measured through the examination and give specific information if the joint is normal or if there is DDH. The examiner designs the bony roof line, a line that passes through the lower limb of ilium in contact to the lateral limit of osseous acetabulum and also the base line, a line that connects the point where the proximal perichondrium meets the iliac bone and is in contact to the outer border of the pelvic bone.[9] The angle that is formed between these two lines is the α angle and signals the osseous coverage of the femoral head by the acetabulum. Another line that begins from the bony rim and follows a straight direction to the labrum is called cartilage roof line and together, with the base line they include an angle (β angle), which defines the cartilaginous coverage of the femoral head by the acetabulum. Being able to measure these two lines gives the examiner the ability to classify the hip joint via Graf method and classification. (**Fig. 2**) The mother also takes part in the examination process, being present during the whole procedure and is responsible to keep the infant calm. The infant is put by the examiner in a specialized device (Sono-Fix) in lateral position with the right hip up. The examiner goes posteriorly of the infant, using the ultrasound machine (Sono-Guide), examining both hip joints by measuring angles α and β. The mother stays in the frontal side, calming the infant. Sometimes, after the ultrasonographic examination, physical examination with Barlow and Ortolani maneuvers is still used for the evaluation of the newborn.[45]

The measurement of α and β angles enables the physicians to classify easily the infantile hips and proceed to the optimal treatment. Graf classification has 4 types and each type is treated with specific option (no treatment, follow-up or medical intervention with conservative treatment). In Type I belong all infant hip joints with the following angle measurements: angle α 60º or more. When angle β is <55º , the subtype is Iα and when angle β is 55º or more, the subtype is Iβ. Both subtypes are normal and no treatment is needed. In Type II belong cases with angle α between 43º-59º. There are subtypes IIα (IIα+ and IIα-) , IIβ, IIc and D. Type IIα are the hip joints with angle α between 50º-59º in babies younger than 3 months of age. Type IIα+ describes immature joints that will probably grow normally the first 3 months (that means with an α angle more than 55º after 6 weeks) and is also a normal condition. Cases that are classified as Type IIα-, are not expected to develop normally in the first 3 months (α angle less than 55º after 6 weeks) and the hip joint needs specific treatment. In type IIβ the angle α is between 50º-59º in child older than 3 months and the joint is defined as dysplastic and also requires specific treatment. Type IIc hip joints with angle α between 43º-49º are considered as dysplastic and immediate treatment is needed. When angle β is bigger than 77º and angle α is between 43º-49º, the joint is considered as type D in Graf classification the femoral head is decentering (dislocating).[46] Finally, types III and IV include cases with angle α less than 43º . In these cases, the infants have decentered (dislocated) hips and immediate treatment is appropriate. In type III, the femoral head pusses upwards the cartilaginous roof and in contrast, in type IV hip joints, the femoral head is completely dislocated posteriorly and upwards and pushes the cartilaginous roof down.[47] (**Fig. 3,4**) Hip sonography with Graf method enables physicians to evaluate properly infantile hip joints, to classify DDH cases with accuracy and to begin with specific treatment when is required. Graf method requires a well trained and experienced physician, because mistakes in angles measurement lead to false results and to non-suitable treatment selection. The main mistakes during hip sonography that may lead to inaccurate measurements are wrong anatomical identification of the structures of the joint and tilting effects due to incorrect positioning of the infant.[48]

Discussion

Musculoskeletal ultrasonography is very useful for soft tissue evaluation and is also widely used to find fluid collection inside the muscle mass or in the joints, or to visualize cartilage and bone surface. With dynamic sonographic examination, examiners are able to assess tendon movement, ligamentous injury, nerve compression and joint.[49] Preventive ultrasound examination in infant age for the diagnosis of DDH has been widely worldwide. Graf method is the most popular among ultrasonographic methods for the diagnosis of DDH and with Graf classification, the responsible physicians are able to categorize the infantile hip joint and to proceed to the appropriate therapeutic protocol, if needed. In cases, when DDH is diagnosed and re-examination or therapeutic intervention is needed, informing the parents is very in order to prepare for the possible long-term treatment and compliance required to achieve centering of the hip joint without the need for surgery.[50] Hip sonography as screening method for the presence of DDH has been established as a standard process in many European countries. The main reason that hip sonography with Graf method should be mandatory screening test for all newborns isa that is a very accurate method that reduces the cases of neglected DDH who develop dysplastic hip joints in early adulthood and to reduce the complex pelvic operations in children with diagnosed DDH, by using the proper conservative treatment option set by Graf classification.[51] It is proven in literature that after the establishment of Graf method as standard screening method for DDH, the open reductions and acetabuloplasties have decreased dramatically.[52] It also seems that Graf method is

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cost-effective as it is much cheaper than the complex operations and rehabilitation programs that were required before the establishment of national screening programs.

The period of time between 4th and 6th week of life is the best for the hip sonography and it is important that the examiner is certified for the Graf method, because possible failures in the process cause errors in classification errors in treatment. Usually, the examiner is orthopedic surgeon or radiologist and is preferable that the examiner is also responsible for the treatment procedure.[53] Another important fact for the Graf method is that this technique is characterized by repeatability. Different studies have shown that experienced examiners have made the same measurements in the same infant hips and the same classification by reading the same ultrasound images, making the method suitable for interdisciplinary communication. Graf method is the most used sonographic technique for the screening of DDH in infants because of the correlation of the measurements (angles α and β) with the classification and therapy. The results have been investigated in literature and it has been proven that since the decade of 1980, when ultrasonographic examination of the hip have commenced (Graf 1980, Harcke 1984, Suzuki 1987 and Terjesen 1988), the neglected cases of DDH have decreased significantly, decreasing the number of adolescents and young adults with dysplastic hip joints.[54] Every newborn and not only when there are known predisposing factors (female gender, positive family history, breech position in utero, low birth weight, oligohydramnios etc) or suspicion during the clinical examination (positive Barlow and Ortolani tests)should undergo hip sonography as screening test.[55,56] Supposing that the screening was selective only to infants who present one or more of the risk factors, the number of the sonographic examinations would also be large, because in essence, only boys without any predisposing factor would be excluded from the examination. Furthermore, published studies form Germany and Austria, where the infant hip screening with Graf method is universal , have shown that after the establishment of this examination as mandatory screening test, very few open reductions have been carried out.[57,58]

According to sonographic findings, Graf method is more effective for children aged form 28-77 days. The best period for the sonographic examination is between the 4th and the 6th week, a period when the hip joint is demarcated well and the doctor is able to commence the appropriate treatment protocol if needed.[59] Graf method seems to be the most reliable method for the screening of DDH as it gives clear information for the pathology of the infantile hip joint and simultaneously enables the examiner to classify the examined joint in a strict classification. A study from Japan showed that the physicians who were trained in just one course for Graf method had a small learning curve and after the course fell safe and confident to perform hip sonography.[60] More orthopaedic surgeons should learn Graf method, because it allows them to understand a DDH case in very early and enables proper conservative treatment without needing complex pelvic or femoral osteotomies.

Outcome

Developmental Dysplasia of the Hip (DDH) is one of the most common musculoskeletal disorders in infants. In previous years the majority of DDH patients were unsuccessfully treated, with treatment protocols that required open reductions and there were also cases that were misdiagnosed and patients developed osteoarthritis of the hip joint in adolescence. The development of ultrasonographic techniques enabled the orthopedic surgeons to diagnose DDH in early stage and to perform the suitable treatment in time. Through the years, different sonographic techniques have been developed, static or dynamic which contributed to the reduce of neglected DDH cases. The most dominant sonographic technique for the diagnosis of DDH is Graf method. Graf method evaluates the osseous and the cartilaginous coverage of the femoral head by the acetabulum, measuring angles α and β respectively. This specific method has objective measurements that are based on anatomical correlations and correspond to a certain classification. Four different types (I, II, III, IV) and some subtypes are included in Graf classification for the DDH and each of them match-

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es with a specific treatment option. In many countries of Central Europe Graf sonographic method for the diagnosis of DDH is included in the mandatory preventive check-up for the infants in the first days after birth. It is proposed that ultrasonographic examination is appropriate only in infants with risk factors for DDH, but in this way no standarised guidelines can control for which children have to be examined. The preventive sonographic examination has increased the accuracy of finding DDH cases in relation to simple clinical examination (Barlow and Ortolani tests) and decreased the neglected DDH cases that required surgical treatment with major operations and pelvic osteotomies. As it has been proven that Graf method is the most accurate and useful, it has to spread furthermore. More orthopaedics should be trained in the this technique in order to be able to evaluate the infantile hip joints and to perform treatment where needed. Hip sonography with Graf method made DDH an easily cured disease treated with conservative means with great success, without requiring complex pelvic operations for the children or total hip arthroplasties in early age during adolescence or adulthood.

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Sioutis S, Kolovos S, Altsitzioglou P, Karampikas V, Koulalis D, Mavrogenis AF. Hip Sonography for Developmental Dysplasia of the Hip: The Graf Method. *Acta Orthop Trauma Hell* 2022; 73(4): 336-346.

Fracture of femoral neck in modular total hip arthroplasty: Report of 3 cases and review of the literature.

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ABSTRACT

Modular stems offer to surgeons the flexibility to adjust intraoperatively the femoral neck version independently of individual femoral geometry that theoretically can minimize the bearing surface wear, potential implant loosening and the rate of dislocation. Excellent functional outcomes and survivorship rates of modular stems has been reported in the literature but increasing modularity also renders several postulated disadvantages such as implant fracture, fretting and galvanic corrosion, pseudotumor formation and increased rate of revisions for stem loosening, dislocation and adverse local tissue reactions. We report here three cases of modular femoral neck fractures in patients who underwent a primary total hip arthroplasty in our department and also, we present a systematic review of similar cases in the literature trying to identify the incidence and the main risk factors.

KEY WORDS: Modular THA, fracture of the neck, corrosion, revision

Introduction

Modular stems in Total Hip Arthroplasty (THA) have been introduced to provide an anatomic restoration of native hip biomechanics, especially the femoral offset, that theoretically can minimize the bearing surface wear, potential implant loosening and the rate of dislocation [1-3]. Excellent mid- and long-term functional outcomes and survivorship of modular stems has been reported in the literature [4,5] but increasing modularity also renders several postulated disadvantages such as implant fracture, fretting and galvanic corrosion, pseudotumor formation and increased rate of revisions for stem loosening, dislocation and adverse local tissue reactions [6-8].

Modular neck fracture carries an estimated incidence of 0.26% and is considered a severe complication of modular THA as it usually requires a major revision stem surgery in an otherwise well-fixed femoral component [9-12]. We report three cases of modular femoral neck fractures in patients who underwent a primary THA in our department and

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Figure 1. *(a) preoperative x-ray of a 44-year-old patient with osteoarthritis, hip dysplasia and slipped capital femoral epiphysis, (b) 2-month postoperative x-ray after THA implantation, (c) fracture of the femoral neck at 4 years postoperatively, (d) intraoperative photo of the broken implant, (e) 3-month postoperative x-ray after revision surgery with a Wagner type stem and extended osteotomy and (f) last follow up x-ray at 3 years post-revision.*

Figure 2. *(a) preoperative x-ray of a 64-year-old patient with osteoarthritis of the hip, (b) 3-month postoperative x-ray after THA implantation, (c) fracture of the femoral neck at 5 years postoperatively, (d) 1-month postoperative x-ray after revision surgery with a Wagner type stem and extended osteotomy and (e) last follow up x-ray at 11 years post-revision.*

also, we present a systematic review of similar cases in the literature.

Cases Presentation

Case 1: A 44-year-old woman, with a BMI of 27.2 and a clear medical history, underwent a left THA in our department due to severe osteoarthritis in the presence of congenital hip dysplasia and slipped capital femoral epiphysis (Fig 1a). Through a mini-posterior approach, a metal-on-metal prosthesis was applied, with a 50 mm CONSERVE MOM acetabular shell, 44 mm medium metal head, and a no. 6 PROFEMUR®-L femoral stem with modular AR/VV 2 long-neck (Wright Medical Technology, Arlington, TN, USA) [Fig 1b]. The regular annual follow-up indicated undisputable integration of the prosthesis and excellent clinical performance. Four years later, she attended the Emergency Department with acute left hip pain and inability for weight bearing. Until that moment, no complications or symptoms by the THA were mentioned and full compliance to all respective instructions and restrictions was reported. On clinical examination she had pain during motion, restricted ROM and shortening of the left limp. Radiological control revealed a fracture of the femoral stem at the neck-stem junction area (Fig 1c). Two days later, she underwent revision THA through the old posterior approach. The fem-

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Figure 3. *(a) preoperative x-ray of a 64-year-old patient with hip osteoarthritis, (b) 15-days postoperative x-ray after THA implantation, (c) fracture of the femoral neck at 6 years postoperatively, (d,e) intraoperative photos of the extended osteotomy and the broken implant, (f) 3-month postoperative x-ray after revision surgery with a Wagner type stem.*

oral stem (Fig. 1d) was firmly integrated and was revised with an open book femoral osteotomy using a cementless Wagner 16mm/265mm prosthesis (Zimmer GmbH, Winterthur, Switzerland) with a short neck and a 44 mm metal head (Fig 1e). Two cerclage wires were used for femoral osteosynthesis. Intraoperative cultures revealed the presence of Enterococcus Faecium and the patient was hospitalized for 3 weeks receiving intravenously linezolid and meropenem. She was discharged afebrile following the usual mobilization protocols. At the 3-year follow up appointment (Fig. 1f) she had normal range of hip motion, painless weight-bearing, no limb-length discrepancy and she demonstrated a Harris-Hip score of 90.

Case 2. A 64-year-old man, with a BMI of 32.3, a medical history of Diabetes, Hyperlipidemia and Arterial Hypertension, underwent a right THA in our department because of primary hip osteoarthritis (Fig 2a). Through a mini-posterior approach an uncomplicated metal-on-metal prosthesis was applied, with 54mm CONSERVE MOM acetabular shell, 48mm medium metal head, and a no. 5 PROFEMUR-L® femoral stem with a long, high offset neck (Wright Medical Technology, Arlington, TN, USA). The postoperative follow-up up to 3 years indicated undisputable integration of the prosthesis and excellent clinical outcome (Fig 2b). Five years later, the patient was transferred to our hospital after a sudden right hip pain and subsequent fall at his home with inability to bear weight thereafter. Until that moment, no complications or symptoms by the THA were mentioned and full compliance to all respective instructions and restrictions was reported. The clinical examination revealed restricted ROM at the right hip, shortening of the right limp and weight bearing inability, because of the acute pain in the area. No other symptoms or signs were reported. The radiological examination revealed a fracture of the femoral stem at the femoral neck-stem junction area (Fig 2c). Three days later he underwent revision right THA through the old posterior approach. The femoral stem was firmly integrated and revised, via an open book femoral osteotomy, to a cementless Wagner 16mm/265mm femoral stem with a standard neck and a 48mm metal head. Three cerclage wires were used for the femoral osteosynthesis and 2 Ethibond no.5 sutures for stabilization of the greater trochanter. The postoperative x-ray control of the revised femoral stem indicated an acceptable femoral osteosynthesis and mounting of the new prosthesis (Fig 2d). The patient was hospitalized for 9 days in total and was released following the usual mobilization protocols. At his last follow up evaluation, 11 years post revision surgery (Fig 2e) he had a painless hip motion, 1 cm length discrepancy without any compromise during walking and a Harris Hip Score of 87.

Case 3. A 64-year-old man with a BMI of 33.4, a medical history of chronic renal failure, left pyonephrosis (fistula), arterial hypertension, eye cataract and hyperuricemia, underwent a right THA because of primary osteoarthritis of his right hip (Fig 3a). Through a mini-posterior approach, an uncom-

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TABLE 1.

Case reports of modular stem fractures in the literature

Study / (year)	No pts	Implant type	Gender	Age	BMI	Failure (m)	Symptoms
1. Lee[15] (2001)	2	Exactech Exactech	male male	69 53	29.3 36	43 45	sudden pain sudden pain
2. Botti[16] (2005)	1	AML; DePuy	male	90	27.2	176	one month pain
3. Skendzel[27] (2010)	2	Profemur Z Profemur Z	male male	55 67	31.2 34.6	44 29	Hip pain, creaking, sudden sensation of hip instability Hip pain, inability to ambulate, creaking
4. Wilson[33] (2010)	1	Profemur Z	male	62	25.6	25	sudden hip pain and inability
5. Wright[3]4 (2010)	1	Profemur Z	male	49	39.3	44	fall from standing height
6. Atwood[3]5 (2010)	1	Profemur Z	male	30	29	22	fall from standing height
7. Dangles[36] (2010)	1	Wright	male	66	NA	42	sudden hip pain and inability
8. Kohler[37] (2010)	2	Metha Metha	male male	69 52	27.8 27.2	18 20	sudden hip pain sudden hip pain
9. Paliwal[38] (2010)	1	Acumatch M-series	male	43	36.5	38	NA
10. Gilbert[39] (2011)	1	Profemur Z	male	56	NA	72	sudden hip pain
11. Vučajnk[17] (2012)	1	GSP	male	56	31.6	144	fall from standing height
12. Ellman[18] (2013)	1	Profemur Z	male	59	29.6	60	hip and groin pain, clicking, subjective instability
13. Sotereanos[19] (2013)	1	Kinectiv stem (Zimmer)	male	49	36.6	15	step off 0.5 m truck - pain
14. Mencière[20] (2014)	1	ProfemurL	female	66	28.7	22	physical activity - hip instability
15. Baratz[21] (2014)	1	Meridian	female	61	32.4	87	sudden hip pain
16. Hernandez[22] (2015)	1	Profemur	male	53	28	42	Sudden hip pain
17. Trieb[23] (2015)	1	NA	female	60	32.27	144	Fall
18. Fokter[24] (2016)	6	Profemur M GSP Profemur Z Profemur Z Profemur Z GSP	male male male male male male	53 42 54 57 37 56	28 30 33 35 34 32	42 37.2 27.6 62.4 72 144	sudden hip pain sudden hip pain sudden hip pain sudden hip pain sudden hip pain sudden hip pain
19. Fokter[25] (2016)	1	Profemur Z	female	54	39.4	93.6	sudden hip pain
20. Ceretti[26] (2016)	1	Metha	female	43	38.6	29	sudden hip pain and inability, clicking
21. Uchiyama[28] (2017)	1	MODULUS	Female	47	32.8	44	carry weight - sudden pain - hip instability
22. Murena[29] (2019)	2	Profemur L	male	48	28.02	48	jump from 1m height - crack
		Profemur	male	77	28.73	48	sudden hip pain
23. Regis[30] (2019)	1	SCL stem	male	64	32.6	144	fall from standing height
24. Lanzuti[31] (2019)	1	Profemur Gladiator	male	66	27.8	45	NA
25. Fokter[32] (2021)	1 (bilateral)	An.C.A. Fit An.C.A. Fit	male	38	31.5	240 (R) 36 (L)	sudden hip pain sudden hip pain

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plicated metal-on-polyethylene prosthesis was applied with a 54mm PERFECTA acetabular shell, 28 acetabular liner, 28mm/10.5 metal head, and a no. 6 PROFEMUR-L® femoral stem with modular AR 15º long neck (Wright Medical Technology, Arlington, TN, USA). The postoperative x-ray control of the THA indicated a totally acceptable mounting and orientation of the prosthesis (Fig 3b). The patient was hospitalized for 7 days, with no postoperative complications and he followed the usual mobilization protocols having an excellent clinical and radiological outcome at his annual examinations. Six years later, he experienced an acute right hip pain while dancing and he fell to the ground being unable for full weight bearing. Until that moment, no complications or symptoms by the THA were mentioned and full compliance to all respective instructions and restrictions was reported. He was transferred to the hospital whereas a radiological control of the right hip revealed a fracture of the femoral stem at the femoral neck-stem junction area (Fig 3c). Three days later he underwent revision right THA through the old posterior approach. The femoral stem was fully integrated and an extended femoral osteotomy was performed (Fig 3d,e) for removal. A cementless Wagner 17mm/265mm femoral stem prosthesis with a standard neck and 28mm standard metal head was applied. Four cerclage wires were used for the femoral and greater trochanter osteosynthesis. There were no intraoperative complications, and the postoperative x-ray control of the revised femoral stem indicated an acceptable femoral osteosynthesis and mounting of the new prosthesis (Fig 3f). The patient was hospitalized for 17 days because of a substantiated urinary tract infection with Pseudomonas Aeruginosa and was discharged following the usual mobilization protocols. At his last follow up 9 years postoperatively, he demonstrated a Harris-Hip score of 90 but he refused to undergo a new radiological examination.

