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

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*or*

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

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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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# What is Abraham Lincoln's connection to Marfan syndrome?

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## ABSTRACT

Abraham Lincoln, a tall and thin young lawyer from Kentucky, who decided in the middle of the 19th century to enter politics, had all the necessary qualifications. His name has become synonymous with the unwavering honesty of a truthful fighter who is unconcerned in the face of adversity. From the first moment he assumed the presidency of the United States, he set as his life's goal the realization of a youthful vision, the abolition of slavery. When diplomatic contacts and attempts at compromise failed, he was forced to resort to the dynamic solution. The American Civil War was the inevitable product of intransigence, but it resulted in mutual agreements bringing order, freedom and democracy to the United States. Lincoln's life was full of difficulties, unexpected obstacles, childhood losses, teenage frustrations, chronic illnesses, and periods of depression, triumphs, victories, but also defeats in politics and on the battlefields. Medicine played an important role in the health problems of the 16th American president, especially those that probably hindered his course and determined his decisions in critical periods. The possibility that he suffered from Marfan syndrome has been the subject of research, in order to justify Lincoln's body type and his special facial features.

**KEYWORDS: Abraham Lincoln, Marfan syndrome, American civil war.**

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## Childhood

Abraham Lincoln was born on February 12, 1809 in a poor one-room hut in the wooded western provinces of the country, a few kilometers south of Hodgenville, Kentucky (Figure 1). He was the second child of Thomas and Nancy Hanks Lincoln. A distant ancestor of his, the weaver Samuel Lincoln, had first immigrated to Massachusetts from England in 1637. The next generations preferred to live in more western areas (New Jersey, Pennsylvania, Virginia). Grandfather Abraham eventually settled in the greater Kentucky area, where he was killed in an Indian raid in 1786 [1, 2].

His father Thomas and his family were forced to move to southwestern Indiana in 1816 under pressure as he faced a lawsuit challenging the title to his Kentucky farm. Abraham's memories of that period can be summed up in a few words: he helped his father with farm work but mostly watched him in his various pursuits. His parents were members of the Separate Baptists church, which forbade alcohol, dancing and human slavery [3].

On October 2, 1818, he experienced one of the worst disasters of his life, the death of his mother. Next to the father, his sister Sarah, only 11 years old, two years older than him, was left to take care of the house. However, his father married a year after Nancy's death, on December 2, 1819. His second wife was Sarah ("Sally") Bush Johnston, a widow with three children, who was to become Lincoln's "angel mother". It seems that this woman instilled in him the mood for constant study. She also instilled in him the subtle sense of humor that so often got him out of difficult situations in the years of big decisions.

When Abraham became an adult, he only knew how to read, write, and do mathematical calculations using the rule of three. The books he read during this period were the King James' *Bible*, Aesop's *Fables*, John Bunyan's *The Pilgrims' Progress*, Daniel Defoe's *Robinson Crusoe*, Mason Locke Weems's *The Life of Washington*, and *The Autobiography of Benjamin Franklin* [4].

## The beginning of a brilliant career

Lincoln was essentially self-taught. He received only occasional lessons from traveling teachers for a total of 12 months. This did not prevent him from turning into an insatiable bookworm. As a teenager, he took on services for neighbors and used to give his father all the proceeds from them, until the age of 21. He was tall, strong, athletic and excellent at chopping wood with an ax (Figure 2). His daring was so great that he once defeated in a wrestling match Jack Armstrong, a notorious bully of a gang of youths called the *Clary's Grove boys*.

In March 1830, the family immigrated to Illinois. The restless Lincoln tried a variety of professions but obeying his natural attraction to knowledge he turned to legal science. In 1836, after passing the licensing exam, he began practicing law. At the same time, he became interested in the opposite sex. His first love affair was with Ann Rutledge when he had moved to New Salem in 1835. It was a "romance with a lot of truth" and Lincoln had never loved so hard. Ann died early of typhoid fever in August 1835. Lincoln never stopped mourning her death. Her memory saddened him but inspired him at the same time.

Another consulship, with Mary Owens of Kentucky, did not prosper. Instead, his acquaintance with Mary Todd, in 1839, resulted in marriage in November 1842. It is said that on the eve of the wedding, when asked where he was going, he replied *"To the Hell, I suppose"*. In 1844, the couple purchased a home in Springfield, near Lincoln's law office [4, 5].

They had 4 children, of whom only one survived. Robert Todd Lincoln was born in 1843 and lived until 1926. He became a millionaire business lawyer, and also served as US Secretary of the Army and Ambassador to Great Britain. The other children died early. Edward Baker (1846-1850) died of tuberculosis, Willie (1850-1862) of an unknown fever and Thomas "Tad" (1853-1871) of a heart attack.

The partnership with William Herndon began in 1844. His partner was highly educated, eloquent and had extreme views. This partnership had the qualities of a critical mass and often proved explosive and highly effective. Lincoln also served on the Illinois Central Railroad, where he worked behind

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***Figure 1.*** *Abraham Lincoln was born in a poor one-room hut.*

***Figure 2.*** *He was tall, strong, athletic and excellent at chopping wood with an axe.*

the scenes to obtain privileges from state authorities. The railway organization retained him in service as a regular attorney. He also handled the affairs of other railway companies, as well as banks, insurance companies and commercial and industrial enterprises.

He soon became one of the most prominent and successful lawyers in the State of Illinois. He became primarily known not only for his intelligence and practical spirit but also for his unswerving and absolute honesty. It was the time when he decided to get involved in politics. His morality and style were soon discernible. As a candidate for Congress in 1846, he printed pamphlets declaring his belief in the doctrine of necessity [1, 2, and 6].

**The road to the presidency**

He was clear in his views. He agreed with US President Andrew Jackson on most points, but disagreed with the view that the government should stay out of economic activity. At the same time, he admired Henry Clay and Daniel Webster for their conceptions of a growth-promoting economic policy. In his opinion, Illinois and the West as a whole needed a similar aid in their economic development. This explains his enlistment from the beginning with the party of Clay and Webster, the Whigs.

Between 1834 and 1840, he was elected four times as a representative of the Whigs party in the Illinois State Legislature. From this position, he devoted himself to promoting an ambitious program to build a network of railways, roads and canals. As a member of the local Assembly, he declared that, despite his opposition to slavery, he did not support its abolition.

He served in the federal Congress only once, in the period 1847-1849. It was then that he introduced a bill for the gradual and, upon compensation of the slave owners, emancipation of the slaves in the administrative division of Columbia.

However, no one took it seriously. Much of his time was devoted to "presidential politics," in the sense of overthrowing a Democratic president and placing a Whig in the presidency. On the occasion of the Mexican-American War, he took the opportunity to put forward a candidate for the presidency. He advocated immediate action while rejecting President James Polk's claim that Mexico had started the war by spilling American blood on American soil. With genuine political sensibility, he voted to disapprove of Polk and the war, while at the same time voting to send munitions and supplies to continue the war [7].

At the same time, he was working to promote Zachary Taylor, a war hero, as a candidate for the presidential election. He took an active part in his election campaign, but after Taylor's success he experienced great disappointment when he was not given the post of head of the general land service as a reward. Meanwhile, his criticisms of the war had

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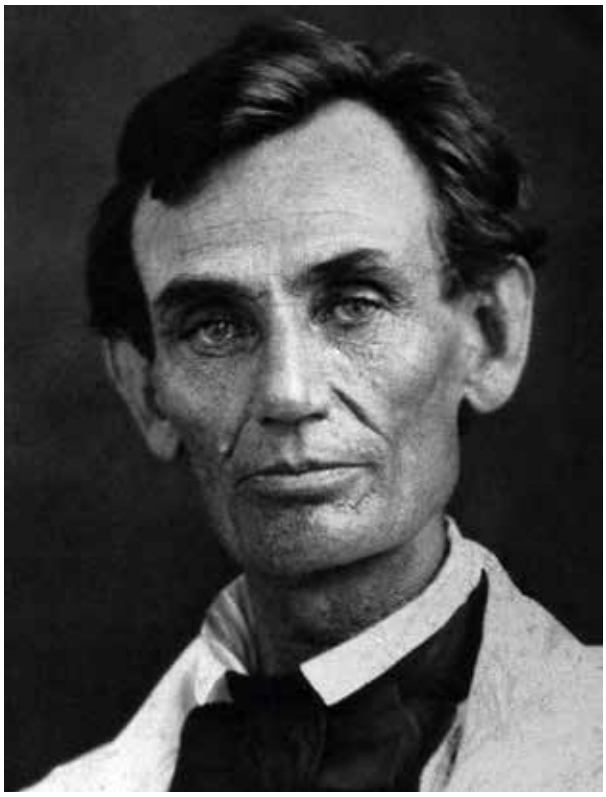

***Figure 3.*** *The emerging tendency of the Southern States to secede gave Abraham Lincoln an opportunity to demonstrate his oratorical skills.*

***Figure 4.*** *During the four years of fratricidal conflict, individual operations by both factions did not form part of a logical sequence leading inexorably to an ultimate goal, the victory.*

not won the approval of the electorate in his district. In his 40s, he had every reason to feel like a failed politician.

For about five years he was little involved in politics. The emerging tendency of the Southern States to secede, however, provided the opportunity he had been waiting for to display his oratorical skills. In 1854, his political opponent Stephen Douglas attempted to get Congress to pass a bill, according to which slavery was to be allowed in the acquired territory of Louisiana, and the settlers of Kansas and Nebraska were to be given the right to decide for themselves whether to allow slavery in these "territorial divisions" **(Figure 3)**.

The Kansas-Nebraska Act caused a violent reaction in Illinois and the other Northwestern States and gave rise to the Republican Party, hastening the disintegration of the Whigs' Party. Along with many thousands of other homeless Whigs, Lincoln joined the Republican Party in 1856. Very soon, some influential Republicans in the Eastern States began to cultivate the view of a partnership between Douglas and his Democratic followers in the West. But Lincoln was determined that he, and not Douglas, should take over the leadership of the Republicans of his State, as well as of all the Northern States.

On May 18, 1860, he was anointed the candidate on the third ballot at the Republican Party Convention in Chicago. Soon after, he left the legal profession for good and devoted his time to managing his election campaign, choosing not to give campaign speeches himself.

With the Republicans united and the Democrats divided, and with a total of four candidates in the race, Lincoln won the election on November 6th. Such was the electoral system that, although not a single person in the Far South voted for him, and although those who voted for him in the whole country did not exceed 40%, he obtained a clear and decisive majority in the body of electors [8].

## American civil war

There are not a few who believe that the presidency of Abraham Lincoln is directly related to the American civil war. Perhaps they are not wrong, if we consider that his election, in 1860 as president of the USA, triggered a chain reaction of secessions. While he himself did not support the immediate or gradual abolition of

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***Figure 5.*** *After taking blue pills, Lincoln's behavior and physical condition were altered. He exhibited anger outbursts and strange behavior, memory loss and insomnia. His hands trembled under stressful situations and he sometimes stumbled.*

***Figure 6.*** *The hypothesis that Lincoln suffered from Marfan syndrome has been called into question due to his physical strength and athletic ability.*

slavery, only the prohibition of its spread, his opponents invoked a number of arguments. They argued that article 4 of the constitution "regarding fugitive slaves" was not respected. They were disturbed by the increasing power of the North in the central government, which threatened the interests and way of life of the South. They claimed that Lincoln's vision of the right of self-determination of the constituent States undermined the foundations of the Union. As Lincoln disagreed and reacted to the secession of the Southern States, the dispute was moved to the battlefields for resolution.

Moreover, there are not a few who today believe that the root cause of the civil war was the institution of slavery. The North fought to abolish it while the South fought to preserve it. The truth is that it developed into a total and absolute war, which could only be ended by the complete supremacy of the Union forces over the Confederate forces, or their complete inability to do so. The gulf that separated them was unbridgeable.

Immediately after Lincoln's election to the presidency, seven Southern States (Alabama, Florida, Georgia, Louisiana, Mississippi, South Carolina and Texas) seceded, forming the *Confederate States of America*, a completely separate and independent polity entity headquartered in Montgomery, Alabama. Later, the capital was moved to Richmond, Virginia.