Discussion

Modular stems offer to surgeons the flexibility to adjust intraoperatively the neck version and limb length independently of stem size and individual femoral geometry. Satisfying functional outcomes have been demonstrated by single center studies after primary THA with modular femoral stems; Vanbiervliet et. al. [13] presented a 100% survivorship of the implant (stem and modular neck) at a mean of 6.5 years without reporting signs of osteolysis or calcar resorption, radiolucent lines, either at the stem-cement or cement-bone interface or important stem subsidence. Krishnan et. al. [14] stated that there is insufficient evidence to confirm the perceived benefits of THA modularity as the additional metal junction is vulnerable to mechanical failure, component disassociation and mechanically assisted crevice corrosion. Other studies [1,6,7] have demonstrated acceptable mid-term clinical results presenting a profile of high risk of early implant failure in males with high BMI, requiring larger neck, offset or head and CoCr material. The published overall complication and revision rate of modular femoral stems are 3.95% and 6.5%, in respect [1, 6]. Colas et al. [8] reported an increased hazard ratio (1.26%) of revision in 324.108 patients with modular stems, using the French national health-insurance databases; after dealing with cause-specific revision, exchangeable neck THAs had a higher incidence of revision for implant failure or periprosthetic fracture (1.68%), and for mechanical complications (1.27%).

Our systematic literature review revealed a total of 25 articles including 35 cases of modular neck fractures after primary THA in 34 patients [15-39] (Table 1). In 20/35 cases the fractured stem was of a PROFEMUR type (Wright Medical Technology, Arlington, TN, USA). The mean age of the patients in the primary THA was 55.85±2.05 years, 28 patients (82.35%) were male, the average BMI was 31.63±0.68 kg/m^2 and the majority of the modular necks were long (29/35: 82.85%). The incidence of modular neck fracture occurred in average 64.53±8.8 months after the primary THA. Most of the patients (24: 68.6%) referred an atraumatic cause, presented with sudden hip pain and hip instability. The treatment consisted of revision procedure; in 27 (77.1%) of the cases the surgeons reported inability to remove the modular neck from the femoral component, thus extended trochanteric osteotomy was needed in order to revise the femoral component.

With the exception of the young female patient with a normal BMI, the other two patients demonstrated all the proposed risk factors for neck fracturing: male gender, > BMI, long modular neck. All of them did not report previously any sign of thigh or hip pain, squeaking or instability and underwent an extended trochanteric osteotomy for stem exchange with good final outcome. Other risk factors that could affect the neck area of the modular femoral stems are the increased lateral offset, varus stem positioning and inconsistency in the assembly of modular heads due to the force of impaction, the vector of applied force and the contamination of the interface as well as defects in welding of neck to the prothesis, the heavy laser etching in the region and the crevice corrosion in the head-neck junction [15,16,39-41].

Conclusion

THA modularity can restore the native hip biomechanics and provide excellent clinical outcome and survivorship, however there is a group of patients in which surgeons should be cautious selecting modular stems due to the increased risk of modular neck fracture. Male patients with increased BMI, and long modular necks should be followed up closely with serial x-rays for early signs of corrosion. If a fracture occurs, an extended osteotomy should be planned for stem revision as usually the broken neck cannot be removed.

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Panagopoulos A, Solou K, Tatani I, Tatarakis D, Megas P. Fracture of femoral neck in modular total hip arthroplasty: Report of 3 cases and review of the literature. *Acta Orthop Trauma Hell* 2022; 73(4): 347-354.

ACTA

YOUNG SCIENTISTS' PAGES

"The effect of mechanical insufflation – exsufflation on spinal cord injury patients with respiratory problems. A systematic scoping review"

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ABSTRACT

Respiratory dysfunction remains a significant cause of morbidity and mortality after spinal cord injury (SCI).
The purpose of this scoping review is to investigate the effectiveness of mechanical insufflation - exsufflation (MI-E) device, for cough augmentation and secretion management, in patients with SCI.
Electronic databases Medline (pubmed), Cochrane, PEDro, DynaMed, CINALH, and electronic libraries Scopus, ScienceDirect and Google Scholar were searched for relevant literature.
Inclusion criteria concerned studies referring to traumatic spinal cord injuries, carried out from 1/1/2000 until 9/12/2021, written in English language. All types of articles were accepted. Studies on children, animals and neuromuscular diseases as well as book chapters and article abstracts were excluded.
The articles were searched systematically. Fifteen studies were found to meet the inclusion criteria. The search revealed 1 randomized control trial (RCT), 5 retrospective studies, 2 cross-sectional studies, 3 observational studies and 4 case reports.
The reviewed evidence of the utilization of MI-E device resulted to improved pulmonary parameters, shorter hospitalization and successful weaning in patients with SCIs. Although, the reviewed evidence is weak and limited, in clinical practice the usage of MI-E device in patients with SCIs, is encouraging.

KEYWORDS: spinal cord injuries, quadriplegia, tetraplegia, mechanical insufflation - exsufflation, cough assist

Introduction

The term 'spinal cord injury (SCI)' refers to damage to the spinal cord resulting from trauma (e.g. a car crash) or from disease or degeneration (e.g. cancer) [1]. Spinal cord injuries often cause disabilities and have social and economic impact on those who suffer from it and on the society. An epidemiological study of spinal cord injuries across 22 European countries (2012), record 1840

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deaths, of which 1084 (59%) were males [2]. Deaths from spinal cord injuries account for 2% (95% CI: 1.8% to 2.2%) of the overall injury related mortality. The 61% of the fatal spinal cord injuries occur to the cervical spine area [2].

In addition to deaths, various other problems arise, depending on the extent and the level of the spinal cord damage. A crucial complication of the spinal cord injury is respiratory dysfunction, which is associated with mortality and morbidity and directly depends on the level and the completeness of the trauma [10].

Higher injury levels affect significantly the respiratory muscles. Therefore, the inspiratory capacity and the expiratory muscle force are decreased, resulting in an inadequate cough [3]. Also, cervical cord injury destroys sympathetic pathways and parasympathetic system domains, which leads to mucus increase [4]. In clinical practice, an impaired cough limits the ability to remove the secretions, resulting to atelectasis, infection and finally to death.

In patients with SCIs, there is limited intervention of cough augmentation and secretion management. A technique, which enhances coughing capacity to spinal cord injured patients, is the utilization of the insufflation – exsufflation device.

This device has been commonly used for cough augmentation and secretion removal, in population with neuromuscular diseases [5, 6]. However, in patients with spinal cord injuries, the evidence is limited.

The purpose of this scoping review is to explore the current evidence regarding the effectiveness of the mechanical insufflation - exsufflation device, in spinal cord injured patients, for cough augmentation and secretion management, in order to enhance pulmonary parameters, to avoid intubation or to succeed weaning and to reduce hospitalization.The study followed the recommendations proposed by Arksey and O'Malley [14].

Study questions

1. Does the mechanical insufflation – exsufflation device (MI-E) enhance cough and respiratory parameters to patients with spinal cord injury (SCI)?
2. Is there an appropriate protocol used by the therapists?
3. What are the suitable settings for the MI-E device?
4. Are the weaning time and the hospitalization reduced?
5. What are the complications which follow the utilization of MI-E device?

Search strategy

The scoping review conducted by searching: a) electronic databases of Medline (PubMed), Cochrane, PEDro, DynaMed, CINAHL, b) electronic libraries Scopus, Sciencedirect and c) the link of the Hellenic Academic Libraries. Additionally, Google Scholar was also searched for relevant literature and manual reference list searches of the included studies were also performed (Table 1). The literature searches, the screening as well as the appraisal of the evidence were performed by the first author of this study (KH).

The keywords used were: "spinal cord injuries, quadriplegia, tetraplegia, mechanical insufflation exsufflation, cough assist".

DynaMed, CINAHL, Scopus, Sciencedirect and HeAL -link were searched through a common platform of the National and Kapodistrian University of Athens.

Inclusion criteria

Only papers with traumatic spinal cord injuries were accepted and the electronic search timeframe ranged between 1/1/2000 to 9/12/2021. There were no exclusions based on the age, gender or the level of injury. The included articles were in English and due to lack of high quality RCTs, all types of research articles were included.

Exclusion criteria

Studies which used children, animals, and other neuromuscular diseases were excluded. Also, book chapters, abstracts and grey literature were excluded. Finally, the reviews were excluded, because their reviewed articles were also found by the search strategy of the present review.

Risk of bias

Although the assessment of the methodological quality of the literature is not necessary in scoping reviews [7] an attempt was made in this review to quality appraise the included studies. The only randomized control trial that found and included in this review was quality appraised with the PEDro scale [8], while the Sackett scale was used to classify the studies to different levels of evidence [9].

Discussion

The search strategy revealed 454 articles in total. After screening the titles and the abstracts, 392 articles were excluded as not relevant. The full-text of the 62 articles was reviewed, and 15 were found to meet the inclusion and exclusion criteria (flowchart).

The results were: 1 randomized control trial (level 2b), 5 retrospective studies (level 3), 2 cross-sectional studies (level 4), 2 observational studies (level 4), 1 observational study (level 5), and 4 case reports (level 5) (table 2). The methodological quality of the RCT was quite low (1/10 in PEDro scale). The retrieved articles were grouped and presented, according to the above-mentioned questions.

Sample characteristics

The sample of the studies ranged from 1 to 86 adult patients. In two studies, the sample size was not mentioned [15, 36]. In total, the sample size of the twelve studies combined was 290 patients. Approximately, the 80% of the patients were males and the 20% females. The age of the sample patients ranged from 16-75 years. Neurological level of injury ranged from C1-T3 [15, 18, 21, 22, 23, 24, 25, 26, 37, 40, 41] and Asia Impairment Scale (AIS) / American Spinal Injury Association (ASIA) classification ranged from A-D. Five studies were referred to AIS /ASIA A injuries [15, 18, 22, 23, 41] and three studies included injuries of AIS / ASIA A-D [21, 24, 26]. Most common SCI was classified in AIS / ASIA A. However, one study did not include injuries of AIS / ASIA A [25].

Of the fifteen studies, five included acute SCIs [15, 22, 23, 24, 41], one study subacute [18], two chronic SCIs [25, 26], one study had mixed acute and chronic SCIs [27] and in four studies the chronicity of the SCI and its neurological level was unspecified [17, 27, 37, 40]. Additionally, two studies included mixed population [17, 40] (subjects with neuromuscular diseases, obesity hypoventilation syndrome, restrictive pulmonary syndromes and SCI). Finally, two of the fifteen studies explored therapists' experiences on using mechanical insufflation – exsufflation device [16, 19].

Patients' and therapists' experience / questionnaires

Four of the fifteen studies used as measurement tools, questionnaires [16, 19, 26, 27] and they were retrospective studies. One survey was referred to patients and examined their comfort by a 5-point Likert scale and technique preference (MI-E and endotracheal suctioning) by questions [26]. Two articles were referred to therapists and their experiences on using MI-E to patients with SCI [16, 19]. Finally, one survey, which was used questionnaire, had mixed sample, therapists and patients with SCI [27].

Schmitt et al. [27] and Garstang et al. [26] reported that patients were satisfied and preferred the MI-E device rather than the endotracheal suctioning for secretion removal. Moreover, these authors found that there was lack of the device utilization in many institutions.

Similarly, Rose et al [19] questioned Canadian and UK therapists about the utilization of MI-E device. They found moderate awareness of the guidelines for the assessment of cough effectiveness and airway-clearance interventions, which hinder therapists' adoption and performance [34]. Also, Cough peak flow (CPF) reported as the most common cough assessment for both countries.

This is in line with Prevost et al [16], who used a questionnaire to assess the MI-E utilization (protocols, guidelines, MI-E parameters, cough assessment). They found that one-third of the Ontario hospitals researched had an MIE device. The device applied in various pressures. The most common (54%) pressure spans were 35 cmH_2O to 40 cmH_2O. Similar results were found by Schmitt et al [27]. However, the use of protocols and guidelines were: 70% had a specific protocol and 29% had staff competencies, in contrary to Schmitt et al [27] who found: 56% had a specific protocol and 63% had staff competencies. The MI-E device was commonly assessed by Vital Capacity (VC), Peak Cough Flow (CPF), maximal inspiratory/expiratory pressures.

Hospitalization

Hospitalization was evaluated in patients with SCIs by Crew et al. [21]. This was a retrospective cohort study of 40 patients with SCIs who were prescribed MI-E devices for outpatient use. There was a nonsignificant reduction in respiratory hospitalization rates by 34% (0.314/y before MIE vs 0.208/y after MIE; $p = 0.21$). A post hoc subgroup analysis showed a significant reduction in respiratory hospitalizations per year for patients with smoking history ($p=0.03$). Furthermore, Ehsanian et al. [41] present the pharyngeal clearance maneuver, a technique which uses a modified application of the mechanical insufflation-exsufflation device to remove secretions above the tracheostomy cuff during cuff deflation. The proposed

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technique eliminates the risk of pneumonia from aspiration of accumulated secretions and contributes to success rates of ventilator liberation. Also, the reduction in risk of aspiration potentially allows the patient to recover neurologically, to be active and to reduce the risk of mortality associated with pneumonia [42].

Pulmonary Parameter Outcome.

Pulmonary parameters were evaluated in almost all studies. CPF was the most common indicator. The only randomized control trial was the review of Pillastrini et al. [15] examining the effect of MI-E on respiratory volumes and flows during bronchial clearance. The experimental group was treated with manual respiratory physiotherapy in conjunction with MI-E (pressure: 15 cmH_2O - 45 cmH_2O). The control group was treated with manual respiratory physiotherapy only. At the end of the treatment the experimental group showed a significant increase in Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 s (FEV1) and Peak Expiratory Flow (PEF) ($P<0.01$). The control group did not change significantly. That was in line to the findings of Bach et al [20].

The observational study by Sugiyama et al. [25] evaluated the effects of MI-E on volume change of the chest wall and each compartment, in 14 male patients with cervical spinal cord injury using optoelectronic plethysmography. The compliance was evaluated by the summation of the volume of the upper thorax (V_{UT}), the volume of the lower thorax (V_{LT}), and the volume of the abdomen (V_{AB}): $V_{chestwall}=V_{UT}+V_{LT}+V_{AB.}$ The volume of the chest wall and the upper and lower thorax compartments were significantly greater during MI-E ≥ ±30 cmH_2O compared to deep breath. However, the appliance of MI-E had no significant difference to the volume of the upper and lower thorax and abdomen compartment in the pressures range between ±30 and ±50 cmH_2O. Goldman et al. [36] described the compliance of the abdominal wall of quadriplegic participants. They found that compliance was 2 times greater than the normal subjects. FVC, FEV, maximal Inspiratory/Expiratory Pressures (PImax, PEmax) and CPF were also improved.

Moreover, Chang et al [23] in a case report, presented their experience of a successful weaning by using M-mode ultrasonography and a cough-assist device for secretion removal in a quadriplegic patient neurological level C2 (near complete quadriplegia). The case was a man 65 years old. Criteria for weaning were diaphragm assessment and the parameter PCF. However, his respiratory muscles were weak and secretion removal was inadequate. Diaphragm was evaluated by M-mode ultrasonography and PCF was enhanced by MI-E device. Extubation was successful and the patient was stable with good vital signs and arterial blood gases from 2 hours after extubation for 5 days and then he was transferred to his hometown hospital. This is further supported by studies that suggest that the MI-E is preferable by the patients with SCIs than other techniques [26, 27, 37]. Furthermore, the utilization of MI-E can induce low rates of ventilator pneumonia and has reduced the complications of the respiratory impairment [37]. Vital capacity, forced vital capacity, peak cough flow and arterial blood gases were also, improved.

Additionally, McCaughey et al. [18] conducted a case report to evaluate the combination of the Abdominal Functional Electrical Stimulation (AFES) with the MI-E, during a 14 week period, in a tetraplegic patient. FVC and PEF were measured before and after the intervention. The parameters of the MI-E device were chosen according to clinical judgement and the pressures used were lower when compared to the standard clinical practice [27, 33], because the patient was not in the need of intensive secretion removal. The patient made 5 unassisted insufflation - exsufflation cycles and another 5 assisted cycles by AFES and MI-E. There was no statistically significant difference between stimulated and unstimulated expiratory volume (EV) ($P=0.64$) and peak expiratory flow (PEF) ($p=0.44$). Nevertheless, in most of the sessions, stimulated EV and PEF were higher than the unstimulated and therefore, there was the potential for these parameters to be clinically significant. Nevertheless, judging by the increased respiratory volumes, the combination of AFES and MI-E perhaps is more valuable in secretion removal than MI-E alone. Also, AFES and MI-E were synchronized with 96.7% accuracy.

Finally, Fauzi et al. [22] in their case report described two males with spinal cord injuries. In this review there will be reference only to the one man, who had a traumatic injury. The second man had a cord tumor and according to exclusion criteria, he will be excluded. The first man had a C5 fracture dislocation (ASIA A) and difficulty in weaning. His therapy regime in the ICU was respiratory physiotherapy, endotracheal suctioning, mucol-

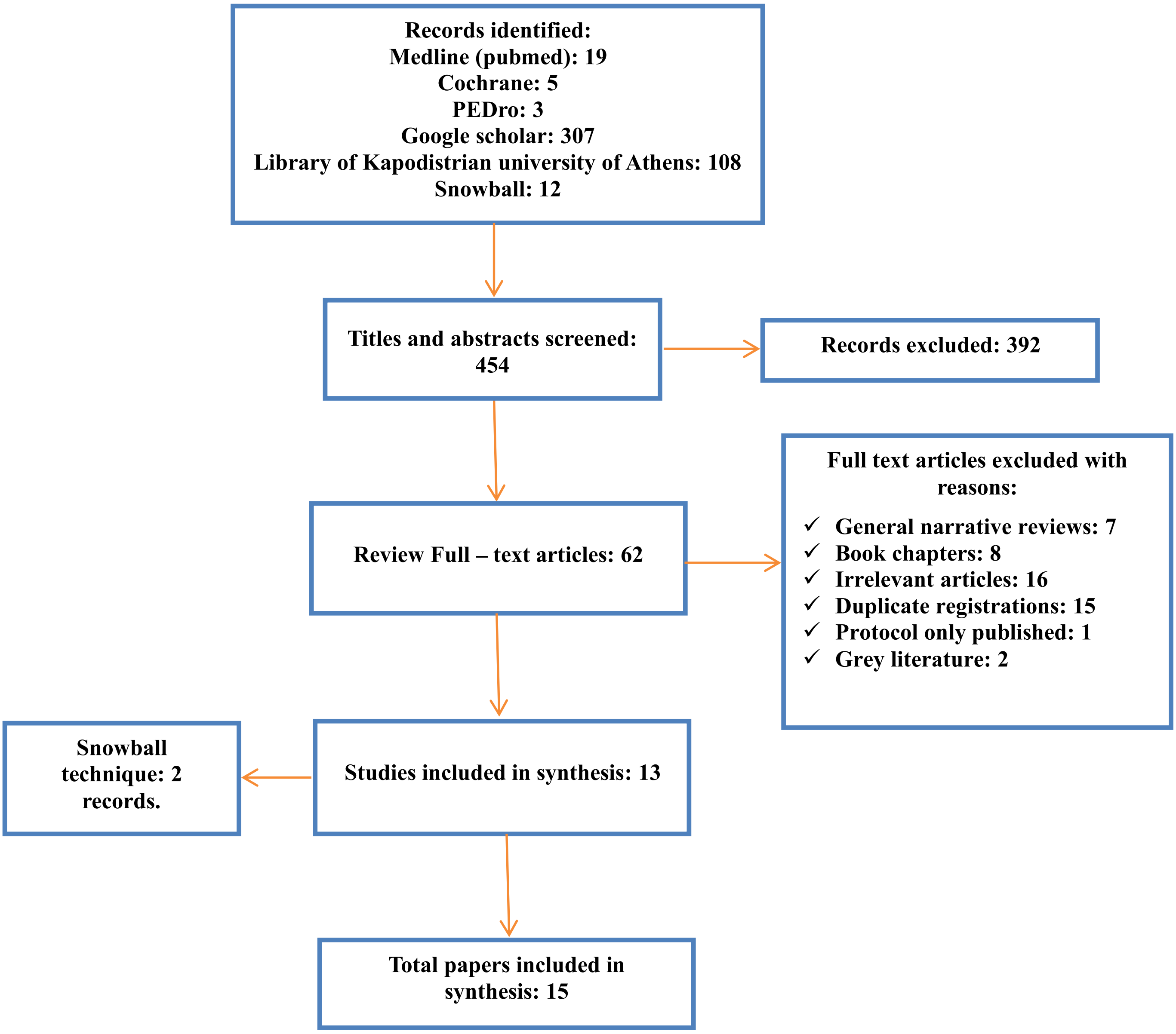

Figure1: Flowchart

ytic agents and MIE therapy. The utilization of MIE was assessed by PCF. He weaned to room air at four months postoperatively. There was a significant increase in FVC and FEV1 by the MI-E utilization similar to the findings reported by Pillastrini et al. [15].

Weaning / decanulation

Four surveys included in this review studied the weaning time and decannulation in patients with SCIs.

Bach et al. [17] studied the efficacy of MI-E on decannulation of 61 patients with severe respiratory muscle insufficiency. The patients with SCIs were only 4 and their mean age was 43.4 years. The VC of 61 patients increased significantly ($p < 0.001$) from presentation to immediately pre-decannulation and in the 3 weeks post-decannulation. For patients with SCIs, vital capacity mean, was 775ml (SD =358), 3 weeks post-decannulation. All patients, apart from one with SCI were decannulated. Saturation of pO_2 (SpO_2) and CPF were also improved.

A year later, the research team of Bach [40] found that unweanable subjects, with respiratory muscle failure can firstly be extubated to continuous noninvasive ventilatory support (CNVS) and MIE. Then they can normalize their O2 saturation and increase their vital capacity (VC) in order to facilitate their extubation ($p < 0.001$). Ninety seven of ninety eight subjects were successfully extubated despite 45 having been CNVS-dependent for 4 months to 18 y before being intubated. Weaning from CNVS to part-time noninvasive ventilatory support (NVS) was achieved by all 52 subjects who had not been CNVS-dependent before intubation. Bach and the other researchers accept that the use of the MI-E device is beneficial to any patient with airway secretions and inadequate cough flows.

Additionally, Wong et al. [24] conducted a retrospective study to examine the efficacy of High Tidal Volume Ventilation (HVtV), Intrapulmonary Percussive Ventilation (IPV) and MIE treatments on the respiratory status of patients with acute high level cervical injury. The sample consisted of 24 patients and 23 were weaned to room air in an average time of 16.3 days (SD 20.8). The above intervention improved respiratory parameters within 7 days of its application. A secondary outcome was tidal volume (average tidal volume after application: 1037.50 mL; SD 140.8). HVtV, IPV and MIE for mucus removal for the patients with SCIs were suggested as a clinical guideline of the Consortium for Spinal Cord Medicine. However, according to Schimtt et al. [27] only the 64% of the therapists of the Acute Rehabilitation Facility, were using the MIE device. Wong et al [24] also used the three interventions to almost all patients and they could not distinguish which one was more effective.

Finally, Liszner et al. [37] made an effort to establish MI-E guidelines for patients with SCIs. They found low rate of ventilator pneumonia (<1%) and low incidence of atelectasis, when the MI-E was used. Weaning success was about 97%, for injuries below C4 with the MI-E utilization.

Protocols/ settings of MI-E device

There was variation in the settings and the way that the MI-E device was used. In five studies, the time of inhale and exhale was 2 and 3 sec respectively [15, 18, 21, 23, 26]. In the other eight studies, there was no mention about the inhale and exhale time [17, 19, 22, 24, 25, 27, 40, 41]. However, the ideal insufflation time to provide higher exsufflation volume and flow, according to Sancho et al. [33] is 3 sec. Insufflation time less than 3 sec probably will not expand the lungs completely. However, according to Prevost et al. [16] most of the therapists (40%) apply more than 3 sec inspiration time.

In the present review, the applied pressures of the device ranged from ±15 cmH_2O to ±70 cmH_2O. Insufflation-exsufflation spans <±35 cmH2O achieve expiratory flows less than 160 L/min, which are inadequate to expand completely the lungs [34]. Moreover, Winck et al. found significant improvement in blood oxygen saturation only after 40 cmH_2O [39]. Prevost et al. [16] described that pressures of ±35 to ±40 cmH_2O were used by most of the therapists. Bach et al. [17, 40] in both of their studies, used the MI-E device in pressure range of 50 – 70 cmH_2O and Ehsanianet al. used the MI-E device in lower pressure range (40–60 cmH_2O) [41].

Additionally, in the study of Rose et al. [19] the device settings were not mentioned.

Therefore, based on the current evidence, it is not clear about which are the most suitable device settings for insufflation time and pressure range.

Considering of the frequency that the device was applied, Prevost et al [16] reported that when patients were stable, most of the therapists performed MI-E two times per day. In contrast, during infection, 3, 4 or more times per day may be needed. Also, Wong et al. [24] and Bach et al. [17] suggest its use every 2 to 4 hours around the clock. Bach et al. [40] in their recent study of 2015 applied MI-E device every hour around the clock.

Moreover, according to Prevost et al. [16] and Schmitt et al. [27] most therapists followed a specific protocol, which however was not described or justified.

In six studies, MI-E was combined with other therapies, such as Intrapulmonary Percussive Ventilation (IPV), High frequency percussive ventilation (HFPV), bronchoscopy, mucolytic agents, chest physiotherapy, endotracheal suctioning and Abdominal Functional Electrical Stimulation [15, 16, 18, 22, 23, 24].

Finally, in the study of Liszner et al. [37], the pressures of the MI-E, which were used, were the following: For patients with tracheostomy the applied pressure was ±35 cmH_2O and for patients with mask or mouthpiece interface the applied pressure was ±15 cmH_2O. The pressures were gradually increased until the limit of 55 cmH_2O. The

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time of insufflation was 2 to 3 sec and of exsufflation 3 to 4 sec. There were 4 -5 cycles max.

MI-E complications

The complications of the use of MI-E devices are not common and can include: nausea, bradycardia, tachycardia, and abdominal distension [11]. Additional, exsufflation can cause a rapid decrease of intrathoracic pressure and consequently may provoke gastroesophageal reflux and aspiration [12]. However, in clinical practice, this complication is rarely reported [13]. Finally, Sivasothy et al, have described barotrauma as complication [38].

Strength and limitations

This is the first review that systematically searched and summarized the evidence regarding the use of MI-E device in SCI patients. However, the poor methodological quality and the different study designs of the included studies increase the risk of bias. Most of the studies were observational and case studies and there was only 1 low quality RCT (PEDro 1/10).

Additionally, the included studies had generally small and heterogeneous sample sizes and lacked control groups of randomization procedures. Also, various protocols and parameters of MI-E device were used and in most of the studies the methodology was not described clearly.

Finally, the introduction of systematic bias in this review due to inclusion of literature published only in English is unlikely, due to fact that English is the main language used in conventional medicine publications [28-32].

Conclusion

In this scoping review, an attempt was made to identify and summarize the evidence regarding the utilization of MI-E device in patients with spinal cord injury. Most studies suggested that the use of the MI-E device in patients with SCI's, resulted to better pulmonary parameters, shorter hospitalization, and successful weaning and this is encouraging. However, no firm conclusions can be drawn due to the current limited, heterogeneous, and low-quality evidence. It is imperative that further high-quality research is required to explore the efficacy of the MI-E device in SCI patients.

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Kaliva H and Vlamis J. The effect of mechanical insufflation – exsufflation on spinal cord injury patients with respiratory problems. A systematic scoping review. *Acta Orthop Trauma Hell* 2022; 73(4): 356-364.

Spasticity and pain: the effect on quality of life in individuals with spinal cord injury

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ABSTRACT

The following article is a literature review on how spasticity and pain affect the quality of life in individuals with spinal cord injury (SCI). Spinal cord injury affects a patient's life in many ways, particularly following initial trauma, to confront numerous secondary health conditions. Spasticity and pain represent major SCI complications. Another significant factor for persons with spinal cord injury is the quality of their life and how it is affected by spasticity and pain. Patients with SCI demonstrate lower quality of life than the general population but there also seems to exist a negative correlation among pain, spasticity and quality of life. Patients that experience pain or/and spasticity have lower quality of life as it is indicated by some studies. In addition, there is a possibility that spasticity and pain correlate in a bilateral way via common neural mechanisms. However, quality of life is affected by many factors and it is difficult to conduct specific results without further research.

KEYWORDS: spinal cord injury, pain, spasticity, quality of life, life satisfaction

Introduction

During the last decades, with the progress in medicine and rehabilitation, patients with spinal cord injury (SCI) demonstrate higher survival rate and life expectancy than before [1-5]. Following initial post-injury phase, people with SCI have to come up against secondary health issues, with the most common being loss of locomotor function and sensation, pressure ulcers, bladder and bowel disorders, sexual and autonomic dysfunction, pain and spasticity [3,5-7].

Up to 70% of SCI patients develop spasticity within the first year after injury [6,8]. Spasticity has been defined by Pandyan et al. to be 'a disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles' [9]. Spasticity can create difficulties in patients' everyday life and activities, causing mobility and transfer disorders, contractures, pain, hygiene and personal care problems, as well as health care systems' economic burden [1,8,10,11]. However, spasticity can present several benefits including improved circulation, prevention of thrombosis and muscle weakness and facilitation of daily activities [11,12].

Pain has also a high prevalence in patients with SCI, approximately 67% of them experience pain [4,5,6,13-18]. The most common types of pain are nociceptive (musculoskeletal), neuropathic and visceral [5,6,17,19], but in most cases, patients present pain of more than

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one aitiology [17,18,20]. Pain interferes with patients' everyday activities, sexuality, sleep, mood and has a negative psychosocial impact, leading to a higher risk of depression [14-18,20]. Although, neuropathic and nociceptive pain demonstrate no significant difference in prevalence, neuropathic pain is described by the patients as more severe [5,6,14,18,21].

It has been shown that in SCI patients, pain and spasticity overlap and this can be explained as they both result from central neuroplastic changes following SCI. Spasms or excessive tone may cause pain and both of them can be evoked by non-harmful stimuli. Moreover, SCI patients with pain tend to present spasticity symptoms compared with those who does not have pain [6,22].

Patients with SCI have lower quality of life (Qol) than the general population [3,5,6,8,16,23]. To provide SCI patients optimal treatment, one has to understand how major secondary problems, such us pain and spasticity affect the quality of their life.

The database used for tis literature review was Pubmed. From the 630 titles and abstracts that were screened 602 articles were excluded. The remaining 28 articles were assessed for eligibility and 6 of them were excluded, 3 of them because they were descriptive studies, 1 because it was a discussion paper, 1 because it had poor patient perception and 1 because it had small sample. There were 2 more studies included, that were identified through review of the reference lists of included articles. The total number of papers that were included in the synthesis for this literature review are 24.

Discussion

Pain

Studies associating pain and quality of life demonstrate variable results. Richardson et al. and Gibbs et al. have found correlation between pain and quality of life, but it was not significant for neither of them [13,14]. Wollars et al. found that there is no strong evidence to support that pain itself affects the quality of life, but they suggested that dealing with pain, as a psychological factor, negatively relates with quality of life [17]. Another interesting finding was that of Norma A. Erosa et al. Their findings didn't relate pain directly with the quality of life. Pain had an influence on SCI patients' mobility and that mobility levels affected patients' life satisfaction [24].

The results of Hassanijirdehi et al. showed that patients with pain reported more discomfort than those without pain. They also found that for those with lumbar pain along with those with shoulder pain, the feeling of discomfort was greater and that the lumbar pain group had a significantly higher influence in daily life. These were the only domains of quality of life that were found significant. However, this study had some limitations, as the sample size was rather small and consisted only by male patients [19].

Burke et al. and N. Nagoshi et al. found that among SCI patients with pain, the ones with neuropathic pain had greater reductions in some quality of life domains. Burke et al. showed that SCI patients who didn't report pain had quality of life similar to the general population while those who reported severe pain had the lowest quality of life, independently of pain type [5,15].

It is interesting to assess pain-predictors of SCI patients, in long term. J.D. Putzke et al. designed two studies to evaluate the predictors of pain and impact of pain in the quality of life in SCI patients. They examined these factors at year one post-injury and at year two post-injury and found the associations and predictors for pain and Qol. Initially, there seemed to be a reduction, from year 1 to year 2, in interference with day-to-day activities secondary to pain from 71% to 63%. Furthermore, the results at year 2 showed that the patients who didn't report a change in pain between year 1 and 2, didn't present a change in self-reported Qol as well. In contrast, patients who reported change in pain at year 2, demonstrated changes in self-reported Qol. In the cases that pain interference resolved, there was an increase in Qol, while those presenting pain showed a decrease in Qol. The Qol domains that showed the highest associations with pain were life satisfaction, physical health and mental health [4].

There are also other studies that indicate an indirect association between pain and life satisfaction. C.M.C. van Leeuwen et al. reported that less pain was associated with higher life satisfaction but there also seems to be a connection between pain and functional independence in relation to life satisfaction. A patient with high functional independence and/or low pain has a higher life satisfaction score than a patient with low functional independence and/or high pain [25]. R. Müller et al. and E. Ataoglu et al. also indicated that pain had a neg-

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ative effect in some domains of Qol. However, R. Müller et al. emphasized that participation and social support seem to protect patients from the negative effects of pain on mental health and Qol [16,20].

Spasticity

The results of Vural et al. suggest that there is a negative association between severity of spasticity and Qol, particularly for physical health and social relationship items [12]. In accordance to Vural et al., a systematic review from K. Milinis and C. A. Young indicated that spasticity has worse influence on Qol 's physical components than mental health. They also express the probability that spasticity may have an impact on Qol via related conditions such as fatigue, depression, anxiety and pain [10].

Findings of Westerkam et al. also reveal that spasticity is negatively correlated with life satisfaction and quality of life. Another finding was that perceptions of spasticity were related to psychological outcomes and suggested that there is a possibility, that psychological factors might have an impact on spasticity itself and that this relationship might be bidirectional [12].

Not many studies have categorized spasticity to detect specific relations among spasms, stiffness, clonus and Qol. W. B. McKay et al. performed this categorization and concluded that although both spasms and stiffness had a negative impact on participation in daily activities and quality of life, patients indicated stiffness to be the most problematic factor of spasticity in comparison to spasms and clonus. Stiffness was also more prevalent and had the worst influence in daily activities and psychological agitation [8].

Pain and spasticity

There are a few studies that have examined the relationship between pain and spasticity, whether this relationship is bilateral and the way these factors influence quality of life. J. J. E. Adriaansen et al. revealed an association between musculoskeletal pain, spasticity and Qol. However, these associations were weak. One reason for that was that patients who had experienced those secondary health conditions for a long time, had gotten accustomed to them, therefore they no longer influence their Qol. Another interesting finding was that, in this study, only musculoskeletal pain appears to be associated (weekly) with Qol but neuropathic pain does not [23]. On the contrary, Noonan et al. indicated that neither pain, nor spasticity were associated with Qol and only patients with neuropathic pain appeared to be significantly more dissatisfied with their condition [2].

SR. Andersen et al. revealed that patients with spasticity had lower satisfaction with physical health than those without spasticity, while patients with pain had lower satisfaction, not only with physical health but also with mental health. Additionally, interference with pain was related with decreased Qol, but spasticity was not. Neuropathic pain in particular was found to be more severe and had greater interference in Qol. This study in addition examined the relationship between pain and spasticity and it appears that individuals with pain had higher spasticity prevalence than those without. Possibly this happened because spasticity could provoke musculoskeletal pain and because it is believed that pain and spasticity share common neurological origin [6].