The trigger for escalation came on April 12, 1861, when the Confederacy bombarded the frontier *Sumter*, at the entrance to Charleston Harbor Channel. Lincoln managed by clever manipulations to provoke the Confederacy to take that initiative of attack and the responsibility of starting the war [8, 9].

In the four years of fratricidal conflict, it is a fact that the individual operations by both factions did not form part of a logical sequence leading inexorably to an ultimate goal, the victory. On the contrary, they were fragmentary with a strong local character, without interdependence among themselves. The objectives of the operations were not aimed at victories integrated into a more general strategic plan, but at the acquisition of advantages that would ensure the continuation of the war with the same intensity, without a prognosis for a possible exit from it.

The leaders of the North were rotated in the early

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***Figure 7.*** *Nancy Hanks Lincoln was tall, thin, bony, and hunchbacked, with long limbs, a large head, a broad forehead, and a scaphoid shape chest.*

years of the war. Names like those of Winfield Scott, George McClellan, and Henry Halleck were tried, but either failed or did not inspire credibility with their practices or inaction. Finally, Lincoln turned to Ulysses Grant. He recognized his military intelligence and made him commander-in-chief in March 1864. The difference was immediately apparent. Military operations were now conducted within the framework of a specific master plan with a defined end goal and an obsession with its fulfillment **(Figure 4)**.

In the opposing camp, things were developing differently. The capable General Robert Lee assumed command in the second year of the war, struggling with poorly supplied forces, in attacks and defensive distractions. However, the balance had now turned towards the Northerners. The finishing blow was delivered by assigning initiatives to William Sherman.

Sherman's famous "March to the Sea" began on November 15, 1864. It was the beginning of the end. Along the way, Northerners ravaged Georgia's countryside and burned its towns in order to force the inhabitants to turn against their government for their plight, destroying every available supply. Sherman pretended to attack one city, while actually attacking another [9, 10].

Finally, the capitulation was signed in the early afternoon of April 9, 1865. Lee went first, formally dressed, carrying his sword and waiting for Grant who arrived a short time later unarmed in mud-covered campaign uniform and with his rank insignia faded.

On the evening of April 14, John Wilkes Booth shot Lincoln at Ford's Theater in Washington. It was Good Friday. Early the next morning, Lincoln passed away.

**Blue Pills**

Abraham Lincoln's health problem has concerned researchers for a long time. The periods of depression that affected some of his decisions, but above all the change in his behavior after taking pills of dubious identity, forced the scientific community to investigate the matter in depth.

When he was only 9 years old, he was kicked in the head by a horse and was knocked unconscious for several hours. He once cut his hand with an axe chopping wood. In 1828, he was hit on the head in a robbery attempt at his home, while he suffered frostbites on his feet in the winter of 1830-1831.

Lincoln contracted malaria twice, in the five years 1830-1835. The second time, his condition was deemed more serious and he was required to remain bedridden, in isolation, in a neighboring house until he recovered. In November 1863, he contracted smallpox. Although the true severity of the disease was not publicized at the time, recent studies suggest that it was severe enough to weaken his strength and force him to curtail scheduled public meetings. Periods of depression have also been reported, mainly due to the loss of loved ones, family strife or some defeats during the civil war.

Most of Lincoln's biographers report that he often resorted to blue pills, implying the ones that doctors of the time prescribed to patients with symptoms of

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hypochondriasis and melancholia. The main active ingredient of these pills was the element mercury. We know that this substance was used from the 16th century to treat syphilis, although it was also administered in other pathological cases. It is more than certain that Lincoln did not suffer from syphilis, but the same cannot be said about possible poisoning from chronic mercury intake [1-3].

It has been written that after taking blue pills, his behavior and physical condition changed. He exhibited anger outbursts, adopted strange behavior, experienced memory loss and insomnia. Hands trembled under stressful situations and he sometimes stumbled, signs that can be attributed to mercury **(Figure 5)**. People around him have pointed out the irritation that characterized him after taking the blue pills, while, immediately after stopping them, he behaved like a "saint" [3, 4].

After being sworn in and assuming his duties in the White House, Lincoln displayed anger during an official meeting. Because he considered the blue pills guilty, he decided from August 1861 to discontinue them. What is important in the case of his irritable character is not how often the outbursts occurred, but how rarely. Because the challenges were countless. He had to manage soberly the insolence of officers, the insults of friends and foes, the selfishness of editors, representatives, senators, governors, cabinet members and generals. And at the same time he had to tolerate the paradoxes of a multitude of diverse people who irritated him excessively.

It is certain that he never contracted syphilis. The long-term intake of mercury pills is focused on a single word: "syphilophobia". Lincoln, like many of his contemporaries, feared contracting the disease, preferring to take every protective measure against it, even in the absence of symptoms [11].

**Controversies about Marfan syndrome**

The figure of Lincoln is deeply etched in the collective memory in all its details. In a report of the time, he is described as "tall, languid, thin, reaching the height of 2 meters, with hunched shoulders and upper limbs that swing and end in long-fingered hands, disproportionately long compared to the legs." [5]. His tall and lean body shape, the long and thin face, as well as the huge hands and feet, raised suspicions that he was suffering from Marfan syndrome already in the early 1960s.

French pediatrician Antoine Bernard-Jean Marfan first described the syndrome in a young girl with thin fingers (arachnodactyly) and several skeletal abnormalities [12]. The incidence of the disease ranges from 2 to 3 cases per 10,000 people and is inherited in an autosomal dominant manner. Thirty percent of cases are sporadic and represent spontaneous mutations. There is considerable variation within the same family, which suggests that altered genes and/or environmental factors are involved in the development of the disease. The pathogenesis is related to the abnormal biosynthesis of the extracellular protein fibrillin-1 which is the main component of microfibrils, which provide a supportive function in inelastic tissues such as the aortic orifice and eye ligaments. [13].

Diagnosis is based on clinical criteria, from the cardiovascular system, the skeleton and the eyes. Many manifestations depend on age or maturation. Tall stature can be noticed from birth and persists into adulthood. Reduced subcutaneous fat gives the impression of stunted growth in infancy. Mental function is normal. Patients are characterized, in addition to tall stature, by a long length of the upper limbs at full extension, arachnodactyly, loose joints, and ectopy of the eye lens, early myopia, aortic enlargement and mitral valve prolapse in the heart [13].

In 1962, Gordon from Cincinnati first hypothesized that Lincoln suffered from Marfan syndrome, based primarily on his and his mother's body shape [14]. Two years later, Harold Schwartz, a cardiologist from California, in his article described the case of a 7-year-old patient with Marfan syndrome, whose ancestry coincided with distant ancestors of Lincoln [15]. In 1964, in the scientific journal JAMA, letters were published between Gordon and Schwartz on the same issue. An issue was whether the president had inherited the mutated gene from his mother or father [16, 17]. In this public debate Montgomery took part, who denied the hypothesis that Lincoln suffered from the syndrome, because of his physical size and athletic skills [18] **(Figure 6)**.

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However, it was never reported that Lincoln had loose joints or that he had a heart murmur and eye problems. No aortic abnormalities were revealed at autopsy. In his article, John Sotos, a cardiologist with a special interest in the medical histories of US presidents, proposes a theory based on the new mutations of the gene locus expressed in the known phenotype of the syndrome [19]. We are talking about "marfanoid syndromes", one of which is called multiple endocrine neoplasia type 2B or MEN2B. It is a cancer syndrome characterized by neuromas, thyroid cancer, pheochromocytoma and Marfan syndrome-like features.

Sotos relies on the anatomy of Lincoln and his mother to argue that both had MEN2B. Nancy Hanks Lincoln was tall, thin, bony, and hunchbacked, with long limbs, a large head, a broad forehead, and a scaphoid shape chest **(Figure 7)**. Both of their faces looked alike, both to each other and to the classic face of Marfan syndrome. Both were characterized by muscle weakness and had periods of inexplicable melancholy. Nancy died at the age of 34 and her death was reported as "death from exhaustion", confirming the hypothesis that she was suffering from a cancer syndrome.

DNA analysis of Lincoln himself had also been suggested at one time. The material would come from tufts of hair and small pieces from the skull. A panel of geneticists, forensics and lawyers was formed and met in 1991 to decide whether Lincoln's genetic material contained mutations in the gene that codes for fibrillin-1. However, bioethical issues arose [20]. How sure are we that this analysis does not violate personal data? We also know the positive psychological effects that the discovery that a successful US president suffered from Marfan syndrome would have for those suffering from the genetic disease and have low self-esteem. Many argued that Lincoln himself would have viewed analysis favorably if he was convinced that it would contribute to the common good. However, the analysis was never performed due to technical difficulties.

## Conclusions

The current opinion holds that Abraham Lincoln suffered from roughly the same cancerous marfanoid syndrome that his mother suffered from. However, the hypothesis that he suffered from Marfan syndrome itself has not completely collapsed. A patient once said: "*The fact that Lincoln may have suffered from a genetic disease gives all of us hope that one day we will be able to contribute to society and be useful.*"

### *Conflict of interest*

*The authors declared no conflicts of interest.*

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# Application of Nanotechnology in Medicine. Smart Biomaterials and Biosensors

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## ABSTRACT

Nanomaterials have found a wide field of application in medicine in terms of diagnosis, tracing, and treatment. This nanomedical technology involves drug delivery couriers, in vivo medical imaging, in vitro diagnostics, therapeutic techniques, biomaterials and tissue engineering products. In nanobiomedicine, tissue engineered scaffolds establish a tissue specific nanoenvironment to maintain and regulate cell behavior and function. Nanoscaffolds play a vital role in storing, releasing and activating a wide range of biological factors, along with aiding cell-to-cell communication and cell-soluble factor interaction. Certain fabrication methods such as self-assembly, phase separation, and electrospinning technology form 2D and 3D nanopatterns that play different roles in cell manipulation and functional tissue formation. Localized and controlled delivery of biological factors, response to certain stimuli, degradation rate of the nanomaterials and reproduction of the forming tissues, are issues with emerging research.

Recently, nanotechnology has revolutionized the development of biosensors. The transduction mechanisms have been significantly improved with the use of nanomaterials and nanostructures. Hybrid nanostructures, quantum dots, nanoparticles for enzyme immobilization, are widely used for the merging of chemical and biological sensors. The application of these nanomaterials for sensing several key pathways and regulatory events made the overall process fast, easy to execute, and better in terms of performance providing a friendly and result-oriented experimental support. Nanobiosensors are highly versatile and multifunctional so they can find application in broad biomedical and environmental fields.

**KEYWORDS: Nanobiomedicine, smart biomaterials, nanomaterials, nanobiosensors.**

## 1. Nanobiomedical technology

The engineering of human tissues to cure diseases is an interdisciplinary and a very attractive field of research both in academia and the biotechnology industrial sector. Three-dimensional (3D) biomaterial scaffolds can play a critical role in the development of new tissue morphogenesis via interacting with human cells.