In accordance with SR. Andersen et al., J. A. Tibbett et al. also found a relationship between painful spasticity and chronic pain and suggested that painful spasticity may depend on mechanisms alike to those of neuropathic pain. SCI patients who develop neuropathic pain are believed to have higher chances to experience spasticity, than those with non-neuropathic pain [22]. In agreement with the previous study, W.B. McKay et al. demonstrated that pain and spasticity appear to be related and there is a possibility that they share common neural mechanisms. One justification for that is, that several treatments for one of them are also effective for the other [8].

Quality of life

Many studies have investigated the association between secondary health conditions following SCI and quality of life. However, it is very difficult to define exactly what affects patients' quality of life, as it is influenced by numerous factors, not only physical but also psychosocial. Another difficulty is that although there are several tools measuring Qol, only limited studies apply identical tools, thus making comparison among different studies non-significant. In addition, as it is stated by Noonan et al., there are two terms used to describe patients' condition, "quality of life" and "life satisfaction"

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and it is not known whether these two are equivalent and compatible [2].

An interesting fact about life satisfaction was reported by C.M.C. van Leeuwen et al., in their study conducted in three stages (when a patient is discharged from inpatient rehabilitation, two years after discharge and five years after discharge). They detected no changes in mean life satisfaction, between discharge and at year 2 after discharge, however there were small but significant increases in life satisfaction between 2 years and 5 years after discharge [25]. This is also supported by S. Jorgensen et al. who mentioned that life satisfaction remains relatively the same for a long time after injury and may even increase as the patient lives longer with SCI [3]. There is a possibility, that patients living for a long time after their injury tend to get used to their current health situation and things that used to annoy and discomfort them don't affect their life satisfaction anymore.

Pain and spasticity seem to play an important role in SCI patients' quality of life. However, there is no agreement among studies. It is possible that pain and spasticity interact not only in relation with Qol, but also with one another in a bilateral way. These correlations may be either direct or via other factors such as psychological or social. Either way, it is important to understand SCI patients and what impacts their Qol, especially the first years after injury to help them cope with their problems. Therefore, it is essential that surveys continue to be conducted, ideally gold standard tools to be found, so that we can learn more about these relations and as a result, how to treat people more efficiently and according to their specific needs.

Conflict of interest
The authors declared no conflict of interest.

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Mathiopoulou P, Evangelopoulos ME. Spasticity and pain: the effect on quality of life in individuals with spinal cord injury. *Acta Orthop Trauma Hell* 2022; 73(4): 365-369.

Pain and depression in patients with spinal cord injuries

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ABSTRACT

Spinal cord injury (SCI) causes many health-related problems and affects not only patient's physical condition but also other aspects of his life, such as mood and quality of life.

Chronic pain is a common and important complication seen in patients with SCI. As pain is known to affect various activities of the individual, such as recreational and occupational status, sleep quality and sexuality, pain seems to play an important role in quality of life, mood and rehabilitation. In addition, chronic pain and psychological disorders are closely linked, affecting the physical and psychosocial function of the patient. Similarly, various studies have shown that a significant proportion of patients with SCI suffer from depression while at the same time it has been shown that chronic pain is associated with depressive symptoms in these patients.

The purpose of this study is to conduct a literature review concerning the relationship between pain and depression in patients with SCI. From the 27 studies included in this paper, we can safely conclude that pain and depression are strongly connected although the nature of this connection is still to be clarified.

KEYWORDS: SCI, depression, pain

Introduction

Spinal cord injury (SCI) is a life-changing condition that can have life-threatening complications since it causes paralysis, aesthetic loss and consequently damage to a wide range of body functions (1). The annual incidence of spinal cord injuries in the United States is 54 cases per one million while in Greece these rates are 33.6 cases per million people (2,3). The main causes leading to spinal cord injuries include road accidents, falls and accidents during sports activities (4).

International Association for the Study of Pain (IASP) describes pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain is quite common in individuals with SCI, although its prevalence varies significantly (5,6). About 70-80% of SCI patients report experiencing some kind of pain (7), while almost half of them describe it as severe with effects on daily functioning, occupational activities and basic needs such as sleep, quality of life and mood (8). The pain may be constant over time and in some cases worsens (9). It is therefore worth noting that pain,

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among other complications, is consistently associated with lower quality of life in these patients (10). There are three types of pain connected to SCI: nociceptive, neuropathic, or visceral (11). Some studies showed that pain prevalence is higher five years post injury than at six months, thus highlighting the importance of treating pain in long-term (12). However, few pharmacological treatments are effective for this purpose, especially for neuropathic pain (13).

Spinal cord injury can affect both physically and psychologically the individual. Therefore, it's quite common for SCI patients to develop mental health problems such as depression and/or anxiety (14). In more detail, it has been shown that the one quarter to one third of individuals with spinal cord injuries develop depression at some point after injury (15). Depression is a common secondary condition after spinal cord injury that occurs in cases of poor health, reduced functionality and high mortality rates. It is also associated with psychological problems caused by injury, such as perceived low quality of life and increased stress (16). Depression is well studied in SCI patients. Prevalence of depression in this patient group varies from 11% to 37% (17). The corresponding percentage in Greece was found to be 18.2% (18). Severe depression is the most common psychological condition associated with spinal cord injury and is estimated to be experienced by 30% of patients. The presence of depression is associated with increased length of hospital-stay and secondary medical conditions, as well as decreased social reintegration, quality of life, and self-care (19,20). There are many different factors that can be associated with depression, such as, stressful life events, such as a serious injury, personal characteristics, environmental factors, such as social support and personal safety, genetic factors, medical conditions and some medicines (20).

Pain includes aesthetic, cognitive and mainly emotional aspects. The emotional component of pain includes feelings of discomfort, sadness, anxiety, and depression in response to a painful stimulus, and in this case, chronic pain. Pain and depression are frequent secondary complications in patients with spinal cord injuries having an effect on the patient wellbeing (21). Clinically, the coexistence of pain and depressive symptoms has been measured by researchers at 52-59%. Depression may affect the onset of disability or chronic pain, according to studies (22-24).

Pain and depression, and the systems through which they are regulated, share common biological pathways and neurotransmitter mechanisms. Thus, it is not surprising that pain has been shown to impair the effectiveness of treatment for depression (25). Moreover, depression and pain can affect the recovery process of the patient due to many reasons.

The aim of this paper is to review the existing literature to specify the connection between pain and depression in patients with SCI. For this purpose, we conducted a literature review, using temporal criteria in order to access the literature of the last 30 years (from 1986 to 2022). Only papers that were published in English were included in this study. The keywords that were used included spinal cord injury, depression, and pain.

Discussion

The search of the databases demonstrated 8994 papers. Our search revealed 25 studies in total. In more detail, the majority of the studies included investigated the effect of depression and pain in patients with traumatic and non-traumatic SCI (17 studies), while 7 studies focused on traumatic SCI patients and one on individuals with chronic SCI (Figure 1).

The first ever study that examined the psycho-social aspects of chronic pain in patients with SCI was conducted in 1980 (26). Their results demonstrated that patients with chronic pain were more prone to depression in comparison to subjects that did not experienced pain. This study was the first reporting the importance that psycho-social variants play in the comprehension of pain in SCI individuals. A cross-sectional study conducted by Ataoglu et al., (2012) assessing the role of pain in quality of life as well as depression in 140 patients with spinal cord injuries, showed that patients with chronic pain had higher depression rates in comparison to patients with no chronic pain (27). Another cross-sectional study that investigated the correlation of pain and depression in 44 patients with traumatic SCI manifested a positive connection between pain intensity and depression ($p=.001$), suggesting that the long-term emotional distress is significantly influenced by pain (28).

A study that examined the relationship between pain and depression in traumatic SCI patients at a rehabilitation center, demonstrated correlation between pain and depression at discharge and that changes in pain affected depression levels more than depression affecting pain (29).

Craig et al., (1994), investigating the determinants that can lead to depression after spinal cord injuries, showed that pain was a significant variant correlated to depression (p<.01) (30). Another study investigating the psychological determinants of pain among patients with SCI demonstrated that depressive symptoms were more common in patients that experienced pain than in patients without pain (31). Molton et al., (2009) in a study of 130 SCI patients reported similar results (32). A longitudinal study concerning depression in SCI patients also showed that pain was one of the risk factors of developing depression (33). In addition, Kennedy and Hasson (2017) investigating the connection between depression and pain during SCI rehabilitation (34), reported that both have an additive effect.

A cross-sectional study investigating the role that pain can play in the development of depressive symptoms as well as in quality of life in SCI patients (35) showed that there is a connection between pain and depression in these patients. Simultaneously, a study conducted by the same research group described the relationships between usual pain intensity, mood, disability and both pain and SCI-related psychological factors, such as depression and anxiety in a rehabilitation center (7). Their results confirmed a significant connection between pain and depression in these subjects, suggesting that pain-related psychological factors are important in the clinical practice after spinal cord injury. An earlier cross-sectional study that investigated life satisfaction in 230 SCI patients regarding pain, demonstrated that lower levels of life satisfaction were reported in individuals with pain, while higher levels of depression and anxiety can be used as predictors (36). Therefore, the association between depression and pain suggests that the long-term emotional distress that these patients experience is significantly influenced by the experience of pain as well.

A survey regarding chronic pain after SCI including 216 patients, showed that chronic pain played a great role in developing depressive symptoms (43% of the subjects) (37). A cohort study examined depression in 801 patients with spinal cord injuries as well as the risk factors for developing depression over time (38). Many factors were significantly associated with major depression in these patients and pain was one of them. A similar study that investigated the role of psychological factors in pain activity and depressive symptoms in 70 adults with SCI, concluded that pain and depression are positively associated (39). Furthermore, two studies examining the correlates of chronic pain in SCI men showed that chronic pain was associated with more depressive symptoms (40,41). Another study aiming to identify the role of pain in ambulation and depressive symptoms detected significant relationship between pain and depressive symptoms in patients after SCI (42).

Since daily fluctuation in pain acceptance and the effect that pain has in physical and psychological aspects of life in SCI patients has not been examined, Kim et al., (2020) studied these factors in 124 SCI individuals with chronic pain (43). Their results demonstrated that pain acceptance was correlated to pain intensity and depressive symptoms among other. Moreover, Cuff et al., (2014) (24) demonstrated that pain interference and pain intensity are related to depression in SCI patients.

Although all the studies stressed the importance of pain to SCI, there were few of them that did not find any connection between pain and depression in these patients. Specifically, the results of a study that examined the depressive symptoms in patients with acute spinal cord injuries showed that although the two thirds of the subjects experienced pain, there was a very low correlation between the two variants (44). In addition, a study that examined the psychological characteristics of 45 SCI patients and pain in a pain management center also failed to detect associations between pain and depression (45). An early study that tried to clarify the phychosocial factors in chronic pain in SCI patients manifested that depression did not have a significant impact on pain interference in these patients (46). Also, Tate et al., (2013) conducted a cross-sectional study that examined the connection between pain and depression in SCI patients in a rehabilitation center (47). Their findings suggest that there is no connection between depressive symptoms and pain in this study cohort upon admission, similar to those of a previous study (29).

Wollaars et al., (2007) studied the role of psycholog-

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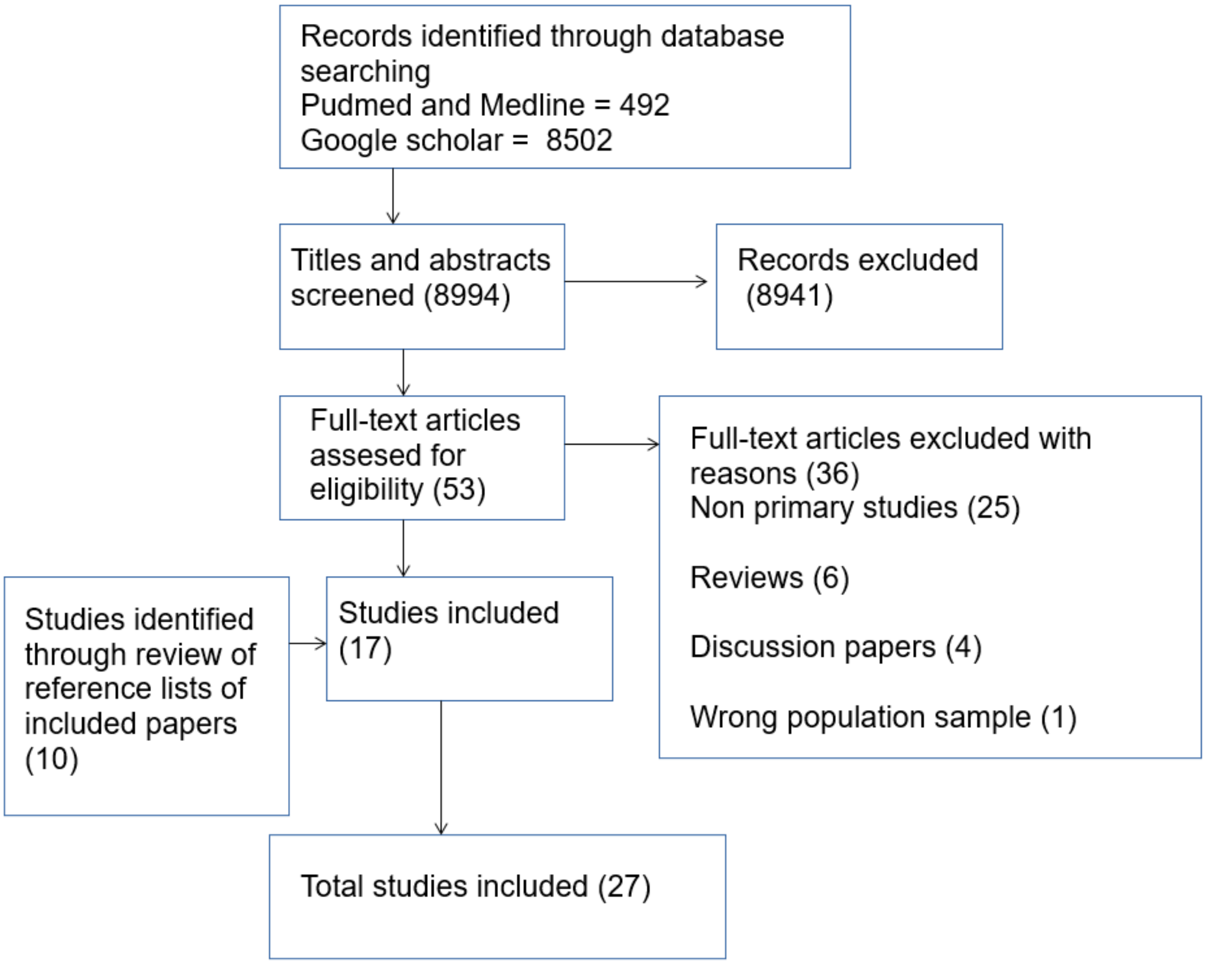

Figure1: Flowchart

ic determinants on SCI pain in 575 patients (48). Depression was not associated with pain in the regression analysis of this study. The authors concluded that the quality of life is more dependent of psychologic variables like dealing with pain and SCI, than of pain and the injury itself. Moreover, in a study that included 37 patients with chronic spinal cord injuries no statistically significant connection was found between clinical factors, such as pain and psychological distress (49). Last, Matin et al., (2015) evaluated the role of fatigue, depression and neuropathic pain among 30 Iranian SCI patients (50). They showed that although patients who had lost their ability to walk demonstrated fatigue and depressive mood more often, pain was not associated neither with fatigue nor with depression in these patients.

A lot of studies have demonstrated that pain is quite common after SCI injury. However, there are not so many studies that explore its effects on quality of life as well as mood. Depression and pain are quite common in SCI patients and seem to have a negative effect on quality of life for these patients. However, our search revealed few studies (7 studies) that showed no statistically significant correlation between the two determinants (44-50). This may be due to various reasons. In the studies conducted by Hassanpour et al., (2012) and Shin et al., (2012) the results can be interpreted by the relatively early observation time window used in these studies. Another reason in some studies (44-45, 49), was that the small sample size was not sufficient to draw safe conclusions. Also, in the study conducted by Tate et al., their results may suggest that symptoms

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could develop later during the course of rehabilitation but are unlikely to be present when patients first enter the unit. Moreover, sample variation may also explain these findings (47). The design of the study conducted by Wollaars et al., (2007) may be the reason why there was no correlation between pain and depression in these patients (48). The reason of the controversies found in the study of Matin et al (use of subjective pain assessment, in which expression of pain severity by depressed or stressed individuals) may be underestimated or exaggerated (50).

The correlation between pain and depression in patients with SCI is confirmed by many studies in the literature. For instance, a systematic review that investigated the determinants of pain in individuals with spinal cord injuries demonstrated a positive connection between pain and depression (51). Also, the results of a systematic review and meta-analysis that was conducted in the Iranian population showed clearly that there is high prevalence of pain as well as depression among patients with SCI (52). These results were confirmed by another meta-analysis conducted by Tran et al., (2016) (53). Literature reviews investigating depression and pain comorbidity concluded that depressed patients experienced more pain in comparison to non-depressed patients and also (54,55).

Pain affects different aspects of the person's daily life and moreover can have an effect on the mental health (56). SCI patients that experience pain believe that their disability has a negative influence on their lives due to pain. Therefore, this negative view may have as a result the depressive symptomatology in addition to pain (30). The recent literature has shown new light into the understanding of the pain–depression relationship and hence, many researchers support that pain and depression should be treated simultaneously (57,58). Many methods have been proposed for the treatment of depression and pain in these patients. In more detail, mindfulness, self-management and directed rehabilitation are some of them. However, all of these methods did not provide clear data on their effectiveness in patients with SCI, emphasizing the need for additional studies in that field (57,59,60). Since depression and pain often occur at the same time, comprehending the common mechanisms that are linked with depression and pain is of great importance to develop an effective treatment for both of them. There are common factors involved in both depression and pain (55). Targeting these shared mechanisms may manifest an increased result for these patients. Therefore, more research must be done towards the factors that affect the mechanisms in order to treat pain and depression.

In conclusion, this literature review demonstrated that pain and depression affect significantly patients with spinal cord injury. Therefore, it is of great importance that health care professionals should pay attention not only to the clinical examination but also to a pain management strategy by the use of psychosocial interventions in order to address not only chronic pain but also depression in individuals with SCI. Many researchers have suggested that SCI patients who experience pain should be treated in a multidisciplinary setting where there is a combination of pharmacological, physical and psychological therapies. By determining who is at risk for these symptoms, clinicians can adopt treatments that prevent these from becoming chronic conditions. Early detection and treatment both of the determinants can lead to reduced costs both for the patients and the health system of each country.

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Mentziou K, Vlamis JA. Pain and depression in patients with spinal cord injuries. *Acta Orthop Trauma Hell* 2022; 73(4): 370-378.

The role of adapted/therapeutic exercise for paraplegic patients

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ABSTRACT

Paraplegia is a severe condition leading to paralysis and significant limitations to individuals' lives. Secondary health complications, psychological disorders and social difficulties, make persons with spinal injuries susceptible to serious hazards in various aspects. Considering the fact individuals with SCI are one of the most inactive parts of society, the objective of this overview is to present the role and benefits of adapted exercise for SCI population. The outcome of studies yield credible evidence that becoming physically active post SCI, is a critical factor for preserving overall health and health-related quality of life. Systematic physical activity and/or sport have important positive impact upon physical and psychosocial well-being by improving fitness, physical conditioning and health, helping in medical risks prevention, affecting the psychological status, promoting social participation and facilitating functional independence and quality of life of individuals. Exercise recommendations, guidelines and special considerations for the spinal injured people –with emphasis in paraplegia- are also discussed, since it must be specialized and adapted to the demands and restrictions of this condition. Acknowledging this multidimensional role of physical activity, future research is needed to further determine health outcomes in specific domains and the optimal elements and guidelines for physical activity.

KEYWORDS: adapted exercise, physical activity, paraplegia, Spinal Cord Injury

Introduction

Paraplegia, and Spinal Cord Injury in general, is a severe lesion, caused usually by a great force imposed on the spinal cord, which interrupts completely or partially its function, i.e. the transferring of neural signals from the brain to the various body systems and vice versa. This results in various types of motor and sensory disabilities and may also interrupt the autonomic function below the point of lesion, depending on the level and structure of the lesion [1-3]. This severe neurological deficit affects dramatically the lives of people who suffer it in all possible ways [1,4]. Individuals with SCI are physically deconditioned and susceptible to serious health complications, dysfunctions and psychosocial difficulties [3,5-9].

Thousands of people suffer every year SCI. It is estimated that there are 15-40 new cases per million of population every year [3,10]. The estimated global in-

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cidence rate is 23 per million, resulting in almost 18.000 new cases every year, mainly young people [1,11]. Although SCI remains an incurable condition, the survival has increased over the last years due to successful therapies for life threatening complications, early intervention and rehabilitation processes following SCI [12].

The preservation of fitness and physical wellness is a key factor in coping with spinal injuries and preventing secondary complications. Systematic physical activity seems to function in a beneficial way in order to adapt and overcome barriers in daily activities and protect health and well-being [7,13-17]. Adapted exercise has the potential to improve fitness, biological functions and provide the prerequisites for psychological adaptation, independence, social participation [5,18]. Nevertheless, the majority of the SCI population is physically inactive –maybe the most inactive part of society- or not active enough in order to gain the positive effects of exercise [19,20]. Thus, it is of great importance to facilitate and encourage the participation of this population in a systematic physical activity program and to promote the prescription of exercise.

Method –Material: This narrative review was conducted through searches in PubMedC and Google Scholar databases, using the keywords *adapted exercise, physical activity, paraplegia, Spinal Cord Injury.* Non English publications and articles before 2000 were excluded. This resulted in 672 publications. After removing duplicates and scanning irrelevant publications 119 articles remained. A second scanning of the abstracts excluded another 27 publications, as their main research referred to animals, exclusively quadriplegia or did not focus on the role of physical activity (e.g. purely medical issues). Three highly relevant Greek publications were also added. All the above resulted in 95 articles which were fully read. Well known and recognized scientific reports (e.g. WHO reports) that focus on exercise prescription and guidelines for adapted exercise have been also included.

Health risks and consequences after SCI

Individuals with paraplegia -and SCI in general- face a variety of health problems, even years after the injury. Some are immediate related to the injury, whereas others are secondary complications. Multisystem dysfunctions of various degrees accompany SCI, depending on the degree and level of lesion [3].

The most important threat, a common cause of death for people with SCI, are cardiovascular diseases (CVD) [20,21]. The lack of physical activity, the sedentary way of life, in combination with metabolic disorders, contribute to a higher risk of cardiovascular complications [22,23]. Metabolic diseases, as impaired glucose tolerance or diabetes mellitus, are common in people with SCI. Astorino points out that they have double percentages of suffering from CVD, mainly due to lack of physical activity, adiposity, glycemic and lipemic dysregulations, hypertension, adverse lipid profiles disorders of carbohydrate metabolism [24]. Moreover, body fat increases after the SCI leading to prevalent obesity, more burden in everyday life, but also CVD [3,21,25]. Insulin resistance and sarcopenic obesity constitute great hazard for cardiometabolic syndrome, which affects 60-80% of persons with chronic SCI [26,27] and may lead to serious coronary artery disease or myocardiac infraction[7,28].

Dysfunctions of the autonomous nervous system lead to severe neurological deficit. Orthostatic hypotension and autonomic dysreflexia are dangerous complications in high level lesions [8]. Moreover, autonomic dysfunctions negatively affect genitourary organs, thermoregulation and blood pressure regulation mechanism [3]. They also lead in neuropathic bladder and bowel and sexual dysfunctions, considered as priority by paraplegics [29]. The loss of urogenital and bowel control leads to infections, but also limits the person's willingness to be socially active and is critically linked with quality of life (QoL) [30,31].

SCI affects negatively the vascular characteristics and the sufficiency of the arterial circulation [21]. Blood pooling in the lower extremities increases the risk of thrombosis [3,24]. In addition, respiratory complications often accompany SCI, especially at high level lesions, as it decreases the elasticity of the lungs, reduces the vital capacity and lead to insufficient function of the respiratory muscles [8,32].

The musculoskeletal system is also highly affected. The paralyzed muscles and muscle fibers below the lesion loose gradually their properties, distribution and volume and undergo morphological and contractile changes [24,25]. Lack of activity and loading result

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in deteriorating muscle atrophy below the lesion [21]. Bone and joint deterioration are often experienced, even by young individuals [3]. Bone demineralization and osteoporosis manifests rapidly after the injury and continues to climax some years after [14,33]. Bone fractures are common, particularly after falls [34,35]. Other complications are spasticity, affecting approximately 70% of the individuals [36], and fatigue, a physical tiredness, hindering mobility and function [37].

Chronic pain, a devastating problem, affects heavily their QoL [5,38]. It can be neuropathic pain, nociceptive, visceral or musculoskeletal [38-40]. The most prevalent is shoulder pain, as the hands must do the work of both, hands and legs [2]. Poor circulation and sensory loss are the main causes of pressure ulcers development, which can lead to dangerous infections [31].

All these complications are not mere medical conditions. They have psychosocial effects. After the injury, the person usually loses the ability to live independently, has many medical problems, must adapt to a sedentary-passive life, experience fear about the future, feels isolated. The feeling of helplessness, depression, anger, stress, isolation, affect dramatically their QoL [41].

Adapted exercise - Barriers and facilitators

Individuals with paraplegia and spinal injuries face many constrictions in physical activities, due to limited exercise options, reduction in exercise capacity, but also health complications stemming from the injury. Exercise should be designed carefully and personalized-adapted to the individuals' condition, needs and personal characteristics.

Systematic training is a non-invasive, but effective way to improve and maintain physical fitness, overall health and wellness for persons sustained SCI [2,20,40]. The majority, although inactive [43], acknowledge the benefits of exercise and are willing to begin some kind of physical activity, but encounter many barriers, internal and resource impediments [43-47].

Exercise for persons with disabilities is determined by many factors, as special training opportunities, appropriate infrastructure, social interaction, policies and public services [46]. Experts need to take into account barriers and facilitators affecting participation and adherence [19]. Typical barriers recognized by individuals are physical health factors (e.g. impairment, pain), psychological factors (e.g. depression), social support, accessibility (transport, equipment), financial cost, lack of information-awareness and experts [14,19,45-48].

Thus, physical activity counseling, accessibility solutions, support organizations, evidence-based resources and experts, are very important in planning those programs [48-50]. Specialized activities and equipment, instruction/supervision by exercise professionals, accessible facilities, and community-based programs facilitate exercise [7,14,45,51-52]. Psychological factors also play an important role [53]. Gaining fitness and avoiding health problems is the most important motivation [54]. Strategies as action planning, goal setting, social support and self-regulation also act as strong facilitators [49].

Physical activity for adults with paraplegia should have long term fitness targets [14,49], as the benefits tend to diminish after a non-active period [55-56], starting from rehabilitation and the transitional period after discharge [6,57].

The beneficial role of exercise intervention in health and physical fitness

It is well documented that systematic exercise plays an important role in physical fitness, strength and functional aspects in SCI. It also seems to have positive effect on various health systems and improve psychosocial factors and QoL [2,10,14,49,58].

Physical fitness has great impact on the person's level of autonomy and overall heath [10,60-61]. Nevertheless, all aspects of physical fitness deteriorate after the spinal lesion. Physical capacity, an important fitness component, indicating the work one is able to perform, decreases post injury, resulting in the decline of two important factors: aerobic capacity (AC) and power output (PO).

Systematic training has a direct effect on AC, by increasing peak oxygen consumption (VO2peak)[14-15, 61-62]. It is associated with cardiovascular and cardiorespiratory health, endurance and functioning [8,16,20,26]. There is credible evidence that systematic aerobic or circuit training has positive cardiorespiratory responses, even if restricted in the upper part of the body [2,15,63]. The same result is observed with resistance training in paraplegics [64]. Moreover, exercise targeting at the accessory respiratory muscles, leads to ventilation efficiency [61] and improved fatigue resistance [15].

Aerobic and mixed training result in significant improvements in PO too, confirmed by many studies [15,61-61,65-67]. PO is an indirect indication of muscle strength and has great impact on the individuals' functional efficiency in daily activities, e.g. wheelchair propulsion [14,15].

Muscle strength, associated with muscle mass is a key factor for paraplegics, but decreases rapidly post injury. There is strong evidence that systematic endurance and resistance training leads to improvements in muscle strength and physical capacity, which are closely related to everyday tasks e.g. self-care, transfer [68-71]. Muscle strength also reduces risk factors associated with pain and injuries, mainly due to overuse [72]. Studies report better pain management options and pain decrease during exercise participation [38-39,45]. Shoulder pain, typical for manual wheelchair users, decreases as shoulder muscular strength increases after training, which optimizes the joint mobility and activates upper muscles, especially in paraplegics [73-75]. Thus muscle strength exercise has great impact on physical/functional efficiency and biomechanical economy [15,49,76]. This is of great importance considering that only 25 % of healthy young paraplegics are in the position to maintain their independence [14]. A meta-analysis of exercise benefits for wheelchair users found positive correlation between exercise and functionality, everyday activities, balance, movement, depression, sleep and spasticity [77]. Body composition is another indicator of fitness status [15,34,78]. Regular participation in exercise showed favorable results, mainly in muscle mass, which is related to muscle strength [15,70,73].

Considering the great risk of CVD complications, indications that exercise or sports elicit positive cardiovascular and cardiometabolic outcomes, must be seriously considered [2,10,72,79-80]. Blood glucose and body fat percentage decrease through increased caloric energy expenditure [13,69,72]. The lipid profile shows improvements, mainly due to increase in cardioprotective HDL-cholesterol, which tend to be proportionate to the exercise intensity and amount [14,21,42,62]. The same holds for insulin sensitivity [73]. Systematic intense exercise, in combination with nutritional management, are critical factors for attenuating cardiometabolic syndrome risk, as sarcopenic obesity and insulin resistance, and preserving health [26].

Apart from the traditional exercise modes, involuntary training of paralyzed limbs with the assistance of electrical stimulation methods, body weight support equipment and passive exercise, are also effective options in order to improve overall fitness, physical capacity, muscular strength and elicit health outcomes of different systems [14,15].

Beyond potential improvements in ambulation, studies have found evidence that Body Weight Supported Treadmill Training (BWSTT) results in reduced hazard for health complications and cardiovascular gains via favorable metabolic alteration, blood pressure, heart rate, body and muscle composition [14,21,78]. Locomotor training with BWST seems to have positive impact on the neural control of the urogenital and bower function and improvements in bladder capacity, voiding pressure, nocturia and time required for defecation [29]. This implies benefits not only for motor rehabilitation, but also in the neural circuitries of autonomic functions. Reduction of pain has also been documented [81].

Functional Electrical Stimulation (FES) training also results in positive outcomes. Regular intense FES exercise at the lower extremities, facilitates bone metabolism and formation, due to activation and mechanical loading imposed to the lower limbs and improvements in bone vasculature circulation [34]. Thus in chronic SCI, FES training seems to have effect on bone mineral density [21]. A current systematic review about the role of FES cycling reported improvements in aerobic fitness, PO and muscle health, particularly in fiber composition and muscle mass of the lower part of the body [82].

Another mode for training paralyzed limbs is passive exercise, as passive leg cycling. A systematic review examining the musculoskeletal, cardiovascular and neurological outcome of this method, concluded that multiple sessions have indeed positive impact on reflex excitability, spasticity, blood flow in the lower extremities, and range of motion [83].

Not only the physical but also the psychological and

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social well-being improved significantly from systematic training programs [84-85]. The beneficial effect is linked with psychological balance, achieved through the promotion of functional independence, perceived health status, reduced stress and pain levels [7,53-56]. Psychological health is closely related to autonomy. Every intervention that improves fitness, strength and physical capacity, enhances the individual's functional performance, the ability to be socially active and personally autonomous, and thus has a critical impact on psychosocial status [86-87].

The above findings are confirmed by systematic reviews and studies demonstrating positive impact of training on mental health, and psychological factors. Indices like depression feelings, anger, stress and satisfaction from functioning and life, were significantly associated with participation in sports and exercise [14]. Studies revealed that life satisfaction measures, improved significantly after participation in a systematic training program [14,84]. Koppenhagen et al found a significant association between wheelchair exercise capacity and life satisfaction, defined as the persons' subjective well-being [88].

Bonnell et al studied the social relations of people with disability and showed that exercise programs were a key factor [46]. Social contact, reintegration and participation post injury is a complex procedure, but crucial to ones' perception of satisfaction and QoL [87]. Participation in team sports and training programs enhances social skills, interpersonal relations between co-athletes and peers and generates socialization and life satisfaction [87,89]. Particularly community-based programs post rehabilitation seem to function as a stable basis for SCI people to sustain participation in social and physical activities [20].

Quality of life is a multidimensional concept [89]. Individuals with SCI are reported to have a dramatic deterioration in their perceived QoL in comparison with non-disabled peers [90]. Leisure time physical activity is a strong predictive factor of QoL and many studies have shown their positive relation [9-10,53,56,59,87]. Exercise affects the objective and subjective QoL in the physical, psychological and social domain [85].

Generally, physical and emotional well-being, self-determination and integration are higher in physically active SCI persons [87]. A great promoting factor of physical activity is the realization of the exercise participation benefits, which include control over their lives, enhanced self- esteem and autonomy [15,54,72].

Exercise prescription

Special considerations: All the above make the prescription of exercise an important but complicated task, which must be carefully designed, personalized and adapted to special characteristics. Experts should begin with a thorough description/evaluation of the individual's condition, based on the medical status, the exact type and extend of paralysis, personal factors, way of life, time since injury, age, comorbidities [2,91].

The completeness and level of the lesion play a very important role in the exercise capacity and prescription. Dysfunctions of the sympathetic system in higher level lesions, may reduce maximal heart rate to 110-130 beats/min [3,42,92]. Thus, maintenance or cardiac output in maximal exercise due to compensatory HR increase, is hardly possible.

The active muscle mass reduces post injury, leading to reduction in oxygen uptake. Impairments in venous return is also affected by the lesion level and completeness [2,92]. Researchers stress the fact that VO2peak, PO, and consequently the exercise capacity, are inversely related to the level of the lesion [3.92]. Muscle mass, respiratory function, blood redistribution capacity, cardiovascular adaptation during exercise, have also an inverse relation with the injury level. Individuals with paraplegia have elevated HR responses and lower stroke volume [3], but may achieve high VO2peak in arm ergometry, depending on the lesion level[2].

Orthostatic or exercise-induced hypotension, due to circulation dysfunctions, may lead in nausea or syncope and need blood pressure monitoring, slow position alteration and progressive exercise introduction [2,20,55]. The same manipulation decreases the possibility of painful spasticity incidents. Sensory impairments may lead to ulcers and professionals should monitor skin areas frequently, adapt material and equipment and relief pressure regularly [2,63]. There is also increased hazard of bone fractures after falls or stretching of paralyzed limbs, especially in team sport, due to osteoporosis and lack of sensation, leading in delayed detection [2]. Musculoskeletal injuries must be prevented, mainly by gradual exercise introduc-

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tion and pain self-report [42]. Thermoregulation and sweating dysfunctions may cause overheating and need cooling strategies [2,63]. Nevertheless, there is no doubt that beneficial outcomes outweigh the dangers and the adverse incidents are rare and usually not severe [2,68].

Onset time: Individuals should be motivated by experts from the early stages of the injury to gain body control and everyday functionality [14]. Mobilization should begin as soon as the medical condition allows it, initially with passive activation of musculature with stretching and joint mobilization, and then with energetic exercise. During the subacute phase a strength and aerobic program should be implemented, followed by a systematic program afterwards [71].

The initial period after the injury, is considered to be crucial for better rehabilitation results and adoption of positive behavior towards physical activity. Immediate exercise participation, which continues after discharge, optimizes recovery and reduces health complication risks. Rimmer and Lai propose the transformative exercise model which begins in the acute phase. It presuppose the cooperation of the therapist and the training specialist in order to transform the patient to a life-long physical activity participant [6].

Exercise recommendations: Activity recommendations have to address all elements of exercise, type, frequency, intensity and duration [42], depending on cardiovascular responses and oxygen uptake measures. The ergometer is a safe way to determine cardiovascular capacity. The intensity threshold according to researchers should not exceed the 70% of the HRmax and last 20min at least [71]. On the other hand studies support that in higher level lesions, HR is not a reliable marker due to autonomic dysregulations which distort the data, although it could be a secure measure in most paraplegias. Measures of VO2peak are more complex, but precise, and exercise should aim at 60-80% [42]. A more practical measure is the Rate of Perceived Exertion of Borg [93], applicable for all ages. Generally, the training programs should develop conservatively and gradually.

In paraplegia, most types of exercise mainly rely on the upper part of the body, which demands more physiological strain than exercise involving legs. This modality restriction seems to yield lower PO and VO2peak values and higher HR during arm cranking than leg cycling [92]. Thus the exercise capacity is limited and the intensity level difficult to determine. Nevertheless, cardiovascular endurance and strength improve with systematic exercise. Pelletier et al found no difference in energy demand between arm only and arm and leg training in incomplete lesions, where persons were able to perform leg activation [20]. Hybrid exercise types show a metabolic advantage in complete lesions, where FES or BWSTT can be utilized in order to activate large inactive/paralyzed muscle groups of the lower extremities. FES has been reported to provoke physical, functional and psychological benefits for person with paraplegia [94]. Depending on the lesion level, a combination of arm aerobic exercise and passive leg cycling or FES leg training might be needed for improving aerobic capacity. Torhaug et al found that aerobic training -with arm crank ergometry only- elicits increased VO2peak in individuals with lesion below T6, but did not enhance cardiovascular fitness in persons with higher level lesion, unless an additional passive leg cycling or FES hybrid cycling was used[69].