Biomaterials after implantation experience a tremendously dynamic environment in physiological complexes that demand better techniques and meth-

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TABLE 1.

| Nanobiomedicine applications |
|---|
| • Scintillation crystal materials for medical PET imaging devices<br>• Multimode imaging<br>• Intelligent nanoscale contrast agents for imaging and treatment<br>• Early cancer diagnosis<br>• Molecular diagnostics and disease pathology<br>• Drug storage, targeting and delivery<br>• Nanotech approaches to drug design<br>• Biologicals and targeted therapies<br>• Biological basis of compound activity<br>• Pharmacology and toxicology of nanoparticles<br>• Using biological building blocks to create novel materials and devices<br>• Mechanics of biological and bioinspired materials<br>• Using materials to probe, alter, and control biological responses<br>• Understanding biological responses to implanted or injected materials<br>• Gene delivery |
| **Nanobiomedicine developing research fields** |
| • Computational biology<br>• Developmental biology<br>• Cancer Research<br>• Stem Cells<br>• Biosurfaces and biointerfaces<br>• Cellular transport<br>• Protein-protein interactions<br>• Subcellular targeting<br>• Simulation of biological systems<br>• Systems approaches<br>• Genome analyses and techniques<br>• Cellular and molecular dynamics<br>• Medical diagnosis and treatment<br>• Placental Studies<br>• Drug kinetics<br>• Gene therapy<br>• Ethnics and legislation |

*All values are presented as mean±SD*

odology to monitor (a) their molecular interactions with the host, (b) their biodegradation to structural integrity changes, and (c) their effect on functional tissue formation. Simple polymeric biomaterials act as scaffold and provide mechanical and physical properties required for tissue ingrowth. However, they provide insufficient biomimetic property and lack of interactions with human progenitor cells for the promotion of functional tissue formation. Therefore, the development of advanced functional biomaterials that respond to stimuli is the next choice to generate smart 3D biomimetic scaffolds, actively interacting with human stem cells and progenitors along with structural integrity to form functional tissue within a short period.

To date, the use of nanotechnology offer the design of smart biomaterials that interact with biological systems for a wide range of biomedical applications, from the delivery of bioactive molecules and cell adhesion mediators to cellular functioning for the engineering of functional tissues to treat diseases. (**Table 1**) Therefore the rational design of smart biomaterials and their creation in an economically viable route remain an interesting and upcoming field.

### *1.1 Nanomaterials and their applications in nanomedicine*

Nanomaterials are defined as materials composed of natural or synthetic components with at least one dimension ranging between 1-100nm. The predominance of quantum mechanical phenomena at the nanoscale produces unique surface and bulk properties that do not manifest at larger scales. These have been used in a wide range of biomedical applications. This nanobiomedical technology includes: (1) drug delivery couriers, (2) in vivo medical imaging, (3) in vitro diagnostics, (4) therapeutic techniques, (5) biomaterials and (6) tissue engineering products. [1-3]

**(1) Drug delivery.** Nanoscale delivery vehicles can enhance the therapeutic efficacy and minimize adversities associated with available drugs, enable new classes of therapeutics, and encourage the re-investigation of pharmaceutically suboptimal but biologically active new molecular entities that were previously considered undevelopable

**(2) In vitro diagnostics.** Nanotechnology-based sensors (nanowires, nanotubes, nanoparticles, cantilevers, and micro-/nanoarrays) can enable fast and high throughput detection of disease biomarkers with higher sensitivity and lower sample consumption. It is also promising for the early detection of viruses, bacteria, and circulating tumor cells, as well as for single cell analysis.

**(3) In vivo imaging.** Nanoprobes (magnetic nanoparticles, quantum dots, and carbon nanotubes) pro-

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TABLE 2.

| Smart biomaterial for cellular/TE applications that respond to various types of stimuli (PEO= polyethylene oxide, PO=polypropylene oxide, DOX=doxorubicin, T=temperature) | | |
|---|---|---|
| Poly N-isopropylamide | T | Patterned cells seeding and co-culture |
| PEO-PO-PEO | T | Tissue engineering for cartilage formation |
| PNIPAm-Arg-Gly-Asp | T | Controlling osteoblasts adhesion and proliferation |
| Poly(2propylacrilic acid) | pH | Protein/DNA intercellular delivery |
| Chitosan/Polyethyleneimine (CS/PEI) blend | pH | Scaffold for cellular functioning and cartilage tissue engineering |
| Self-assembling peptide | T | Neural tissue engineering.<br>Dermal fibroblasts growth and proliferation. |
| Azobenzen | Light | Human umbilical vein endothelial cells |
| Spiropyran | Light | Cell capture and release |
| Poly(2Acrylamido-2-methyl-propane-sulphonic acid-co-N-butylmethacrylate) | Electric Field | Controlled delivery of drug and cells |
| Poly(N-isopropylamide-acrylamide-chitosan) (PAC)-coated magnetic nanoparticles (MNPs) | Magnetic field, T, pH | Human dermal fibroblasts and normal prostate epithelial cells culture and cancer drug delivery |
| Poly(6-)-methacryloyl-D-galactopyranose)-SS-poly(γ-benzyl-S-glutamate) (PMAgala)-SS-PBLG) | Redox reaction | DOX delivery and human hepatoma cell receptor targeting |
| Poly(ethytlene-glycol)-Poly-acrylate | Light | Human mesenchymal stems cells (MSCs) growth, proliferation and chondrogenic differentiation |
| Gold (AU) membrane microchip | Electrochemical | Controlled release in implants |
| Antibacterial Ti-Ni-Cu shape memory alloys | T | Cellular compatibility (e.g. L929, MG63) |

vide a faster, less invasive, and more accurate way to diagnose diseases, especially neoplasmatic pathologies, at their earliest stages and monitor disease progression. Other fields of future application are: (a) reporting in vivo efficacy of therapeutics, (b) tracking nanocarrier bio-distribution in the body, (c) helping surgeons to locate tumors and their margins, (d) identify important adjacent structures, and (e) mapping sentinel lymph nodes.

**(4) Therapeutic techniques.** Certain nanomaterials have unique therapeutic properties that differ from conventional drugs, and can, therefore, be directly used to treat diseases. It is proved that hafnium oxide- and gold-based nanoparticles can greatly enhance X-ray therapy, gold nanoshells/nanorods, carbon nanotubes and magnetic nanoparticles can induce hypothermia to kill cancer cells and finally, nanocrystalline silver is being used as an antimicrobial agent.

**(5) Biomaterials.** Biocompatible nanomaterials that have optimal mechanical properties can be used as dental restoratives and bone substitutes. Nanocoatings or nanostructured surfaces can also improve the biocompatibility and adhesion of biomaterials.

**(6) Tissue engineering.** Nanotechnology can enable the design and fabrication of biocompatible scaffolds at the nanoscale and control the spatiotemporal release of biological factors. These biocompatible scaffolds may resemble the native extracellular matrix to direct cell behaviors and eventually lead to the creation of implantable "ready for use" tissues or even organs.

### 1.2 Nanobiomedical technology for the formation of functional tissues

In normal tissues, cells are surrounded by extracellular matrix (ECM) which is characterized by a natural web of hierarchically organized nanofibers. Early artificial scaffolds were designed to provide cells sup-

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TABLE 3.

| Nanomaterials used for improving biosensor technology | |
|---|---|
| **Nanomaterial used** | **Key benefits** |
| Carbon nanotubes | • Improve enzyme loading<br>• Higher aspect ratios<br>• Ability to be functionalized<br>• Better electrical communication |
| Nanoparticles | • Aid in immobilization<br>• Better loading of bioanalyte<br>• Better catalytic properties |
| Quantum dots | • Excellent fluorescence<br>• Quantum confinement of charge carriers<br>• Size tunable band energy |
| Nanowires | • Highly versatile<br>• Good electrical and sensing properties for bio-and chemical sensing<br>• Better charge conduction |
| Nanorods | • Good plasmonic materials which can couple sensing phenomenon well<br>• Size tunable energy regulation<br>• Can be coupled with NEMS (NanoElectroMechanical Systems)<br>• Induce specific field responses |

*All values are presented as mean SD*

port and structural integrity on a macroscopic level. In nanotechnology, scaffolds also establish a tissue specific nanoenvironment to maintain and regulate cell behavior and function. Nanoscaffolds play a vital role in storing, releasing and activating a wide range of biological factors, along with aiding cell-to-cell communication and cell-soluble factor interaction. [4,5]

**(1)** By **emulating the complexity and functionality of ECM**, nano-topographic surfaces and nano-featured scaffolds encapsulate and control the spatiotemporal release of drugs and growth factors and eventually direct cellular behaviors that range from cell adhesion to gene expression. Living cells are highly sensitive to local nanoscale topographic patterns within ECM. The 2D cell-nano-topography interactions enable investigators to direct cell behavior whereas 3D artificial scaffolds exhibit a very similar physical structure to protein nanofibers in ECM. [6]

**(2)** The 2D and 3d morphology of the designed nanoconstructs plays **significant role in cell manipulation and eventually in functional tissue formation**. [7] (**Fig.1**) The creation of engineered substrates such as nanospheres, nanotubes, and nanofibers as well as various nanopatterns, such as gratings, pillars, and pits with different nanofeatures, have enabled the exploration of cell nanotopography interactions, and the manipulation of cell morphology, signaling, orientation, adhesion, migration, proliferation, and differentiation. (**Fig.2**) Aligned nanofibers and nanogratings can rule the alignment and elongation of many different cell types. Polymer nanogratings, disordered nanopits and vertically aligned TiO2 nanotubes help the differentiation of mesenchymal stem cells. In nanograting substrates the endothelial cells can be organized into multicellular band structures forming aligned capillary-like tubes. [8-12]

**(3) The fabrication methods** used for the final nanotechnology design is crucial for the role that the nanopattern will assume. *(a) Self-assembly technology*, emulates the process of ECM assembly and can thus produce very thin nanofibers. *(b) Phase separation technology*, allows for continuous fiber network fabrication with tunable pore structure, and the formation of sponge-like scaffolding. *(c) Electrospinning*, is a very simple and practical technique, suitable for the creation of aligned and complex 3D structures. Nanofibers with core-shell structures prepared by electrospinning can be internally loaded with growth factors.

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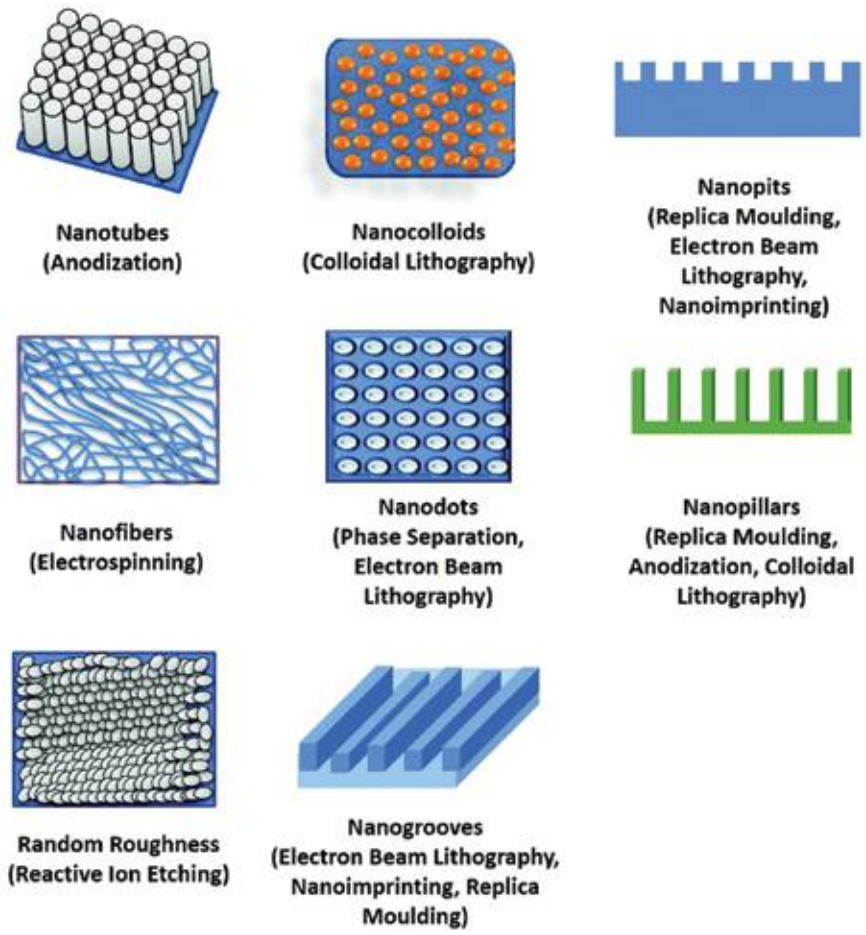


***Figure 1.*** *Schematic of fabricated nanotopographic features used to guide cell behaviors via cell-nanotopography interactions. (Adapted from ref [7])*