Exercise guidelines: Experts and international organizations have developed guidelines in order to define the elements of physical activity, appropriate and effective for the SCI population. Exercise guidelines show a rising tendency over the last decade, as far as frequency, intensity or duration is concerned [2,55,95-96].

World Health Organization introduced in 2020 the first evidence-based Global Physical Activity and Sedentary Behavior Guidelines for People Living with Disabilities [97]. SCI was one of the conditions described. Recommendations were based on the general population fitness guidelines [68]. 150-300 min of moderate aerobic exercise per week is considered to be the minimum in order to achieve health gains, combined with strengthening exercise for all major muscle groups and balance training to enhance functional capacity.

A multidisciplinary panel developed in 2011 the first SCI-specific, evidence-based Physical Activity Guidelines [55]. The goal of it was to improve fitness and determine elements of exercise in a feasible way. The recommended frequency was 2 times/week of aerobic and strength training in a moderate-vigorous intensity for at least 20min, but 30min would elicit better results. An update of 2018, emphasizing on cardiometabolic

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health, recommended aerobic exercise, performed 3 times/week for at least 30min in a moderate-intense mode [95].

The Consortium for Spinal Cord Medicine (USA) focusing on the high cardiometabolic risk for spinal injured persons, proposes at least 150min/week of physical exercise, even from the acute phase, stratified during the weekdays [79].

Another approach designed for professionals and targeting in cardiometabolic health and fitness, is the Exercise and Sports Science Australia (ESSA) Position Statement [2], which proposes a program based on the able bodied population, with SCI evidence-based adaptations and international organizations recommendations [98-100]. Arm aerobic or circuit training are recommended and resistance training, especially for paraplegics. Moderate (HRR 40-59%) aerobic exercise should be performed 5 times/week for at least 30min or vigorous exercise (HRR 60-89%) 3 times/week for at least 20min. Strength and flexibility exercise at least 2 times/week with no pain or internal shoulder rotation are also important.

Nevertheless other studies report that Moderate Intensity Continuous Training (60-70% intensity) is not enough to yield positive outcomes, especially cardiometabolic [26,96]. An alternative is High Intensity Interval Training (80-100% HRmax with 1-3 min intervals), which has shown greater physiological outcomes in able-bodied population and seems to have the potential to reduce cardiorespiratory, vascular and cardiometabolic risks [1,96]. A systematic review of the results of HIIT concluded that, despite the benefits in VO2max and PO in SCI population, it is premature to recommend this mode, as more studies must confirm its safety and effectiveness [1].

Conclusion

Individuals with paraplegia experience a dramatic change in their lives and are susceptible to a range of health complications, many of which are related with inactivity, due to paralysis. Moreover, their general fitness level deteriorates rapidly, the exercise options decrease greatly, leaving less space for physical activity interventions. Nevertheless emphasis should be given in accessible, adapted exercise programs and early education of the these population about the benefits of systematic training in disease prevention and coping, but also in fitness level, functional aspects and psychosocial gains, related to exercise. Acknowledging the beneficial role of exercise, experts propose special exercise recommendations and guidelines for persons with SCI in general. The ultimate goal is to reverse the sedentary way of life consequences, prevent secondary complications and achieve the most of functional independence and quality of life. More research is needed to further determine the benefits of exercise in specific body functions, as well as the optimal exercise adaptations, physical activity elements and interventions, needed to accomplish this goal.

Conflict of interest

The authors declared no conflict of interest

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Hyperbaric oxygen treatment: functional and neurological recovery, following spinal cord injury

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ABSTRACT

Spinal Cord Injury (SCI) is an urgent condition with a high rate of clinical disability. Therefore, it is mandatory for clinical research to find effective therapies to recover from SCI and improve mobility and sensation. The purpose of this study is to review the use of hyperbaric oxygen in the functional and neurological rehabilitation of SCI patients. This is a narrative literature review. The following keywords were searched in the PUBMED literature: "hyperbaric oxygen" AND "spinal cord injury". Inclusion criteria were clinical trials and animal studies investigating the use of hyperbaric oxygen in spinal cord injury recovery. Non-English language studies, systematic reviews, case reports, in vitro studies and research protocols were excluded from the study. Search results showed 100 posts. After checking titles and abstracts, 28 articles were rejected. Of the 72 publications evaluated, 10 were rejected for various reasons, leaving 62 studies (51 animal studies and 11 human studies) for the present review. Hyperbaric oxygen treatment has been found to have neuroprotective properties when administered after SCI. Animal studies have shown promising results and revealed various mechanisms contributing to these neuroprotective effects, including reduction of neuronal inflammation and apoptosis, reduction of oxidative stress, reduction of spinal cord edema and improvement of angiogenesis and autophagy. However, the number of clinical studies is rather small, with small sample sizes, showing various results. Regarding the use of hyperbaric oxygen treatment after SCI, the optimal timing, duration, frequency and pressure of hyperbaric oxygen treatment after SCI has not been clarified. Further high quality human studies are needed to fully elucidate the role of hyperbaric oxygen therapy in SCI management.

KEYWORDS: hyperbaric oxygen, spinal cord injury

Introduction

Spinal cord injury (SCI) refers to the complete or partial loss of spinal cord function often leading to serious consequences, ranging from partial motor and sensory less, incontinence, tetraplegia and even brain death. Symptoms of SCI depend on the extent of the injury or non-traumatic cause, and may include loss of sensation or motor control of the lower limbs, trunk and upper limbs, as well as loss of control of body functions such as breathing, heart rate, blood pressure, body temperature, bladder and bowel control, and sexual function (1, 2).

SCI is a relatively rare but costly disease that changes patients' lives, with the risk of mortality varying great-

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ly depending on the financial status of the country and largely depending on the availability of qualitative clinical care and rehabilitation services. The number of SCI patients today is unclear, but international data on the incidence indicate that each year more than 250.000 people suffer from SCI. The majority of these cases involve traumatic SCI, with the main causes being traffic accidents, falls and violence. Recent data show that SCI is associated with an increased risk of death. The cost of SCI varies greatly and many of these costs are covered by SCI patients (3).

Hyperbaric oxygen therapy is a safe and non-invasive treatment that involves placing patients in a pressure chamber and inhaling oxygen at higher than atmospheric pressure to increase dissolved oxygen in the blood to relieve symptoms and treat disease with fewer side effects. The benefits of hyperbaric oxygen therapy are plentiful including improvement of blood circulation, promotion of healing, suppression of inflammation, regeneration of blood vessels, nerves and bones. Moreover, it induces the release of stem cells from the bone marrow and their activation for tissue repair (4).

Taking into consideration that ischemia is one of the most important mechanisms responsible for secondary SCI injury, a treatment method that increases oxygen tension of the injured spinal cord should theoretically help patients' recovery (5). When administered at an increased pressure, oxygen can increase the concentration of dissolved oxygen, creating a larger pressure gradient that can drive oxygen into ischemic tissue (6).

Cells surviving the primary SCI are sensitive to secondary damage, particularly through apoptosis (7). Hyperbaric oxygen therapy mainly affects secondary SCI and can prevent further SCI caused by spinal cord ischemia-reperfusion injury. Furthermore, it inhibits cell apoptosis and autophagy, reduces oxidative stress, diminishes inflammation, promotes angiogenesis, reduces spinal cord edema and effectively promotes neuronal regeneration (8,9). Recently, hyperbaric oxygen therapy for SCI has been increasingly studied having shown promising neuroprotective results in several experimental studies; however a limited number of clinical reports have shown mixed findings.

SCI is a condition with a high rate of clinical disability. Therefore, it is urgent for clinical research to find effective ways to recover from SCI and improve mobility and sensation. The purpose of this study is to review the use of hyperbaric oxygen in the functional and neurological rehabilitation of SCI patients.

A literature review was performed in the PUBMED literature with the keywords: "hyperbaric oxygen" AND "spinal cord injury". Inclusion criteria were clinical trials and animal studies investigating the use of hyperbaric oxygen in spinal cord injury recovery. Non-English language studies, systematic reviews, case reports, in vitro studies and research protocols were excluded from the study (Figure 1).

Discussion

Search results showed 100 posts. After checking titles and abstracts, 28 articles were rejected. Of the 72 remained publications, 10 were rejected for various reasons (see flowchart), leaving 62 studies for the present review and including 51 animal studies (5, 10-63), 4 prospective randomized studies (64-67), 3 prospective case series (68-70) and 4 retrospective studies (71-74).

Animal studies

Impact of hyperbaric oxygen treatment on cell apoptosis

Plenty of studies have used the TUNEL staining to show that hyperbaric oxygen treatment significantly diminishes cellular apoptosis in injured spinal cord tissue, with a plethora of proposed mechanisms (5,33,35,37,44,47,57). Lu suggested that hyperbaric oxygen preconditioning may decrease the number of apoptotic cells and enhance the nerve functional recovery in rats after SCI (36,37).

High amounts of nitric oxide (NO) are associated with inflammation, while smaller concentrations have neuroprotective effects (75). iNOS, the enzyme that is responsible for NO production, has been found to induce cell apoptosis by increasing NO after SCI. In 2004, an experimental study by Yu et al observed that hyperbaric oxygen treatment attenuates apoptosis after traumatic SCI through the downregulation of the hypoxia-induced expression of the iNOS gene, implicating that NO regulates apoptosis (57). In 2010, in a rat SCI model, IL-1β and TNF-α were significantly decreased in the hyperbaric oxygen treatment group, a finding accompanied by reduced apoptosis by TUNEL staining (47). In 2013, Huang et al, showed that, in 36

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SCI rats, hyperbaric oxygen treatment affects the iNOS mRNA-iNOS-NO signaling pathway, by decreasing iNOS mRNA and protein expression and NO serum levels (22).

CHOP is a transcription factor that plays a significant role in endoplasmic reticulum stress-induced apoptosis (76). Caspases comprise a family of intracellular enzymes that mediate cellular apoptosis (77). An experimental study by Liu et al found that the upregulation of CHOP, caspase-12, and caspase-3 was mitigated in the SCI rats that received daily hyperbaric oxygen treatment initiated 6 hours after SCI, suggesting that hyperbaric oxygen therapy reduces SCI-induced neuronal apoptosis by downregulating the ER-stress-induced apoptotic pathway (33). Pan et al concluded that hyperbaric oxygen preconditioning protects neuron cells by reducing cell apoptosis and calcium overload, through the inhibition of expression of caspase-3, -7, -8 and -12. Moreover, it reduces neural apoptosis by inhibiting the endoplasmatic reticulum pathway; thus it may reduce the loss of motor function in SCI rats (41).

In 2014, Long et al found that mRNA and protein expression of the pro-apoptotic protein adaptor molecule ASC increased after SCI but significantly decreased when daily hyperbaric oxygen treatment was initiated immediately after SCI (35). An animal study by Chen et al showed that hyperbaric oxygen therapy may inactivate mTOR signaling pathway, leading to suppression of apoptosis and improving motor disability in SCI rats (11). Hou et al observed a protective effect on SCI through reduction of neural cells apoptosis and decreased expression of MMP-2 and MMP-9 in rats with SCI (19). Recently, Ying et al found that hyperbaric oxygen treatment diminished dendritic/synaptic degeneration and lessened apoptosis, increasing BDNF and TrkB expression and improving neurological recovery in SCI rats (56). The combination of hyperbaric oxygen therapy and erythropoietin administration enhanced the recovery of locomotor function in the hind limbs of SCI rats by attenuating neuronal apoptosis (63).

Impact of hyperbaric oxygen treatment on oxidative stress

ROS production occurs at the early stages after SCI and plays an important role in secondary injury. Nerve tissue is sensitive to alterations of the oxidative stress because of its high lipid concentration. Several studies have shown the property of hyperbaric oxygen therapy to reduce oxidative stress, but the precise mechanism by which hyperbaric oxygen therapy influences lipid peroxidation has not yet been clarified (78).

Many animal studies have shown that hyperbaric oxygen treatment leads to upregulation of antioxidant enzyme levels, such as SOD, catalase, and GPx, after SCI (13,21). Two animal studies concluded that hyperbaric oxygen treatment increased ROS and NO levels and induced heat shock protein (HSP) 32 expression through a ROS/p38 MAPK/Nrf2 pathway (20,60). Sun et al found that hyperbaric oxygen treatment in SCI rats reduced SOD and MDA levels after SCI, resulting in better clinical scores and less cystic degeneration of spinal cord (46).

Malondialdehyde (MDA) and TBARS are markers of lipid peroxidation (79). The experimental study by Topuz et al evaluated a 90-minute hyperbaric oxygen regime immediately after SCI in 40 rats. Hyperbaric oxygen treatment increased GPx, SOD and catalase levels, while significantly attenuating MDA levels in comparison to the control group. Hyperbaric oxygen therapy was found to improve neurological outcomes through reduction of oxidative stress (49). In 2007, a comparative animal study by Kahraman et al found that hyperbaric oxygen therapy and not methylprednisolone, led to a significant decrease of TBARS levels and an increase of SOD activity 5 days after SCI, further indicating the ability of hyperbaric oxygen therapy to reduce oxidative stress and thus alleviate secondary SCI (23).

The combination of hyperbaric oxygen treatment with the administration of chondroitinase ABC was found to improve neuromotor function in a rat model of SCI, compared with the hyperbaric oxygen treatment or chondroitinase ABC treatment alone. Hyperbaric oxygen treatment with or without chondroitinase ABC significantly increased SOD and decreased MDA levels, as well as GSK3β expression. The combination of hyperbaric oxygen treatment with the administration of chondroitinase ABC was found to significantly inhibit SCI-induced AQP-4 expression (32).

In animals with mid-cervical SCI, hyperbaric oxygen treatment may preserve diaphragm function and respiratory health, through an increase in antioxidant

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capacity (43). The combination of hyperbaric oxygen treatment with N-acetylcysteine administration was found to have synergistic neuroprotective effects in SCI rats, along with upregulation of IL-10 expression and downregulation of TNF-α, IL-1β and caspase-3 (58). Hyperbaric oxygen therapy combined with the administration of the nitroxide antioxidant tempol had no neuroprotective effect in rats with SCI (18).

Impact of hyperbaric oxygen treatment on inflammation

The effect of hyperbaric oxygen treatment on the inflammatory processes after SCI has been extensively investigated (5, 11, 16, 24, 25, 47, 48, 52, 53, 59). In 2010, Tai et al observed that a single hyperbaric oxygen treatment immediately after SCI, resulted in increased levels of IL-10 and decreased levels of IL-1β, TNF-α and myeloperoxidase, a marker of neutrophil infiltration, in SCI rats (47). MCP-1 is a chemokine with a role in the recruitment of monocytes and lymphocytes to inflammation sites. In 2016, the upregulation of MCP-1 after SCI was significantly decreased by hyperbaric oxygen treatment and was associated with improvement of neurological scores in a rat SCI model (50). Liang et al observed that hyperbaric oxygen therapy resulted in decreased expression of NALP3, ASC, caspase-1, and IL-1β in 120 SCI rats (25). Hyperbaric oxygen treatment has been associated with increased IL-4 and IL-13 levels along with decreased TNF-α and IFN-γ in rats with compressive SCI. This modification of the inflammatory environment led to alterations in macrophage phenotype, which may further enhance the axonal extension and functional recovery (16).

MMP-2 and MMP-9 contribute to secondary SCI, by triggering the production of pro-inflammatory cytokines (80). In 2013, a neuroprotective role of hyperbaric oxygen treatment post-SCI was found, along with significantly decreased MMP-2, MMP-9 and IL-6 levels (53). HMGB1 contributes to inflammatory damage following SCI by stimulating TLRs, RAGE and NF-κB signaling pathways, which in turn activate other cytokines, such as IL-1β and TNF-α (81,82). Hyperbaric oxygen has been found to downregulate HMGB1 and its subsequent signaling pathways, including NF-κB, TLR2, TLR4, RAGE, IL-1β and TNF-α (24,48,53). Hyperbaric oxygen treatment may enhance the recovery of neurologic function in SCI rats through the activation of the SDF-1/CXCR4 axis and the promotion of BDNF expression (38).

According to an experimental study by Zhou et al, hyperbaric oxygen therapy decreased the inflammatory reaction and glial scar formation in SCI rats through the inhibition of inflammatory cytokines iNOS and COX-2 and glial scar-related molecules GFAP and NG2 (61). In 2014, Liu et al observed that daily hyperbaric oxygen treatment after SCI decreased CX43 expression, thereby reducing inflammation by blocking the spread of inflammatory cytokines from injured neurons to healthy cells (34). Combination of hyperbaric oxygen treatment and bone marrow stem cells transplantation has a synergistic effect over the reduction of inflammatory cytokines levels (TNF-α, IL-1β, IL-6, IFN-α), promoting functional recovery after SCI in rats (15). The combination of hyperbaric oxygen therapy with Schwann cell transplantation is more beneficial than either treatment alone in the recovery of spinal cord in rats after SCI (42). In a recent rat study, Ahmadi et al showed that combined therapy with methylprednisolone and hyperbaric oxygen treatment has synergistic effects on SCI treatment (10).

Impact of hyperbaric oxygen treatment on angiogenesis

VEGF is important for angiogenesis in the central nervous system as it stimulates endothelial cell proliferation and migration and promotes neuronal proliferation (83). After SCI, VEGF is increased in order to augment vascular density and restore blood supply to the spinal cord. An animal study by Tai et al reported that a single hyperbaric oxygen treatment started immediately after SCI resulted in increased VEGF (+) cells at 4–7 days after SCI (47). Three other studies involving daily hyperbaric oxygen treatments after SCI have also showed a significant increase in VEGF levels in comparison to control groups (34,53,62). Therefore, the improvement of neurological recovery seen with hyperbaric oxygen treatment of SCI may be partially caused by the increased expression of VEGF (84).

Impact of hyperbaric oxygen treatment on spinal cord edema

Hyperbaric oxygen therapy significantly reduces spinal cord edema after SCI (5,53). MMP-2 and MMP-9 degrade type IV collagen causing increased permeability of the blood-spinal cord barrier and leading to spinal cord edema (85). In 2013, twice daily hyperbaric oxygen treatment in a rat SCI model was associated with a significant reduction in MMP-2 and MMP-9 levels after SCI. A significant reduction in spinal cord water content was also noticed (53). Higgins et al found a neuroprotective effect of hyperbaric oxygen treatment in cats with SCI. These effects were attributed to the preservation of intact nerve fibers of the spinal cord, the reversal of local hypoxia and the reduction of spinal cord edema (17). In a rat animal model, based on MRI studies, hyperbaric oxygen treatment appeared to stop the spread of hemorrhage and resolve spinal cord edema after SCI (40).

Aquaporins are water channels in cellular membranes. In 2014, SCI rats treated with hyperbaric oxygen initiated at 4 hours following SCI were observed to have a significant reduction of AQP4 and AQP9 expression, leading to reduction of water entrance into the spinal cord and decrease of spinal cord edema (5).