Additional adjustments to control the thickness and porosity of the polymer shells will further enhance the release kinetics of growth factors from these particular scaffolds. [13-15]

**(4)** The key factor for tissue regeneration and growth is **the localized and controlled delivery of biological factors** in the 3D scaffolds. Controlled release of angiogenic factors, such as Vascular Endothelium Growth Factors (VEGFs) and beta-Fibroblasts Growth factors (bFGF) enhance vascularization essential for maintaining continuous blood supply to developing tissues. Controlled release of beta-transforming Growth factors (TGFb-1,2) and Insulin-like Growth Factor-2 (IGF-2) enhance cartilage regeneration. [16]

**(5)** The next step for the development of smart 3D biomimetic scaffolds is **the use of advanced functional biomaterials that respond to stimuli**. Externally applied stimuli could be changes in pH, temperature or light that will lead to chemical changes of the smart biomaterials. These chemical changes will provide local cells and progenitors with certain signaling, to form functional tissue within a short period. [17] **(Table 2)**

**(6) The degradation rate** of the smart biomaterials or the secretion rate of growth factors of the stimulated cells is very important for the perpetual function of tissue regenerating or tissue repairing cells. If the degradation rate is too high, the nanomaterial construct will mechanically fail and the cells will stop the protein synthesis and developing extracellular matrix will never be accomplished. If the rate is too low, the cells will never receive the proper amount of stimuli and will never produce the proper amount of extracellular components. The release of factors in a **spa-**

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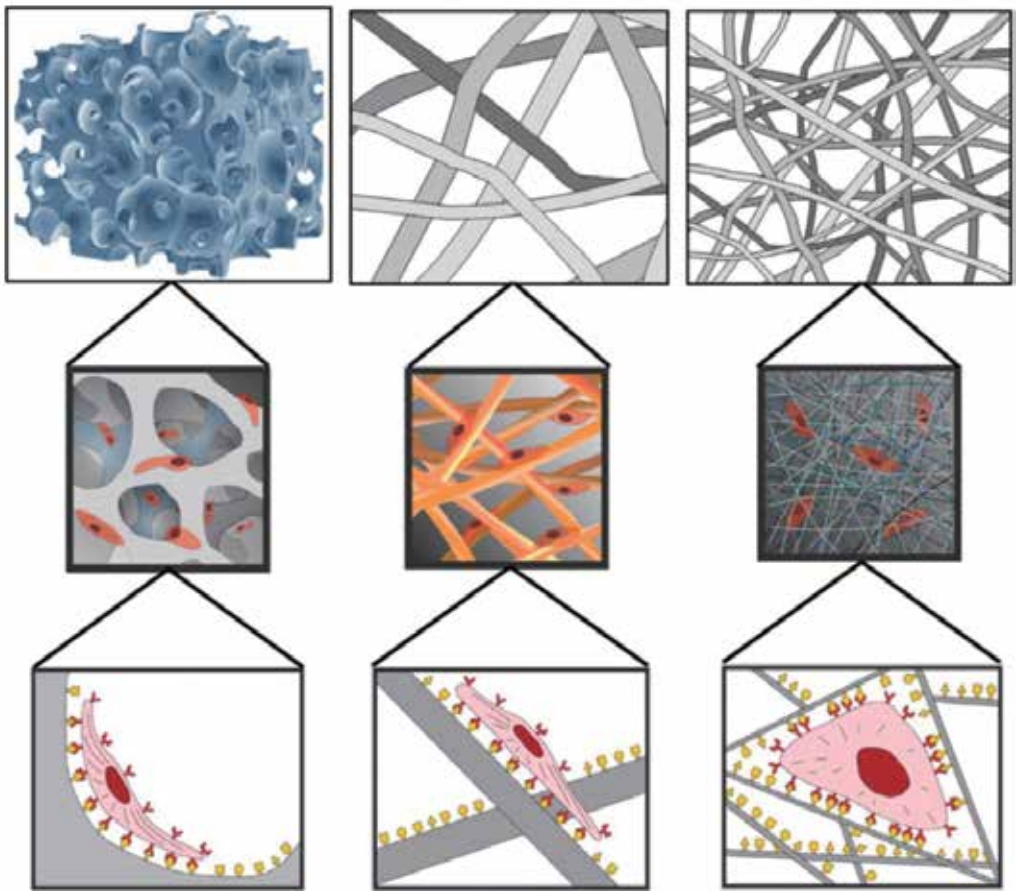

***Figure 2.*** *Illustration of how nanoscale fibrous scaffolds provide an environment for cells which better resemble the fibrous extracellular matrix of cartilage tissue. (Adopted from ref [4])*

**tiotemporally controlled manner** is very important and it is related with tuning particle formulation and composition that could help drive tissue growth to completion. [18]

The idea of "organ-on-a-chip" in the foreseeable future will replace the expensive and life-costing animal testing used for drug development and for evaluation or optimization of nano-particulate systems for drug delivery. It will also replace many steps implantation or transplantation techniques for any tissue repair. [19] In orthopedics, as well in dental surgery, (a) nanofibers reproduce ECM architecture, (b) nanocomposites based scaffolds - such as nano-hydroxyapatite/collagen - play important role on the reconstruction of bone tissue, and finally, (c) carbon nanotubes affect mechanical strength and electrical conductivity as well as they cover implant surfaces to produce adjacent tissues. [20,21] In general, when we try to produce or regenerate complex tissues, cells seeded into biocompatible and nanostructured scaffolds reassemble into functional structures. These functional structures resemble native tissues and under the stimulation of growth factors spatiotemporally delivered by nanoparticles they may be developed into complex tissues or organs.

## 2. Biosensors

A **biosensor** is an analytical device, used for the detection of a bioanalyte. A **bioanalyte** is any substance, chemical or biological element, undergoing chemical analysis. A biosensor can be defined as a sensing device or a measurement system designed specifically for estimation of a material by using the biological interactions and then assessing these interactions into a readable form with the help of a transduction and electromechanical interpretation.

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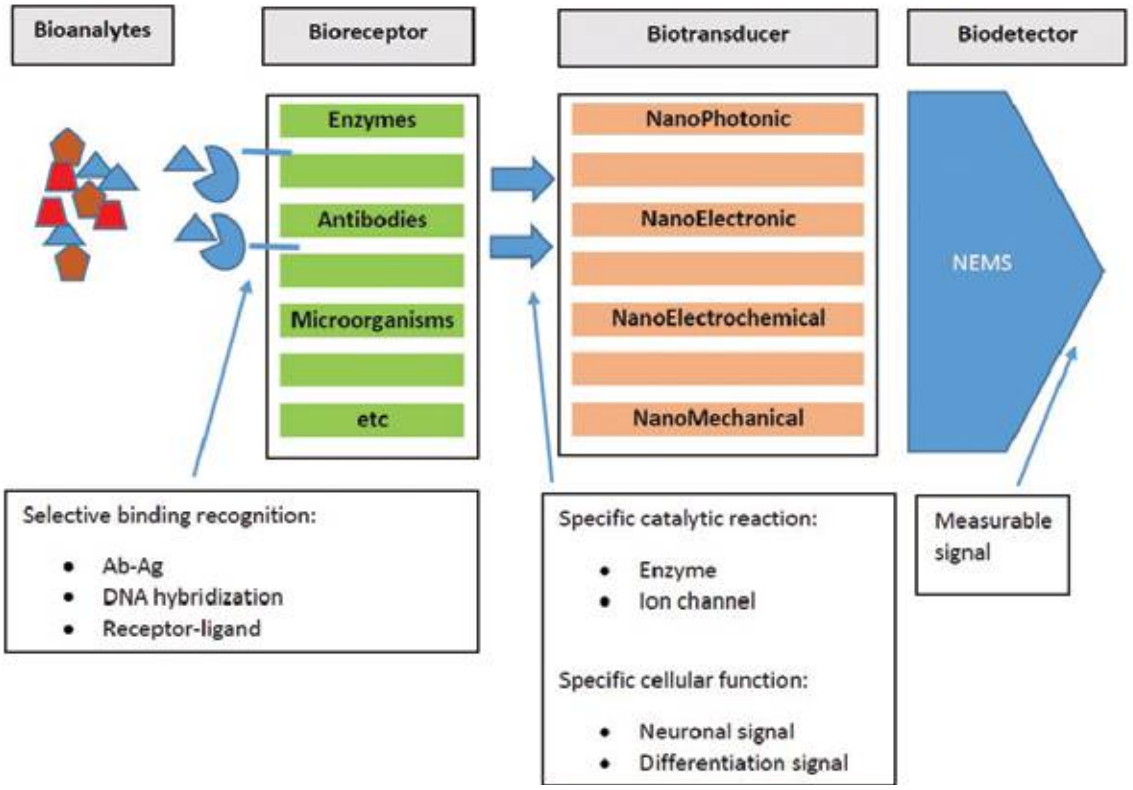


***Figure 3.*** *Schematic of a nanobiosensor (Drawing by the author I.K.T.)*

A biosensor is comprised of three parts: (a) The **bioreceptor,** is that component of a biosensor which serves as a template for the material to be detected. (b) The **biotransducer**, the main function of this device is to convert the interaction of bioanalyte and its corresponding bioreceptor into an electrical form. The name itself defines the word as *trans* means change and *ducer* means energy. So, transducer basically converts one form of energy into another. The first form is biochemical in nature as it is generated by the specific interaction between the bioanalyte and bioreceptor while the second form is usually electrical in nature. (c) The **biodetector** that receives the electrical signal from the biotransducer component and amplifies it suitably so that the corresponding response can be read and studied properly. It is also called bioelectronic system (or bio-sensor reader device) and includes a signal amplifier, a processor and a display. **(Fig.3)**

### *2.1 Nanobiosensors*

**Nanobiosensors** are the sensors which are made up of nanomaterials. The size constraints of these materials makes them very special as they have most of their constituent atoms located at or near their surface and have all vital physicochemical properties highly different from the same materials at the bulk scale. They can play very efficient roles in the sensing mechanism of the biosensor technology. Integrated devices of the nanomaterials with electrical systems give rise to **nanoelectromechanical systems (NEMS)**, which are very active in their electrical transduction mechanisms. Several nanomaterials have been explored on the basis of their electronic and mechanical properties for their use in improved biological signaling and transduction mechanisms. Some of such materials that are widely employed include nanotubes, nanowires, nanorods, nanoparticles, and thin films made up of nanocrystalline matter. [22] **(Table 3)**

### *2.2 Classification of nanobiosensors*

Classic bio-sensors are classified according to (1) the type of their bio-receptors or (2) the type of the con-

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TABLE 4.

| Biosensors' classification | |
|---|---|
| **According to bioreceptor's type** | **According to biosensor's type** |
| • Antibody/antigen interactions | • Electrochemical |
| • Artificial binding proteins | • Optical |
| • Enzymatic interactions | • Electronic |
| • Affinity binding receptors | • Piezoelectric |
| • Nucleic acid interactions | • Gravimetric |
| • Epigenetics | • Pyroelectric |
| • Organelles | |
| • Cells | |

nected bio-transducers. **(Table 4)** However, nanobioreceptors follow a different classification based on the nature of nanomaterials incorporated in the biosensing operation and being involved for improving the sensing mechanism. *Nanoparticle-based biosensors* include all the sensors which employ metallic nanoparticles as the enhancers of the sensing biochemical signals. (**Fig.4**) *Nanotube-based sensors* are these involve carbon nanotubes as enhancers of the reaction specificity and efficiency. *Nanowire-based biosensors* are biosensors using nanowires as charge transport and carriers. *Quantum dots-based sensors* employ quantum dots as the contrast agents for improving optical responses. [23] **(Table 5)**

### 2.3 *Applications of nanobiosensors*

Nanobiosensors are highly versatile and multifunctional so they can find application in biomedical fields, environmental monitoring of pollutants, toxicants, and physical aspects like humidity, heavy metal toxicity, and even presence of carcinogens. [24] **(Table 6)**

**(1) Biomedical Applications.** Biosensors have been used for biological detection of serum antigens, carcinogens, and causative agents of many metabolic disorders. With the addition of nanoscale interventions, diagnosis has been more precise. The incorporation of nanomaterials has enabled the detecting enzyme systems to be immobilized, and this has allowed the recycling and reuse of costly enzymes. The implementation of nanoscale innovations like NEMS improved sensitivity and accuracy. Biochips and microarray based testing have enabled the testing of more than one disease in short time. Magnetic nanoparticles have been synthesized and used for isolating and heavy metals resembling in properties with iron from the blood serum. Magnetic nanoparticles are used to selectively evaluate biochemical responses. Thus, nanobiosensors are developed and used in different ways of their incorporation in sensing mechanisms. [25-33]

**(2) Environmental Applications.** This is a broad application area involving (a) the detection of pollutants, toxic intermediates, heavy metals from waste streams, directly relevant to public health, as well as (b) the monitoring of weather conditions like the estimation of humidity, directly relevant to public safety. The sensors based on nanomaterials can be very versatile in terms of their detection and monitoring. Carcinogens and harmful intermediates leading have been isolated through the use nanofabricated compounds, such as the endocrine-disrupting compounds. Techniques of bioremediation, when engineered with the use of nanomaterials, can be scaled up and used to optimize the environmental quality and decontaminate the

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## TABLE 5.

| **Nanoparticle based** | |
|---|---|
| Acoustic wave | • Preferred particles: gold, platinum, cadmium sulphide, and titanium dioxide<br>• Amplify the sensing responses<br>• Improve overall preciseness of bio detection limits |
| Magnetic | • Preferred particles: iron or ferrite compounds<br>• Screen of specific antigens from mixtures by using antibodies bound to magnetic nanoparticles |
| Electrochemical | • Preferred particle: gold (Au)<br>• Facilitate or analyze biochemical reactions with the help of improved electrical means. |
| Nanotube based | • Preferred particle: carbon<br>• Electronic conductivity, dynamic physicomechanical properties, high mechanical strength, high folding abilities |
| Nanowire based | • Preferred particles: carbon, silicon<br>• Very good electron transport properties<br>• Enhanced detection of biological and chemical species |

## TABLE 6.

| **Applications of Nanobiosensors** | |
|---|---|
| **Biomedical** | |
| • DNA sensors | Genetic monitoring, Diseases |
| • Immunosensors | HIV, hepatitis, viral diseases, drug testing, cancer |
| • Point-of-care sensors | Blood, urine, electrolytes, gases, steroids, drugs, hormones, proteins |
| • Bacteria sensors | Food industry, medicine, environmental |
| • Enzyme sensors | Diabetics, drug testing |
| **Environmental** | |
| | Pollution and toxicity detection |
| | Ground water screening |
| | Agricultural monitoring |
| | Ocean monitoring |
| | Weather conditions |
| **Miscellaneous** | |
| | Metallurgy |

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hazardous contaminants. Specific biosensors have been developed for detection of nitrates, inorganic phosphates, and biological oxygen demand like parameters attributing to environmental restoration. In this manner, all these nanobiosensor applications are highly energy saving, economical and time saving in nature. [34-38]

(**3)Miscellaneous Applications.** In metallurgy, separation of impurities existing in a complexed form is required, and nanobiosensors can be used to separate the impurities selectively by trying out different configurations of the sensing enzymes. There is emerging need for developing microbiological and biochemical assays coupled with nanobioengineering based innovations to produce handy applications of sensing materials. This will have a direct effect on public health and safety. [22]

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ORIGINAL ARTICLE VOLUME 73 | ISSUE 3 | JULY - SEPTEMBER 2022

# Correlation of post-operative anterior knee pain in two different total knee arthroplasty techniques: the conventional instrumentation (CI) and the patient specific instrumentation (PSI).

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## ABSTRACT

**Purpose:** Evaluation of the clinical outcome, as assessed by the Visual Analogue Scale score and clinical questionnaires, in total knee arthroplasty undertaken with patient specific or conventional instrumentation.
**Methods:** This is a prospective comparative clinical study of 115 consecutive patients who underwent total knee arthroplasty in two different orthopedic centers. Patients were assessed using the 0-10 Visual Analog Scale in different activities, the Tegner -Lysholm Functional Score, the Knee Society Scores (KSS), measured preoperatively and at 3-6-12 months postoperatively.
**Results:** Both groups improved significantly over time on all score clinical outcomes. Statistically significant differences were observed between the two groups in the KSS knee score postoperatively at 6 and 12 months (p=0.007 and p=0.004 respectively), and in the Tegner- Lysholm score only at 6 months postoperatively (p=0.001), both in favour of patient specific intrumentation group. The mean KSS was 91.32±4.29 and 93.15±4.72 for the conventional and patient specific groups respectively at 12 months follow up (p=0.063). No statistically significant difference was found at 12 months between two groups when the visual analog scale was measured related to the activity of standing up from the sitting position (conventional group: 1.15±0.36 versus patient specific: 1.10±0.30, p=0.380).
**Conclusion:** We did not find major significant differences for pain scores, functional scores and clinical out-

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comes between the conventional instrumentation and the use of patient specific instrumentation for total knee replacement. The current literature does not suggest patient specific instrumentation techniques as a gold standard. Therefore, patient specific techniques cannot be recommended as a standard procedure and specially in order to minimize the anterior knee pain after total knee arthroplasty.

**KEYWORDS: total knee arthroplasty, anterior knee pain, patient specific instrumentation, visual analog scale, Tegner - Lysholm Score, Knee Society Score**

## Introduction

Patient specific instrumentation (PSI) is a modern technique in total knee arthroplasty (TKA), aiming to facilitate the implant of the prosthesis. PSIs were introduced to increase the accuracy of the surgical technique and avoid issues related to the complexity of the navigation system, such as procedural costs, surgical time, and learning curve. PSI is expected to improve component alignment and positioning, postoperative functional recovery, and patient satisfaction (16,17). The customized cutting blocks of the PSI are generated from pre-operative computer-aided three-dimensional (3D) reconstruction, 3D printing from a disposable template, using computed tomography (CT) or magnetic resonance imaging (MRI), aiming at an accurate intraoperative placement of the cutting blocks and an accurate osteotomy (16,17). A correct surgical plan is mandatory for a good surgical implant. (18,19,23) The PSI guide takes into account any slight deformities or osteophytes and applies preoperative planning for bone resection, using the pre-determined implant size, position, and rotation. PSI is hypothesized to have advantages with respect to improving component alignment, shortening the surgical time and length of hospital stay, and decreasing perioperative blood loss. Many manufacturers have invested in PSIs (19,21,26). Large debates have taken place about this topic during the last years and, now, there is no consensus in the.. current . literature regarding the accuracy and reliability of PSI, as many studies have shown controversial and inconsistent results. (18,20,21,22,24,25,26,27) In a recent comprehensive systematic review and meta-analysis, Gong et al (30) concluded that PSI has advantages for axial alignment of the femoral component, operative time, and perioperative blood loss compared to conventional instrumentation (CI) total knee arthroplasty. However, no significant differences were observed between PSI and CI with respect to the alignment of the remaining components, number of outliers, and length of hospital stay.

As far as we know there is no clinical study comparing especially the postoperative anterior knee pain (AKP) after primary TKA between CI and PSI of the exact same knee prosthesis. Background of the hypothesized less AKP after TKA with patient specific instrumentation were the causal relationship between malalignment and malrotation component mistakes after TKA and more severe amount of AKP on the one hand (41-49), and the already published superiority of the PSI TKA in the coronal and sagittal alignment and component rotation in comparison to the CI TKA on the other hand (50-55).

## Materials and Method

They were 53 patients who took part in the study in the first Orthopaedic center between 2015-2016 (group 1) and 62 patients in the second Orthopaedic center between 2017-2018 (group 2) (Figure 1, Table 1). The inclusion criteria were correct prosthetic components alignment (34), complete one-year follow-up scores, X-rays, and surgery performed by the same OP team for each Orthopaedic center, supervised by an Orthopaedic fellow-trained in Joint Replacement Surgery. Exclusion criteria were major postoperative complications, inflammatory systemic disease, impaired cognitive status and inability

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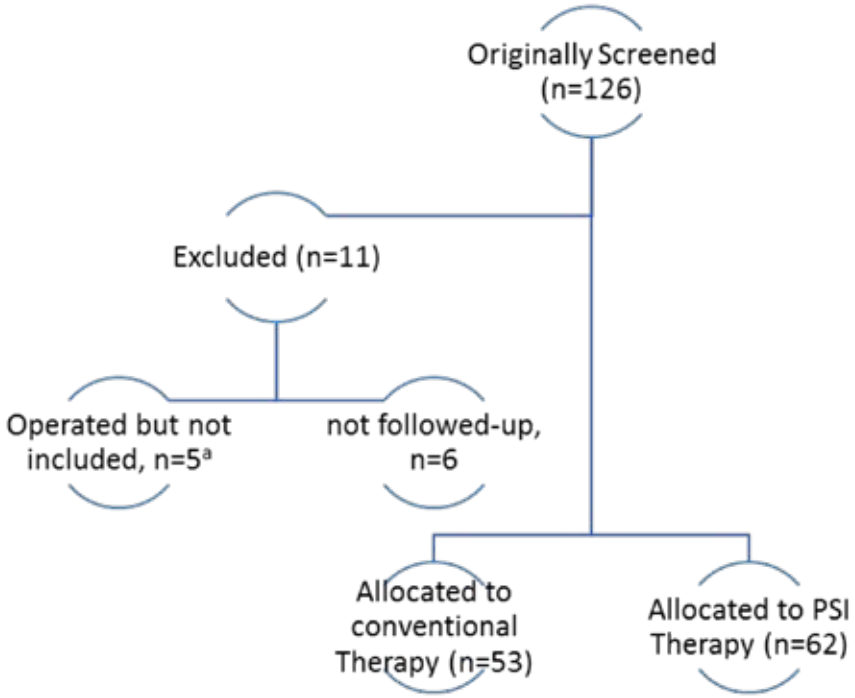


***Figure 1*** *Flow chart of patients to be considered in this study (a=Not included due to post-operative complications, Haematoma, Fracture, Infection, Iatrogenic Intra-OP mistakes)*

TABLE 1.

**Demographic characteristics of patients (SD= standard deviation).**

| **DEMOGRAPHICS** | | |
|---|---|---|
| **FACTOR** | **Conventional** | **PSI** |
| NUMBER OF PATIENTS | 53 | 62 |
| MEN/WOMEN RATION | 14/39 | 12/50 |
| AGE (YEARS) MEAN (SD) | 70,11 (3,55) | 70,35 (3,84) |
| BMI MEAN (SD) | 27,41 (3,10) | 25,91 (4,5) |
| ASA GRADE, NUMBER OF PATIENT | | |
| 1 | 7 | 3 |
| 2 | 40 | 50 |
| 3 | 6 | 9 |
| 4 | 0 | 0 |

for follow up. Finally, 11 patients were excluded from the originally 126 registered patients. Written consent was obtained from each patient of each group, after detailed information about the study, and ethical approval was obtained from each respective local ethical committee about this clinical study.

All patients of the study received no patellar pros-

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TABLE 2.