Impact of hyperbaric oxygen treatment on autophagy

Autophagy is a process of intracellular degradation important for the maintainance of cellular homeostasis (86). Beclin-1 and LC3-II are direct mediators of autophagy (87). The experimental study by Sun et al indicated that daily hyperbaric oxygen treatment upregulates autophagy after SCI, through increased levels of beclin-1 and LC3-II, in order to promote repair and protection (45).

Timing of hyperbaric oxygen treatment

A comparative animal study by Cristante et al showed that hyperbaric oxygen treatment improves the functional recovery of SCIs in rats, if it is administered immediately after SCI or within 24 hours (12). Falavigna et al reported that, in SCI rats, the sooner hyperbaric oxygen therapy is initiated after SCI and the larger the number of sessions, the greater and earlier is the motor recovery and smaller is the tissue injury (14). Ultra-early hyperbaric oxygen treatment (within 3 hours from injury) enhances the production of femoral CGPR in the sensory neurons in posterior horn of spinal cord (27). Hyperbaric oxygen treatment given 30 minutes after SCI had protective effects against ischemic spinal cord damage and attenuated selective motor neuron death in rabbits. Delayed hyperbaric oxygen therapy did not alter the prognosis (39). An experimental study by Yaman et al demonstrated that immediate hyperbaric oxygen treatment after SCI significantly improved clinical recovery in SCI rats. The sooner the hyperbaric oxygen treatment was initiated, the greater was the decrease in nitrite levels (51). Two old studies by Yeo et al, suggested that hyperbaric oxygen therapy initiated within two hours post-SCI resulted in improved motor recovery in SCI sheep along with less central cord cystic necrosis and degeneration in the surrounding white matter (54, 55). Hyperbaric oxygen therapy for 4 weeks has been associated with better clinical scores in comparison to 2 weeks of treatment in rats with SCI (26).

Human studies

While the beneficial properties of hyperbaric oxygen therapy in the treatment of SCI have been depicted in many animal studies, the number of the clinical studies is rather small. In 1978, the study by Yeo et al, involving complete and partial spinal cord lesions showed that hyperbaric oxygen treatment administered within 14 hours from SCI resulted in varying degrees of neurological improvement (70). A small study, in 1980, including 5 patients with cervical and thoracic SCI, depicted promising results in terms of clinical improvement after hyperbaric oxygen treatment (74). The study by Gamache et al in 1981 did not observe a significant change in neurological recovery in patients treated with hyperbaric oxygen (68). In 1989, a retrospective study by Lee et al did not find any significant correlation between hyperbaric oxygen treatment and cure rate in SCI patients (72).

A retrospective comparative study published in 2000, involved 34 patients with cervical SCI. The patients that received 1,5 hours of hyperbaric oxygen treatment once daily for 10 days were observed to have significantly higher clinical improvement rates versus the control group (71). Another recent retrospective comparative study included 40 acute SCI patients. Those patients that received hyperbaric oxygen treatment depicted significant motor and neurological improvement at 15 and 30 days after treatment (73). Zhang et al published a retrospective study, in 2021, including 78 patients with incomplete SCI. After laminectomy and posterior fixation, 40 patients received hyperbaric oxy-

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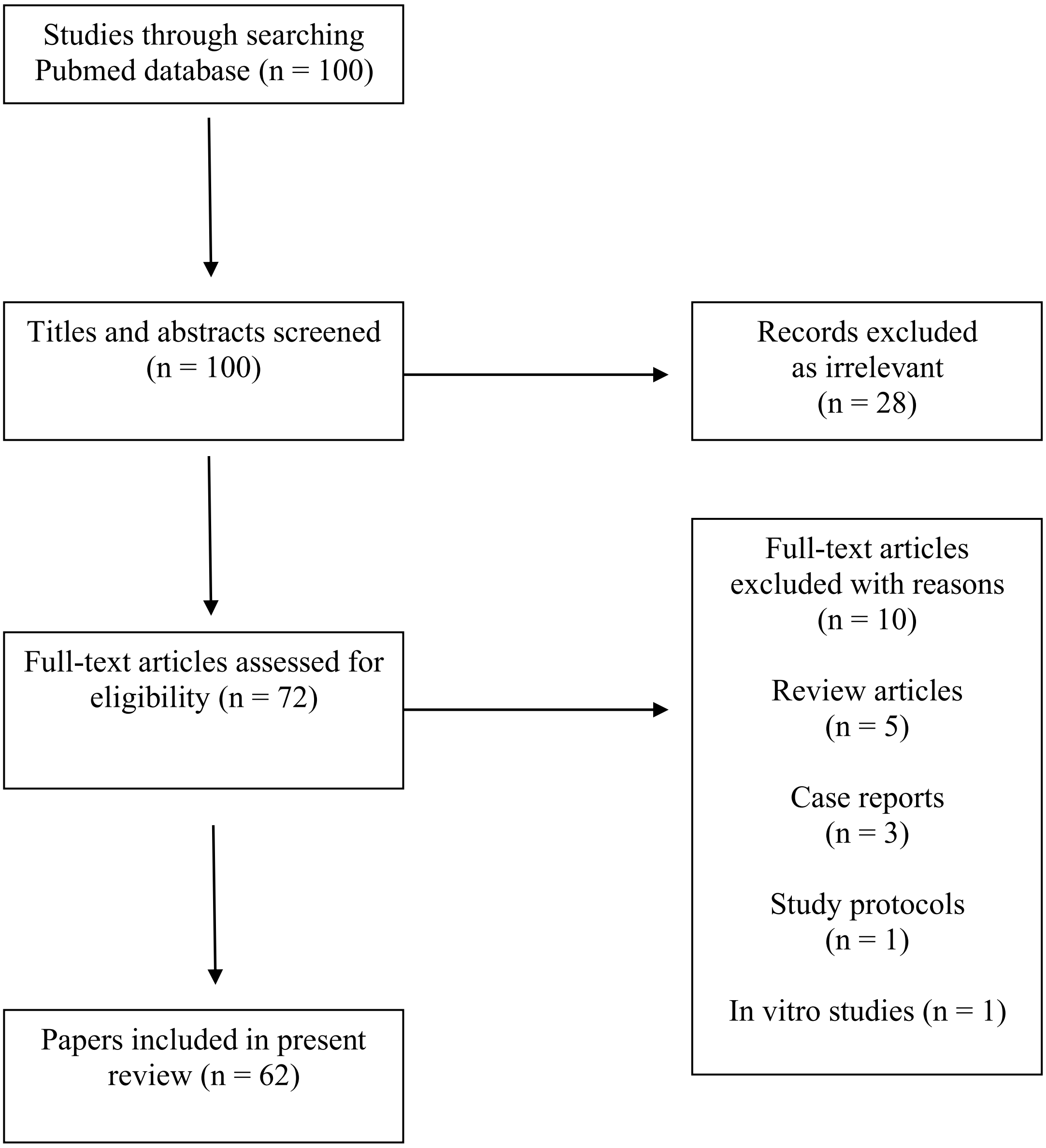
Figure 1



gen treatment while 38 patients received standard care. The study concluded that in all time points, hyperbaric oxygen treatment was associated with better recovery of sensory and motor function. Hyperbaric oxygen treatment was regarded as a safe and effective method for the management of incomplete cervical SCI and the healing effect was corresponding with the duration of therapy. The treatment had a maximum effect in recovery within the first 3 months after surgery (67).

A randomized controlled trial in 2017 compared an 8-week hyperbaric oxygen regime with conventional rehabilitation among 60 SCI patients. Authors found that hyperbaric oxygen treatment significantly improved neurological function and daily activities in SCI patients, but did not have a significant effect on depression and anxiety (64). A cohort study consisting 22 SCI patients found that there was a significant correlation between the hyperbaric oxygen treatment effect and the

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recovery rate of the ASIA motor score (69). A recent randomized controlled trial compared the clinical efficacy of the combination of hyperbaric oxygen treatment with mannitol and riluzole in 80 patients with acute SCI after thoracolumbar fractures treated with posterior laminectomy and fixation. In comparison to the control group, the experimental group showed significant improvement in motor and sensory scores, along with significant decrease of IL-6 and BDNF levels (65). Sun et al, in a recent randomized controlled trial, compared the effect of hyperbaric oxygen treatment, in 79 patients with acute SCI. Authors found that hyperbaric oxygen treatment affected the inflammatory reaction in secondary SCI by reducing serum HMGB1/NF-κB levels thereby enhancing motor and pain scores (66).

Conclusions

Hyperbaric oxygen treatment has been found to have neuroprotective properties when administered after SCI. Animal studies have shown promising results and revealed various mechanisms contributing to these neuroprotective effects, including reduction of neuronal inflammation and apoptosis, reduction of oxidative stress, reduction of spinal cord edema and improvement of angiogenesis and autophagy. However, the number of clinical studies is rather small, with small sample sizes, showing various results. regarding the use of hyperbaric oxygen treatment after SCI. The optimal timing, duration, frequency, and pressure of hyperbaric oxygen treatment after SCI has not been clarified. Further high quality human studies are needed in order to fully elucidate the role of hyperbaric oxygen therapy in SCI management.

Abbreviations List

AQP: Aquaporin
ASC: apoptosis-associated speck-like protein
BDNF: brain-derived neurotrophic factor
CGPR: calcitonin gene-related peptide
CHOP: CCAAT-enhancer-binding protein homologous protein
COX-2: Cyclooxygenase 2
CXCR4: C-X-C Motif Chemokine Receptor 4
IL-1a: Interleukin-1a
IL-1β: Interleukin-1β
IL-4: Interleukin-4
IL-6: Interleukin-6
IL-13: Interleukin-13
iNOS: Inducible Nitric Oxide Synthase
GFAP: Glial fibrillary acidic protein
GPx: Glutathione peroxidase
GSK3β: Glycogen synthase kinase 3 beta
LC3-II: light chain 3 type II
HMGB1: high mobility group box 1
MCP-1: monocyte chemoattractant protein-1
MDA: Malondialdehyde
MMPs: Matrix metalloproteinases
MMP-2: Matrix Metalloproteinase – 2
MMP-9: Matrix Metalloproteinase – 9
mRNA: messenger RNA
MRI: Magnetic resonance imaging
mTOR: mammalian target of rapamycin
NALP3: NAcht Leucine-rich repeat Protein 3
NF-κB: Nuclear factor-κB
NG2: Neuron-glial antigen 2
NO: Nitric oxide
PDGF: Platelet-derived growth factor
PGE2: Prostaglandin E2
RAGE: Receptor for advanced glycation end products
ROS: Reactive oxygen species
SDF-1: stromal cell-derived factor 1
SOD: Superoxide dismutase
TBARS: thiobarbituric acid reactive substances
TGF-β: transforming growth factor – β
TNF-a: Tumor necrosis factor-a
TLR: Toll-like receptor
TrkB: tropomycin receptor kinase B
TUNEL: terminal deoxynucleotidyl transferase (TdT) dUTP nick-end labeling
VEGF: Vascular endothelial growth factor

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Sleeping Disorders and the Effects on Health of Patients with Spinal Cord Injury

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ABSTRACT

Introduction: Spinal cord injury (SCI) is recognized as a disability affecting every aspect of patients' lives. Compared to the able bodied population, sleep disturbances are more frequent in patients with SCI and can lead to dysfunction that negatively affects quality of life. However, many healthcare providers omit to determine the quality of sleep of SCI patients or are not aware of insomnia symptoms such as restless legs or sleep apnea. A review of the current literature was performed in order to highlight the association between SCI and sleep disturbances, the importance of awareness of sleep disturbance symptoms and how these affect the overall health and quality of life of SCI patients. By using the online Pubmed database and the PRISMA guidelines, studies regarding sleeping disorders and their effect on SCI patients were identified. Results: SCI patients often suffer from sleeping disturbances which can cause severe health problems. More specifically, these patients have increased risk of developing depression, obesity, cardiovascular diseases, hypertension and sleep related breathing problems. Patients are also in increased risk for experiencing pain, fatigue, daytime sleepiness and loss of communication. Conclusion: Sleep disturbances are associated with SCI in a great extend and can lead to multiple medical complications. The pivotal role that sleep is having in overall health and quality of life cannot be underestimated.

KEYWORDS: sleep disturbances, spinal cord injury, sleep breathing disorders, sleep movement disorders, sleep quality

Introduction

According to the World Health Organization the term 'spinal cord injury' refersto damage to the spinal cord resulting from trauma (e.g. car crash), disease or degeneration (e.g. cancer). Spinal Cord Injury (SCI) is recognized as a catastrophic disability affecting every

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aspect of life. Most patients with traumatic SCI are between the second and fourth decade of life. Their life expectancy is reduced compared to the general population; however, much of this is due to peri-injury complications and if patients survive the first year past the injury then their life expectancy is impacted less. This means that many SCI patients have the potential to live a long life and for this reason it is important to prevent morbidity and mortality from secondary complications. [1]

Sleep disorders are common in patients with SCI. Indeed, patients with chronic SCI often report poor sleep quality as a consistent outcome. Sleep disordered breathing (SDB), particularly in patients with high thoracic and cervical level injuries, abnormal leg movements during wake and sleep and poor quality of sleep are some of the sleep disorders mentioned in the literature. Poor sleep may be due to pain, insomnia and/or sleep-wake circadian rhythm disturbances. Patients often report daytime symptoms as fatigue, sleepiness, difficulty in concentration and impaired quality of life. Fatigue and excessive daytime sleepiness are also associated with pain, depression, side effects of medications, spasticity and autonomic dysfunction in SCI patients. This likely contributes to reduced social participation and quality of life or in some circumstances leads to premature death. [1,2,3]

SDB is highly prevalent after SCI. There are several factors that may influence the prevalence of SDB in patients with SCI. First, the level of spinal injury affects the occurrence and manifestations of SDB and patients with tetraplegia are more likely to have SDB than patients with paraplegia. Patients with cervical SCI suffer from the full continuum of derangements that impair the ability of the ventilatory system to compensate for physiologicchallenges, including neuromuscular weakness, decreased lung volumes, abnormal chest wall mechanics, frequent use of CNS suppressants, and unopposedparasympathetic system promoting airway narrowing. [2]

The most commonly reported objectively diagnosed sleep disorder in patients with SCI, particularly in those with cervical lesions but also present in thoracic-level injuries, is obstructive sleep apnea (OSA) with an estimated prevalence of 50% to 80%. Reported estimates vary depending on the level of injury and the methodology used to measure OSA. Regardless, the prevalence of OSA in individuals with SCI far exceeds what is reported in the general population. In the general population sleep apnea has been associated with cardiovascular morbidity, and individuals with chronic SCI are also at increased risk for accelerated onset of cardiovascular disease. It is plausible that the combination of SCI and OSA may indeed increase cardiovascular morbidity and mortality. [3]

Periodic leg movements (PLM) are characterized by periodic episodes of repetitive and highly stereotyped limb movements, typically big toe and ankle dorsiflexion which are often accompanied by knee and hip flexion. The prevalence of PLM disorder appears to be markedly elevated in people with SCI, especially in tetraplegic patients. This can result in considerable disruption of sleep quality and is typically associated with excessive daytime sleepiness. Although SDB and PLM are highly prevalent in tetraplegia and can co-exist, there are many studies which strongly suggest that they are independent phenomena in tetraplegia. [4,5]

Moreover, there is evidence that the circadian rhythmicity of melatonin is disrupted in tetraplegia. It appears that complete cervical SCI, which cuts the suprachiasmatic nuclei to superior cervical ganglion pathway, is associated with near abolition of circadian melatonin rhythmicity and a markedly reduced circulating melatonin level. Other endocrine rhythms similarly modified by circadian influences, such as cortisol and thyroid-stimulating hormone, do not appear markedly affected by cervical SCI, however, the temperature is affected. The temperature phase advance observed in tetraplegia may be yet another contributor to the poor sleep quality. [2,3]

Insomnia is highly prevalent in the general population with estimates ranging from 15-30%. Women have a 1.4 times higher risk than men for developing insomnia. This disorder, defined as difficulty falling or staying asleep that persists for at least three nights per week and is accompanied by daytime consequences, is likely less common, but estimates still suggest rates of 10-20% in the population. In a recent study, most SCI patients had insomnia symptoms, although it is not clear that these patients would meet criteria for insomnia disorder as they also had significantly higher risk for SDB and had greater differences in weekday/

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weekend sleep which may be associated with insufficient sleep rather than insomnia disorder. This does suggest that evaluation for insomnia disorder is useful in understanding the effect of other sleep disorders experienced by individuals with SCI and can affect the choice of treatment. [2,6]

Treatment of SDB in SCI patients is challenging, although symptomatic improvements may be observed in many patients. The most commonly used treatment for SDB is continuous positive airway pressure (CPAP) which consists of a mask attached to the nose/face that gives a positive pressure to the upper airway preventing its collapse during sleep. CPAP is effective in eliminating obstructive events during sleep and improving oxygenation. There are challenges related to arm strength/mobility in tetraplegia and additional factors such as increased nasal congestion. This may be the reason that only 20-50% of patients with chronic SCI and SDB reported adherence to CPAP. [3,7,8]

There are multiple challenges in treating insomnia disorder in SCI patients. Pharmacological agents have multiple effects that may be even more significant among individuals with SCI. In ambulatory patients they may further increase the risk of fall and impaired cognition may be exacerbated. For this reason, pharmacological therapy is recommended only after cognitive-behavioral therapy for insomnia (CBT-I) has been attempted. CBT-I is a multi-component psychological treatment that includes behavioral techniques (stimulus control, sleep restriction therapy, sleep hygiene and relaxation/arousal reduction strategies) plus cognitive therapy to address sleep-related thoughts and beliefs. Mehta S et al, in their systematic review found evidence that cognitive-behavioral therapies, in general, are helpful for anxiety, depression, adjustment and coping problems. [9]

The aim of this study was to identify the association between SCI and sleeping disorders and to examine the consequences that sleeping disorders have on patients' overall health and quality of life. For this reason, a review of the current literature was conducted by using the online Pubmed database and following the PRISMA guidelines. Article titles were searched by using the following keywords: "sleep disturbances", "spinal cord injury", "sleep breathing disorders", "sleep moving disorders'', "sleep quality". Studies in non-English language, studies published before 2010, studies in children and adolescents, case reports and study protocols were excluded from this review. Primary search results included 256 articles. After screening of titles and abstracts, 166 articles were excluded as inappropriate. From the remaining 90 studies, 69 were rejected for various reasons (Table 1). Finally, 21 studies were included in this review.