**Comparison of Anterior Knee Pain (AKP) at different activities between groups during the observation period**

| AKP | GROUP | 3 MONTHS | 6 MONTHS | 12 MONTHS | P-VALUE WITH IN GROUP | TIME INDEPENDENT$ MEAN ( 95%CI) |
|---|---|---|---|---|---|---|
| RAISE FROM A CHAIR | CI TKA | 2.74±0.74 | 1.64±0.74 [a] | 1.15±0.36 [a,b] | <0.001 | 1.84 ( 1.71-1.98) |
| | PSI TKA | 2.53±0.59 | 1.55±0.56 [a] | 1.10±0.30 [a,b] | <0.001 | 1.73 (1.60-1.85) |
| | p-value between groups | 0.104 | 0.444 | 0.380 | | 0.206 |
| GOING UPSTAIRS | CI TKA | 2.45±0.72 | 1.51±0.75 [a] | 1.19±0.39 [a,b] | <0.001 | 1.72( 1.58-1.85) |
| | PSI TKA | 2.39±0.55 | 1.34±0.54 [a] | 1.10±0.30 [a,b] | <0.001 | 1.61 (1.49-1.73) |
| | p-value between groups | 0.582 | 0.160 | 0.158 | | 0.229 |
| GOING DOWNSTAIRS | CI TKA | 3,70±0.89 | 2,36±0.83 [a] | 1.32±0.58 [a,b] | <0.001 | 2,46( 2,28-2,64) |
| | PSI TKA | 3,60±0.76 | 2,39±0.71 [a] | 1.32±0.50 [a,b] | <0.001 | 2,43 (2,27-2,60) |
| | p-value between groups | 0.511 | 0.843 | 0.986 | | 0.846 |
| DURING WALKING | CI TKA | 2,62±0.81 | 1,58±0.69 [a] | 1.11±0.32[a,b] | <0.001 | 1,77( 1,64-1,91) |
| | PSI TKA | 2,55±0.59 | 1,58±0.59 [a] | 1.05±0.22 [a,b] | <0.001 | 1,73 (1,60-1,85) |
| | p-value between groups | 0.573 | 0.972 | 0.200 | | 0.601 |

*All values are presented as mean ±SD*

*$ Results based on Two-Way ANOVA model using as factors the intervention and time*

*[a] P< 0.005 vs 3 months, [b] P< 0.005 vs 6 months*

*CI TKA : Conventional Instrumentation Total Knee Arthroplasty*

*PSI TKA : Patient Specific Instrumentation Total Knee Arthroplasty*

thesis, but routine intraoperative denervation of the patella with electro cautery and osteophytes removal. All patients received two doses of first-generation cephalosporin preoperatively and 8 h postoperatively. A standard medial parapatellar approach was used for the CI TKA group, where a subvastus approach for the PSI TKA group.

For the control group of the CI, standard intramedullary instrumentation was used for the femoral component. The femoral rotational axis was defined using Whiteside's line, the epicondyle axis, and posterior condylar axis. The tibial component was placed according to the mechanical axis using extramedullary instrumentation. For the study group, the preoperative planning from 3D reconstructed MRI images was performed using planning software (Materialise NV, Leuven, Belgium). The femoral component was set at 3 degrees of flexion. The surgical epi- condylar axis obtained from 3D MRI reconstructed images was used to set femoral rotational reference. The tibial component was planned according to the ideal mechanical axis and with 3 degrees of posterior slope. Intraoperatively, the patient-specific cutting guides were placed on the femur and tibia guiding the bone resection.

The PSI TKA group received 2 g of tranexamic acid (TXA) perioperatively, a standard analgesic cocktail of periarticular, intermuscular und subcutaneous infiltration consisted of Bupivacaine, Morphine-sulfate, Epinephrine, Methylprednisolone diluted in NaCl 0.,9% perioperatively, and a systemic Patient-controlled analgesia for pain management

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TABLE 3.

**Comparison of VAS for pain at different sites of the knee joint, between groups during the observation period**

| VAS | GROUP | 3 MONTHS | 6 MONTHS | 12 MONTHS | P-VALUE WITH IN GROUP | TIME INDEPENDENT$ MEAN ( 95%CI) |
|---|---|---|---|---|---|---|
| POPLITEAL FOSSA | CI TKA | 3,92±0.85 | 2,49±0.85 [a] | 1.53±0.64[a,b] | <0.001 | 2,65( 2,46-2,83) |
| | PSI TKA | 3,85±0.83 | 2,47±0.74 [a] | 1.48±0.62 [a,b] | <0.001 | 2,60 (2,42-2,77) |
| | p-value between groups | 0.658 | 0.878 | 0.706 | | 0.723 |
| MEDIAL SURFACE OF THE KNEE | CI TKA | 3,45±0.85 | 2,15±0.86 [a] | 1.28±0.50[a,b] | <0.001 | 2,30( 2,12-2,47) |
| | PSI TKA | 3,55±0.74 | 2,39±0.71 [a] | 1.29±0.49 [a,b] | <0.001 | 2,41 (2,25-2,57) |
| | p-value between groups | 0.541 | 0.110 | 0.947 | | 0.347 |
| LATERAL SURFACE OF THE KNEE | CI TKA | 2,72±0.82 | 1,72±0.66 [a] | 1.09±0.30[a,b] | <0.001 | 1,84( 1,70-2,00) |
| | PSI TKA | 3,08±0.77 | 2,10±0.69 [a] | 1.18±0.39 [a,b] | <0.001 | 2,11 (1,98-2,25) |
| | p-value between groups | 0.016 | 0.013 | 0.203 | | 0.006 |

*All values are presented as mean ±SD*

*$ Results based on Two-Way ANOVA model using as factors the intervention and time*

*a P< 0.005 vs 3 months , b P< 0.005 vs 6 months*

*CI TKA : Conventional Instrumentation Total Knee Arthroplasty*

*PSI TKA : Patient Specific Instrumentation Total Knee Arthroplasty*

postoperatively. On the other hand, the patients of the CI TKA group received epidural catheter analgesia until the second postoperative day, and then systemic Patient-controlled analgesia for pain management postoperatively. Both groups received low-molecular-weight heparin for DVT prophylaxis.

The same homogenous rehabilitation protocol for each separate center with an active range of motion exercises and continuous passive motion exercises (CPM) started on the first postoperative day and mobilization with a walker started on the second postoperative day for the CI TKA group. Fast track Knee TKA protocol with CPM motion exercises until full range of knee motion starting in the recovery room at the operation day and mobilization with walker started on the first postoperative day for the PSI TKA group.

Patients were followed up 3 months, 6 months and 1 year postoperatively. The knee pain was assessed between the 2 groups at different sites of the knee joint (Table 3), and the AKP when climbing stairs and standing up from the sitting position (Table 2). Knee function was assessed using KSS Knee and Function Score, and Tegner - Lysholm score (56,57) (Table 4).

Data were expressed as mean±SD or mean±SE (for two way ANOVA analysis results) for continuous variables and as percentages for categorical data. The Kolmogorov-Smirnov test was utilized for normality analysis of the parameters. Homogeneity between compared groups was examined using the Independent samples t-test, Chi-square test and Fisher's exact test. Two-way mixed ANOVA model was used to examine the interaction between "intervention" and "time" factors and compare the variables at each time point and time independently between groups. One factor Repeated Measures ANOVA model was used for the comparison of different time measurements of variables for each

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TABLE 4.

**Comparison of Evaluation knee scores between groups during the observation period**

| SCORES | GROUP | BASELINE | 3 MONTHS | 6 MONTHS | 12 MONTHS | P-VALUE WITH IN GROUP | % CHANGE FROM BASELINE TO | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 3 MONTHS | 6 MONTHS | 12 MONTHS |
| VAS | CI TKA | 8.55±0.70 | 4.09±0.90 [a] | 2.58±20.86 [a,b] | 1.55±0.75 [a,b,c] | <0.001 | -52.0±10.5 | -69.7±10.1 | -81.9±8.6 |
| | PSI TKA | 8.34±0.68 | 3.92±0.77 [a] | 2.52±0.74 [a,b] | 1.45±0.56 [a,b,c] | <0.001 | -53.0±8.7 | -69.9±8.2 | -82.7±6.2 |
| | p-value between groups | 0.107 | 0.266 | 0.647 | 0.437 | | 0.591 | 0.878 | 0.533 |
| TEGNER-LYSHOLM | CI TKA | 46.42±7.70 | 65.70±5.61 [a] | 72.36±5.81 [a,b] | 80.91±4.93 [a,b,c] | <0.001 | 44.85±24.6 | 59.60±26.6 | 78.59±28.88 |
| | PSI TKA | 46.24±4.62 | 66.82±5.63 [a] | 76.23±6.50 [a,b] | 84.74±5.62 [a,b,c] | <0.001 | 45.69±17.1 | 66.10±18.69 | 84.85±20.1 |
| | $p\text{-value}_{bg}$ | 0.882 | 0.287 | 0.001 | <0.001 | | 0.829 | 0.130 | 0.175 |
| KSS KNEE | CI TKA | 54.45±4.94 | 71.81±6.50 [a] | 78.00±5.08 [a,b] | 83.75±4.02 [a,b,c] | <0.001 | 32.55±13.8 | 44.11±13.1 | 54.95±14.72 |
| | PSI TKA | 54.60±4.45 | 74.53±6.80 [a] | 80.60±4.95 [a,b] | 86.03±4.23 [a,b,c] | <0.001 | 36.99±13.1 | 48.33±12.4 | 58.38±12.38 |
| | $p\text{-value}_{bg}$ | 0.870 | 0.031 | 0.007 | 0.004 | | 0.079 | 0.079 | 0.178 |
| KSS FUNCTION | CI TKA | 64.72±6.00 | 75.66±3.93 [a] | 81.98±5.31 [a,b] | 91.32±4.29 [a,b,c] | <0.001 | 17.83±12.0 | 27.74±14.7 | 42.37±15.7 |
| | PSI TKA | 66.13±46.55 | 75.16±4.15 [a] | 82.26±5.48 [a,b] | 93.15±4.72[a,b,c] | <0.001 | 14.48±10.2 | 25.25±11.7 | 41.95±13.1 |
| | $p\text{-value}_{bg}$ | 0.234 | 0.511 | 0.785 | 0.063 | | 0.110 | 0.315 | 0.875 |

*All values are presented as mean ±SD*

*[a] P< 0.005 vs baseline , [b] P< 0.005 vs 3 months , [c] P< 0.005 vs 6 months*

*CI TKA : Conventional Instrumentation Total Knee Arthroplasty*

*PSI TKA : Patient Specific Instrumentation Total Knee Arthroplasty*

intervention. Pairwise multiple comparisons were performed using the Bonferroni test. Comparison of percentage change from baseline to other time points of variables between interventions was analyzed using the Independent samples t-test or Mann-Whitney test in case of violation of normality. All tests are two-sided, statistical significance was set at $p < 0.05$. All analyses were carried out using the statistical package SPSS vr 21.00 (IBM Corporation, Somers, NY, USA).

## Results

There is statistically significant reduction of pain during the observation period for both types of surgical instrumentation for all pain variables (p<0.001). There is no statistically significant difference between the two types of surgical instrumentation in relation to absolute values of anterior knee pain at different activities at 3, 6, 12 months and time independently. (Table 2, 3) There was statistically significant lower pain at the lateral only surface of the knee for the CI group compared with the patient specific instrumentation group at 3 months (p=0.016), 6 months (p=0.013) and time independently (p=0.006)

There is statistically significant increase of functional scores during the observation period for both types of intervention (p<0.001). There is no statistically significant difference between the two types of surgical instrumentation in relation to percentile change from baseline to 3, 6 and 12 months of functional scales.

Statistically significant differences were observed between the 2 groups in the absolute values of the KSS Knee score postoperatively at 6 and 12 months, and in the absolute values of the Tegner - Lysholm

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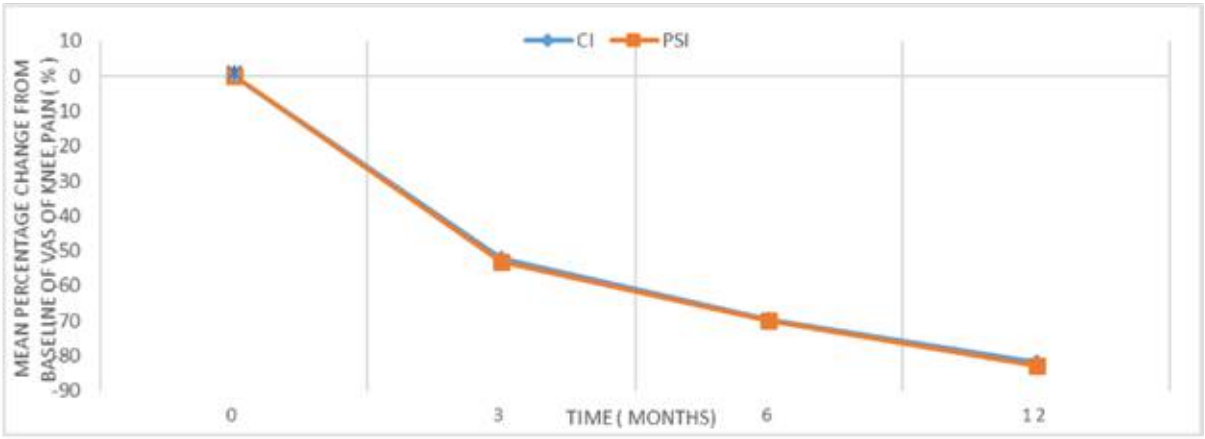


***Figure 2*** *Mean percentage change from baseline of VAS of knee pain ( % ).*

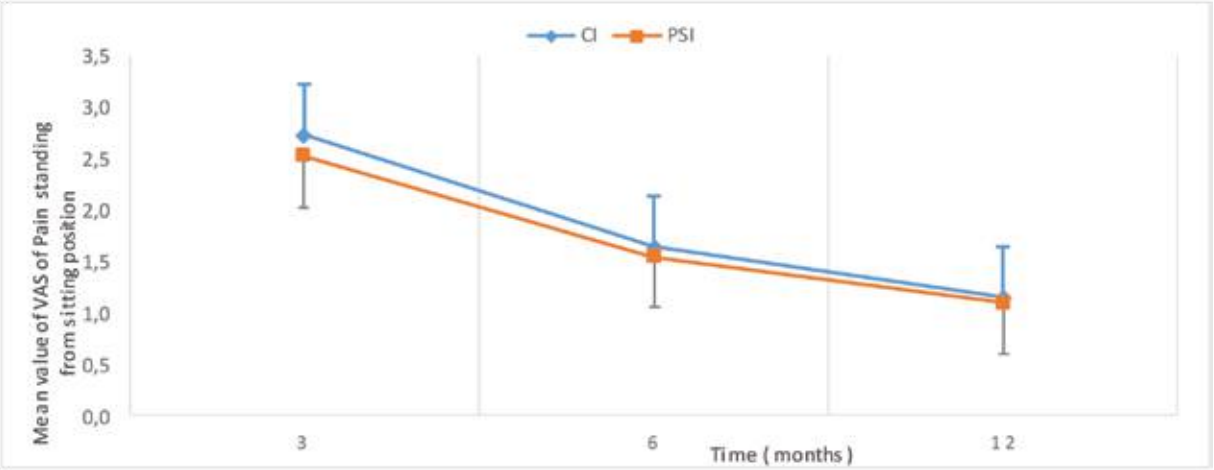


***Figure 3*** *Mean value of VAS of Pain standing from sitting position.*

score only at 6 months postoperatively, both in favour of the PSI group. (Table 4)

## Discussion

The reported incidence of anterior knee pain following primary TKA is 8% (39). Several studies have been conducted to determine the cause of anterior knee pain following TKA with variable results (40). Various causes are responsible for anterior knee pain after primary total knee arthroplasty, such as functional problems due to muscle imbalance, iatrogenic mistakes such as patellofemoral compartment overstuffing, patello-femoral instability or maltracking, different prosthetic design and mainly the design of the femoral component or even patella resurfacing or not strategy (1-15,35,36). Malalignment and malrotation mistakes of the femoral and tibial components play a very important role. Component malalignment following primary TKA has a prevalence ranging between 9.4% and 11.8% (41,42). Isolated internal rotation of the femoral component has been described as a potential source of prosthetic dysfunction, anterior knee pain, and potential early failure (43,44,45). Malrotation of the tibial prosthetic component constitutes another potential cause of a suboptimal clinical outcome following primary TKA (41,43,44). A strong correlation is reported between anterior or medial knee pain and isolated excessive tibial rotation (44). Femoral component rotation also plays a key factor in patellar tracking and can contribute to patellofemoral

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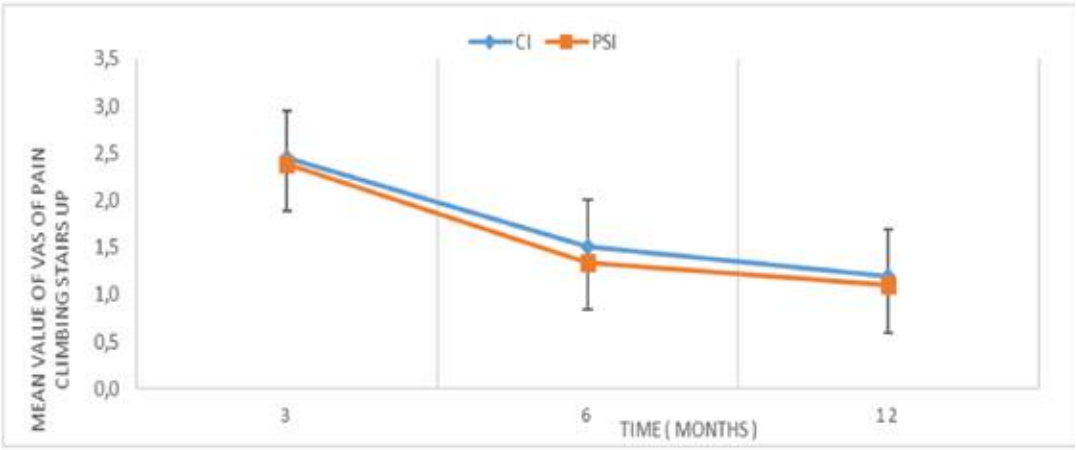


***Figure 4*** *Mean value of VAS of Pain climbing stairs up.*

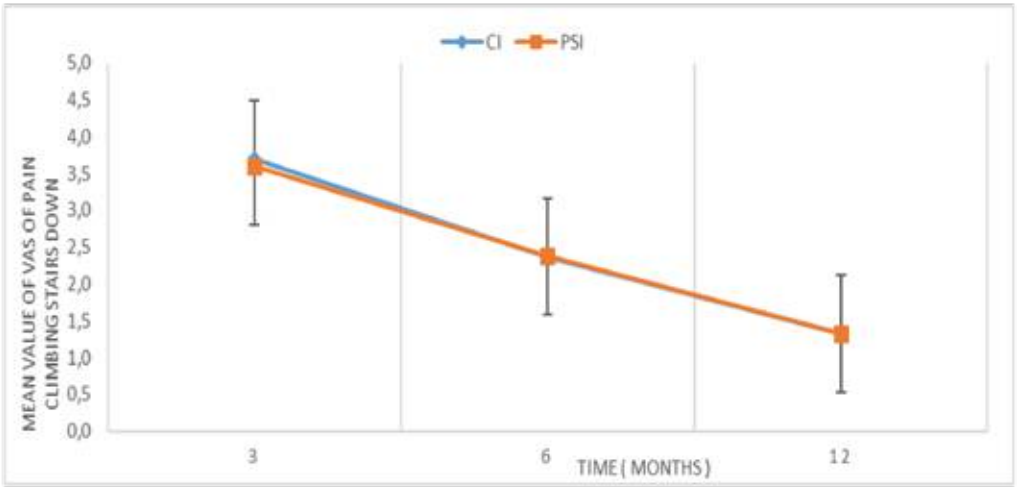


***Figure 5*** *Mean value of VAS of Pain climbing stairs down.*

complications following TKA. External rotation of the femoral component relative to the posterior femoral condyles facilitates central patellar tracking by reducing patellofemoral lateral shear forces (46,47,48). External rotation of the femoral component leads to lateral positioning of the sulcus and preserves sulcus height, which facilitates a more anatomic orientation of the trochlear groove (49). Therefore it is crucial for TKA systems to have instrumentation that allows for perfect external rotation of the femoral component in order to reproduce a more natural patellofemoral joint (47,49).

The effectiveness of patient specific instrumentation (PSI) compared to that of standard instrumentation (SI) is not completely clear, and the existing data are conflicting. There are studies showing that PSI and SI exhibited significant difference in the coronal and sagittal alignment of the femoral and tibial component (50, 51, 52). Morover other published studies have showed improvement of femoral and tibial rotation in primary TKA with PSI systems in comparison with conventional instrumentation (CI) systems (CI) (53). Khuangsirikul et al (54) and Silva et al (55) showed a more accurate rotational alignment of femoral and of tibial components between custom cutting block (PSI) and CI technique in total knee arthroplasty.

Taking into consideration the causal relationship between malalignment and malrotation mistakes of the femoral and tibial components by primary Total Knee Arthroplasty and Anterior Knee Pain on the

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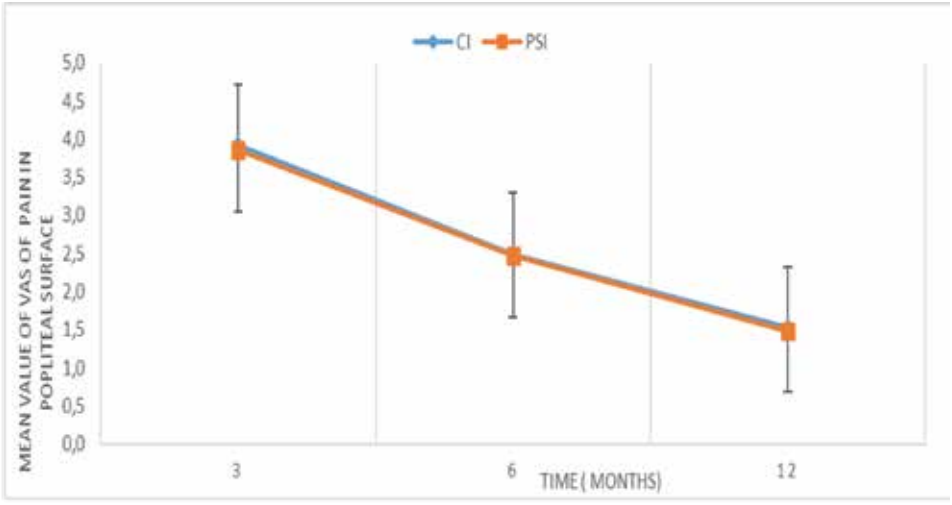


***Figure 6*** *Mean value of VAS of Pain in popliteal surface.*

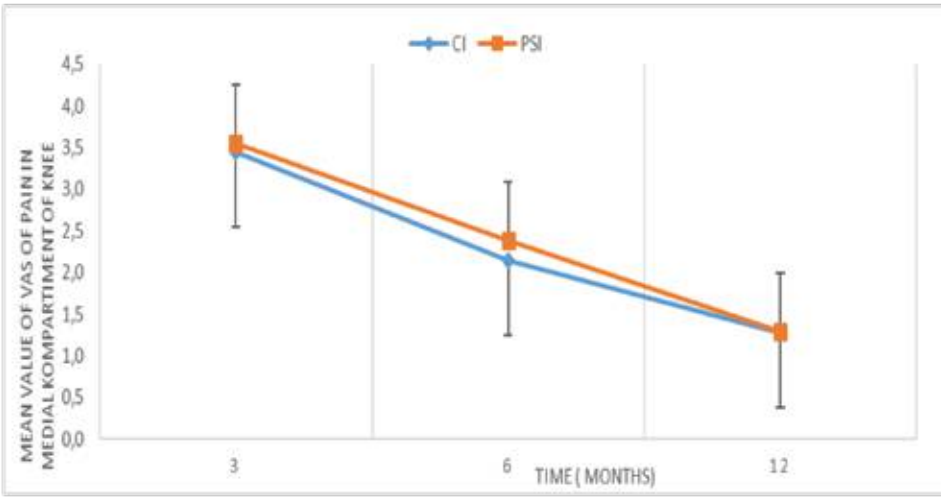


***Figure 7*** *Mean value of VAS of Pain in medial compartment of knee.*

one hand (41-49), and the already published superiority of the PSI TKA in the coronal and sagittal alignment and rotation of the femoral and tibial components in comparison to the CI TKA on the other hand by several authors (50-55), we hypothesized that PSI would have a better clinical outcome for the postoperative anterior knee pain and in general for patients' satisfaction after primary TKA than conventional Instrumentation, reflected in VAS scores after specific activities and in standard functional knee scores. Thus we compared, between the 2 centers, the exact same Prothesis Nex-Gen CR-Flex Fixed Bearing (Zimmer – Biomet Inc, Warsaw, IN USA), which is already worldwide often implanted, with only difference the PSI planning and PSI surgical technique for the second center. As far as we know there is no clinical study comparing specifically the postoperative AKP after primary TKA between CI and PSI of the exact same knee prosthesis.