Discussion

Periodic Leg Movement-Restless Leg Syndrome

In 2010, a study established the occurrence of PLM and Restless Legs Syndrome (RLS) in SCI patients. In this study, Telles et al, compared 24 patients: the control group was composed of 16 patients and the SCI group of 8 patients. As a result they found a 100% relevance of RLS in SCI patients. Most of the patients with RLS also suffered from PLM. These situations led to decreased quality of sleep and were associated with daytime sleepiness. [4]

Furthermore, in 2018 Peters et al, conducted a retrospective study to establish the prevalence of PLM during sleep in patients with tetraplegia, controlling for OSA. 173 participants with acute and 92 with chronic tetraplegia were included in the study. A randomly selected group of 21 patients was assessed for PLM during wakefulness. Of the participants, 41.6 % had a complete motor and sensory lesion. Sleep was poor with both OSA and PLM. There was no difference in the PLM between those with or without OSA. All 21 participants in the subgroup analyzed for PLM during quiet wakefulness, exhibited limb movements. This study confirms the high prevalence of PLM in tetraplegia and the prevalence of leg movements in non REM and REM sleep along with wakefulness after controlling for OSA. No associations between PLM and patient characteristics or injury specific aspects were found. [5]

Shafazand et al, in 2019, made a web based survey to determine sleep quality and presence of sleep disorders in participants with SCI. The study population included 304 male participants with chronic SCI. Symptoms suggestive of sleep apnea were reported by one-third of the study participants. 27% of the respondents reported daily uncomfortable leg sensation

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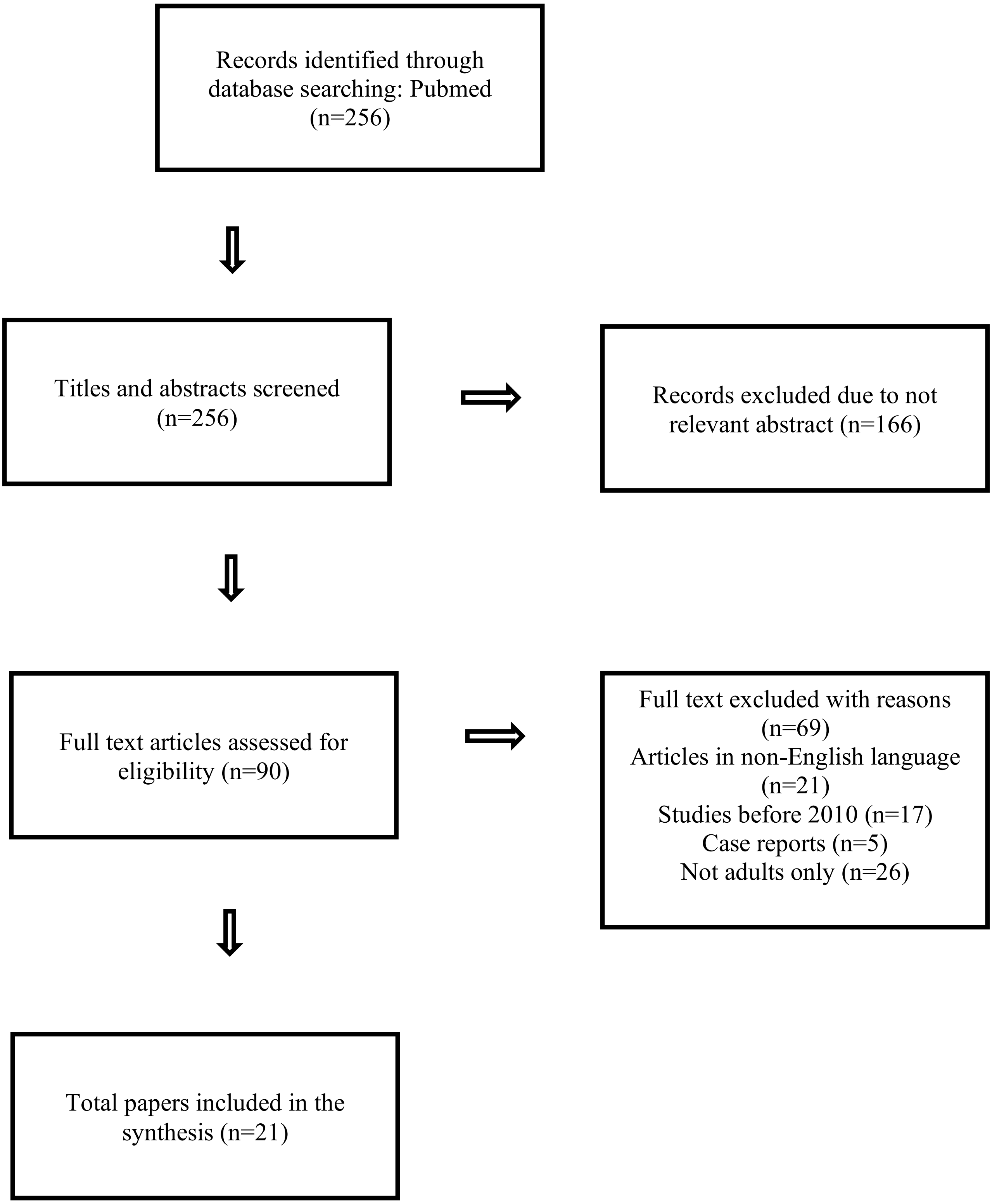
TABLE 1: CURRENT REVIEW FLOWCHART



and 28% found leg symptoms ''moderately to extremely distressing''. Compared to those without insomnia, participants with insomnia were more likely to report nighttime unpleasant leg sensations and 'urge to move legs'. Insomnia symptoms were reported by more than half of the participants, with most complaints being restless sleep or difficulty maintaining sleep. An important finding of this study was that insomnia symptoms coexisted with other sleep disorders including sleep apnea symptoms and symptoms of restless legs. This highlights the need for a comprehensive approach to the management of insomnia complaints in SCI patients, including evaluation for other sleep disorders (sleep apnea, restless legs) and conditions that interfere with sleep quality. It is mentioned that restless legs symptoms coexist with insomnia symptoms. Symptoms of insomnia influence patients' participation in meaningful life tasks and roles. These people are not able to complete daily tasks of living due to lack of energy and can also miss healthcare appointments or work obligations because of fatigue or sleepiness as a result of poor sleep. [6]

Sleep Disordered Breathing-Obstructive Sleep Apnea

Sankari et al, studied 26 chronic SCI patients [15 patients with cervical (C4-C7) and 11 with thoracic (T2-T6) level injury] who had similar demographics. The major findings were that 77% of patients had symptomatic SDB and poor sleep quality. The level of SCI affected the prevalence of SDB and type of respiratory events (more central SDB noted in cervical SCI). Ventilation decreased significantly more in those with cervical SCI than those with thoracic SCI, as evidenced by the greater drop in tidal volumes and the rise in end-tidal CO_2 seen in cervical versus thoracic SCI cases indicating the occurrence of alveolar hypoventilation during sleep. It was also noted that quality of sleep was very poor in the majority of subjects regardless of their level of injury or severity of SDB. [7]

In another study, Bascom et al, studied 18 SCI patients (10 with cervical and 8 with thoracic SCI) and 17 able-bodied participants. The aim of this study was to identify the ventilatory changes at sleep onset. They used overnight polysomnography (PSG) and if the subject had a concern about sleep difficulties Zolpidem was administered orally. Zolpidem dose was selected based on the subject's age. The number of subjects administered Zolpidem was similar for both groups. It was found that chronic SCI patients have hypoventilation on sleep onset compared to able-bodied participants. In addition, sleep onset hypoventilation predominantly presented in participants with cervical but not thoracic SCI and there was no change in upper airway resistance in either group. The study showed the occurrence of significant sleep onset hypoventilation in patients with chronic SCI compared to able-bodied subjects. The magnitude of sleep onset hypoventilation was not associated with increased upper airway resistance and was related to the level of SCI. [8]

Tran et al, conducted a prospective longitudinal observational study to determine the prevalence of SDB in acute SCI and to document the change in SDB over time during the rehabilitation period and to correlate the degree of SDB with ventilatory parameters. 16 patients with acute SCI in T12 level and above with complete motor impairment were recruited. The results showed that 11 of 16 subjects had evidence of sleep apnea and in five of them apnea was moderate to severe. This high incidence persisted during the acute admission, with 9 of 12 subjects (75%) having sleep apnea on PSG 20 weeks following injury. There was no correlation between the severity of SDB and other measures, such as level or completeness of injury, respiratory function tests or measures of ventilatory responses. This study demonstrated a high incidence of sleep apnea in the acute phase of SCI that persisted during the subacute phase of SCI. Despite the high incidence of sleep apnea, patients were relatively asymptomatic. [10]

Berlowitz et al, in 2012, examined the relationships between injury severity, quality of life, sleep symptoms, objectively measured sleep, and sleep disorders in chronic tetraplegia. They used a sample of 79 patients (39 with motor and sensory complete tetraplegia) who were not treated for sleep disorders. They observed that quality of life was worse in the complete lesions group compared with incomplete lesions. In addition, 91% of those who had complete lesions had OSA versus 55.8% of those with incomplete tetraplegia. Multiple regression analyses showed substantially stronger relationships between daytime sleep complaints and abnormalities observed in the sleep study

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in those with complete lesions. The authors concluded that OSA is a major problem, particularly in those with complete tetraplegia, and this single comorbidity is associated with reduced quality of life. In those with incomplete cervical lesions, the relationships between sleepiness, other sleep symptoms, and PSG indices were less precise. [11]

Moreover, Bauman et al, in 2016 also reached the conclusion that there is a high prevalence of OSA and nocturnal hypercapnia in individuals with SCI. 81 adults with C1-T6 SCI were included in the study; however, 10 of them did not complete the study. The authors concluded that unsupervised home sleep apnea testing with transcutaneous capnography effectively identifies sleep-disordered breathing and nocturnal hypercapnia in individuals with SCI. [12]

A prospective study by Brown et al, in 2018 included 91 patients with C1-T6 SCI; however, only 74 patients remained in the study and were evaluated for SDB. Specifically, the authors evaluated bi-level PAP for treatment of SDB in individuals with SCI. They found that PAP therapy was effective at improving OSA and hypercapnia. There was also reduction in symptoms of autonomic dysreflexia and orthostatic hypotension as well as some improved indices of quality of life. [13]

Berlowitz et al, recently assessed the effectiveness of CPAP in patients with SCI. One hundred and sixty patients were randomized to CPAP and no CPAP groups and followed up for three months. Sleepiness was significantly improved with CPAP ($p=0.01$) though other cognitive parameters were unchanged. One issue was that CPAP adherence was relatively low in the study (2.9 hrs/night, with 21% achieving >4 hrs per night) despite only randomizing patients who were able to tolerate a three-day CPAP run-in period. The fact that sleepiness was improved with CPAP despite only partial adherence is encouraging and suggests that if adherence could be improved, more substantial benefits could be achieved.[14]

Factors affecting Quality Of Sleep

In 2011, Wijesuriya et al, included a sample of 82 individuals in their study. 41 participants had chronic SCI and 41 were able-bodied. The aim of this study was to determine the impact of fatigue on health-related quality of life (HR-QOL) associated with SCI. As expected, persons with SCI were found to have significantly lower HR-QOL. Fatigue was found to be more prevalent in the SCI group, and was associated with lower HR-QOL in both groups. Factorial analysis of variance indicated significant interactions in which persons with SCI with low fatigue levels had similar HR-QOL to the able-bodied controls regardless of their fatigue level, while persons with SCI with elevated fatigue had significantly reduced HR-QOL. Factors such as age, education, completeness and level of lesion, and community integration were not associated with increased fatigue levels. However, a shorter time since injury was found to be significantly associated with higher levels of fatigue. [15]

In another study, Thijssen et al, recruited eight healthy recreationally active men and 15 recreationally active male patients with SCI. Eight of the SCI subjects presented with a complete cervical spinal cord lesion (tetraplegics), whereas seven subjects had a complete thoracic spinal lesion (paraplegics). All SCI subjects had a complete spinal cord lesion (ASIA A), varying between C5 and T12 that had existed for at least 5 years. The authors assessed the circadian variation of Tcore in SCI individuals and able-bodied controls matched for the timing of the sleep-wake cycle. Intestinal Tcore (telemetry system) and physical activity (ambulatory activity monitor) levels were measured continuously and simultaneously in 8 tetraplegics, 7 paraplegics, and 8 able-bodied controls during one 24-h period of "normal" living. The three study groups did not differ significantly in terms of the timing of the sleep-wake cycle and sleep length, both during the data collection period and via self-reports of their typical living. However, dependent on lesion level, SCI subjects demonstrated a marked difference in the circadian variation of Tcore. Tetraplegics showed a shorter time period during which the biphasic variation in Tcore was completed and an earlier nocturnal phasing of the Tcore value. The authors concluded that SCI individuals demonstrate a significant disturbance in the circadian variation of Tcore, which is unlikely explained by differences in physical activity levels. Interestingly, the circadian variation of Tcore is altered in tetraplegics, but largely preserved in paraplegics, compared to able-bodied controls. Furthermore, the disturbance in circadian variation of Tcore may contribute to the pathophysiologic mechanism that explains the frequently reported poor sleep quality in subjects with cervical SCI.[16]

A small size pilot study by Spong et al, demonstrated the safety of exogenous melatonin in tetraplegia. Exogenous melatonin may offer unique opportunities for sleep-onset insomnia and sleep phase entertainment. For this reason, they gave to 5 participants with complete tetraplegia 3 mg of melatonin two hours prior to usual sleep time for two weeks. The results showed that 3 mg of melatonin increased salivary melatonin from near zero levels at baseline in all but one participant. A delay in time to REM sleep, and an increase in stage 2 sleep were observed along with improved subjective sleep experience with a reduction in time to fall asleep, improved quality of sleep and fewer awakenings during the night. However, daytime sleepiness increased. [17]

Another cross-sectional survey by LaVela SL et al, observed a significant association of sleep dysfunction with weight gain, smoking, alcohol misuse and select chronic conditions as asthma and chronic obstructive pulmonary disease. According to the authors, sustained sleep dysfunction may contribute to health deterioration and mortality. These results highlight the need to address the high prevalence of sleep dysfunction (independent of sleep apnea) in SCI patients. [18]

A recent study by Clark et al, examined the relationships between self-reported demographics, mental health, physical health, and health behavior factors and subjective cognitive difficulties in a unique cohort of 553 SCI patients. The study conducted a cross-sectional analysis of self reported assessment data collection. Based on the results, greater subjective cognitive difficulties were associated with female gender, elevated anxiety, depression symptoms, sleep disturbance, cardiovascular disease, worse pain, polypharmacy, worse self-rated diet, and tobacco use. Depression, anxiety, pain, sleep disturbance, and injury level remained significant predictors of variance in subjective cognitive symptoms when considering all variables simultaneously. The authors concluded that improving mental health symptoms, pain experiences, and sleep difficulties may also improve subjective cognitive symptoms in individuals with SCI. [19]

Fogelberg et al, in 2016, examined self-reported sleep problems in SCI and Multiple Sclerosis (MS) patients in order to determine how common sleep problems are in these two distinct clinical populations. The study included 1.677 patients (SCI=581, MS=1096). SCI patients reported an average of 30 minutes fewer sleep per night and significantly greater difficulty initiating and maintaining sleep compared to the MS group. Although there were similar sleep problems in these groups, they exhibited different sleep problem profiles. As far as SCI patients are concerned, an additional focus on increasing sleep quantity and reducing sleep disruptions may be warranted. The same authors conducted a similar study in 2017, in order to examine the experience of sleep among SCI patients. The patient sample used was taken from an ethnographic study of community-dwelling adults with SCI. Twenty participants were included; 14 men and 6 women. Eighteen of these participants discussed sleep-related issues. Two participants did not mention sleep in any significant way. Three major categories were assessed: sleep difficulties following SCI, barriers to achieving sufficient amounts of high quality sleep and impact of sleep disturbances on daily function. Participants described diminished sleep duration and irregular sleep patterns. Several factors contributing to poor sleep were identified; including SCI related circumstances and sleep environment. Functional ability and quality of life were negatively influenced by several factors including pain, depression, obesity, and pressure ulcers, all of which can be exacerbated by poor sleep. SCI patients reported shorter sleep duration, more daytime sleepiness and greater difficulty in falling and staying asleep. Sleep disturbances led to feeling tired or fatigued during the day, and in some instances this sense of fatigue impacted patients' cognitive functioning. Some patients responded to daytime fatigue by skipping valued everyday activities while others attempted to complete them despite feeling tired, which often created safety concerns. [20,21]

Pain is a significant problem for many SCI patients. They describe pain as the most difficult medical condition to deal with; more so than the loss of motor or sensory function. Persistent pain associated with SCI, negatively affects functioning and physical health, including sleep, reducing quality of life. Avluk et al, in a cross-sectional study assessed the relationship be-

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tween chronic pain and functional status, depression and sleep quality in SCI patients. They observed that pain severity was positively correlated with impaired sleep. The quality of patients' sleep may be affected by the persistence and intensity of pain. In this study it was also noticed that patients who wake up have trouble maintaining sleep because of pain. [22]

Hassanisirdehi et al, conducted a cross sectional study to establish the relationship between pain and its effects in SCI patients. 58 male veterans suffering from SCI were admitted for a regular follow-up. To evaluate patients' pain quality and the effect of pain on daily life, a 3 part questionnaire concerning lumbar, cervical and shoulder pain was administered. Individuals with lumbar pain felt less recovered after sleep, had more problems going to sleep and reported a significant amount of pain affecting their daily life. Pain was higher in patients with lower General Health Questionnaire score or anxiety/depressive disorder. [23]

Another cross-sectional study by January et al, investigated the medical complications that increase the risk for poor sleep in adult patients with pediatric onset SCI and explored the relation between poor sleep and psychosocial outcomes. The study included 180 participants; 56% with tetraplegia and 74% with complete injuries. Poor sleep occurred with greater frequency in those with tetraplegia and the unemployed. Neck, shoulder, arm and lower extremity pain was associated with increased risk for poor sleep. Individuals suffering from poor sleep reported lower levels of mobility, perceived health and subjective happiness. Pain and secondary complications significantly increased the odds of poor sleep. Additionally, poor sleep was associated with decreased mobility and measures of well being. [24]

A recent study concerning SCI patients concluded that sleep problems, over and above other factors such as health and pain, adversely affect mental health. Patients with poor sleep reported lower levels of independence mobility in community activities and decreased perception of health and happiness. Another recent study showed that quality sleep is an important correlate of wellness in SCI patients. According to Alvaro et al, sleep disturbance and mental health exhibit a reciprocal relation such that mental distress disrupts sleep and poor sleep further exacerbates psychological symptoms. [25]

Conclusion

SCI is a severe condition that affects different aspects of patients' health and everyday life. Sleep disturbances are very common in this patient group. The aim of this study was to increase physicians' awareness of the pivotal role that sleep has in patients' overall health and quality of life and highlight the severe health problems following sleeping disorders. Physicians should always evaluate patients' quality of sleep and firmly address any problems. Further research is needed for finding promising solutions to sleeping disorders in this particular group of patients.

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