The most important finding of this study was that there was no difference in clinical outcome and especially what concerns anterior knee pain after total knee arthroplasty between patient specific and conventional instrumentation 3-6-12 post-operatively, as was hypothesised. We did not find major signifi-

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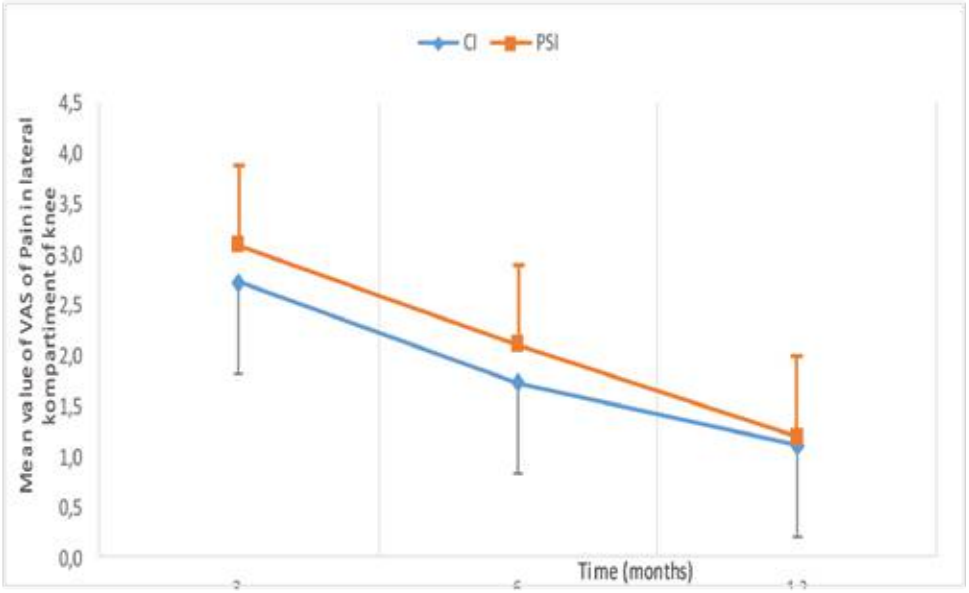


***Figure 8*** *Mean value of VAS of Pain in lateral compartment of knee*

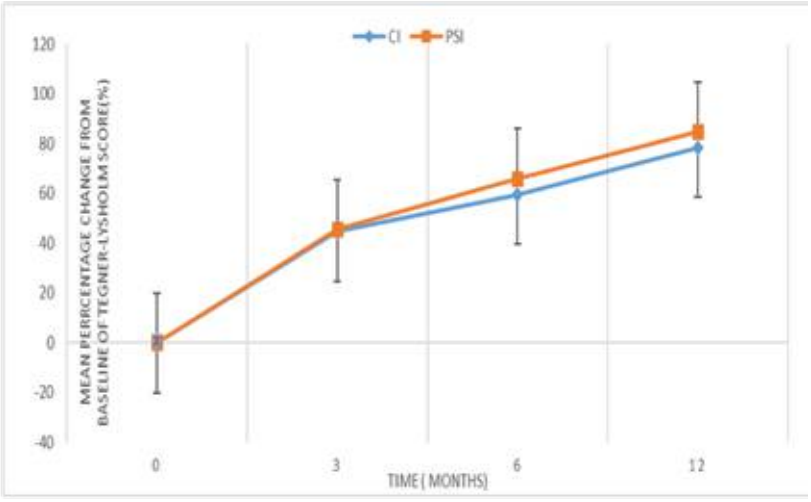


***Figure 9*** *Mean perrcentage change from baseline of Tegner-Lysholm score (%).*

cant differences for pain scores, knee evaluation scores and clinical outcomes between the conventional instrumentation and the use of patient specific instrumentation for total knee replacement. Our observations concerning the clinical outcome are in line with other authors. Yan et al (62) and Abane et al (63) found no difference in clinical outcome on short-term follow-up. Anderl et al (50) and Chen et al (64) also found no difference in clinical outcome two years post-operatively.

In the present study, we make the hypotheses that patients who underwent a patient specific instrumentation total knee arthroplasty (PSI TKA) would have statistically fewer symptoms of anterior knee pain than those who underwent conventional instrumentation total knee arthroplasty (CI TKA), and generally better clinical improvement reflected in standard knee scores and better subjective satisfaction reflected in VAS scores. Actually, we found no statistically significant difference in VAS

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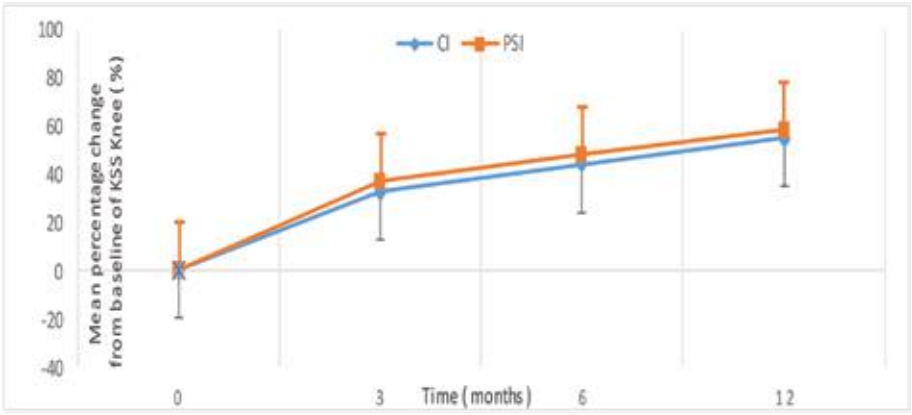


***Figure 10*** *Mean percentage change from baseline of KSS Knee (%).*

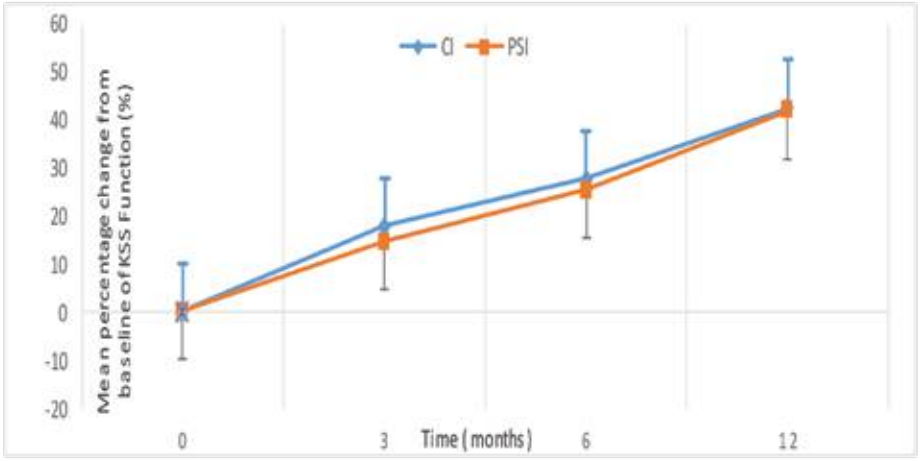


***Figure 11*** *Mean percentage change from baseline of KSS Function (%)*

score for knee pain (Table 4), in VAS score for the popliteal knee pain (Table 3), and in VAS score for AKP by standing from the sitting position and by climbing stairs (Table 2) between the CI and the PSI TKA group. All the used scores (Tegner Lysholm, KSS Function und KSS Knee) showed no magor difference between the two groups (Table 4). The statistically significant lower pain at the lateral surface for the CI group at 3 months and 6 months postoperativly, and the statistically significant better clinical scores of the KSS Knee score postoperatively at 6 and 12 months, and of the Tegner - Lysholm score only at 6 months postoperatively (both in favour of the PSI group), could be attributed to the lower preoperative BMI score of the patients of the PSI group, and to the more aggressive rehabilitation of the patients of the PSI group (all the patients rehabilitate to special Reha-Clinics, with daily Reha-Sport program). Boonen et al. (32) did not show a significant difference between the conventional and patient specific instrumentation operation when using the Oxford Knee score and did not find a difference for the pain scores also. Woolson et al. (33) did not report any significant difference in range of motion between the 2 operation methods, consistent with our findings. Van Leeuwen J. et al. (31) showed that all KOOS sub-scores and the pain scores were similar between groups of conventional and patient specific instrumentation total knee arthroplasty.

There are limitations to our study. First, the total number of included patients was lower than planned, which was mainly due to problems of follow-up. Second, our study did not compare radiological alignment postoperatively, due to inability

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for postoperatively long leg view and patella axial in the first Orthopaedic center. Third, we assessed no interobserver agreement between the different clinical scores. Forth, the two different Orthopaedic centers used different surgical approaches and different rehabilitation protocols, but still homogenous for each group. Fifth, the data of this study were based on only one type of patient specific instrumentation of one specific company and the findings should therefore not be generalized for other PSI systems. Sixth, the follow up time of one year was relatively short and as a result, no reliable data could be provided on the survival of the TKA in both groups.

The strengths of our study were the double center head to head study design, with homogeneity of demographic and clinical characteristics between compared groups and the fact that same surgeons team for each center respectively, performed the primary knee arthroplasties, implanting exactly the same knee prosthesis of one specific company. Before the study start the surgeons of the second Orthopaedic center were already familiar with the PSI technique.

No clear advantage of PSI seems to exist over conventional instruments. The cost effectiveness of the PSI technique needs to be considered. Potential cost savings include a shortened operating time (51), reduction in the number of sets of instruments (and additional sterilisation costs in most cases), reduced processing time (65). On the other hand, additional costs include the cost of an MRI or CT scans (hospital specific), costs of the patient specific instrumentation (manufacturer and hospital specific), and time needed for logistical tasks, depending on the available personnel. These requirements include the scanning process, transfer of the images to the manufacturer, monitoring the delivery of PSI to the hospital and approval of the digital plan by the surgeon prior to fabrication of the PSI. This last item is essential when using PSI in order to avoid time-consuming intra-operative changes to the proposed size of the components and the levels of resection (66). Literature does not suggest PSI techniques as a gold standard in TKA, and therefore it cannot be recommended as a standard technique and specifically in order to minimize the anterior knee pain (AKP) after TKA. One could only suggest a positive effect of the PSI instrumentation for the less experienced surgeons and in cases of preoperatively femoral or tibia posttraumatic deformities, by minimizing femoral and tibia cutting, without needing intramedullary orientation and therefore minimizing OP time (22,23).

## Conclusion

Patient specific instrumentation leads to equal clinical outcome in the short term with no major difference in anterior knee pain and other clinical scores when compared with conventional instruments in TKA surgery.

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REVIEW

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# Achilles Tendon Enthesopathy. Current Therapeutic Treatments.

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## ABSTRACT

Achilles tendon enthesopathy (AE) involves four different pathologic entities of the tendon's distal insertion to the calcaneus. These entities are described as (a) insertional Achilles tendinitis, (b) retrocalcaneal bursitis, (c) Haglund's deformity, and (d) intrasubstance calcification. There are many causative factors that lead to the development of AE, such as overuse, trauma, inadequate training or sport equipment, metabolic disorders and autoimmune diseases. The treatment can be initially conservative and in refractive cases surgical.

**KEYWORDS: Achilles tendon, enthesopathy, retrocalcaneal bursitis, Haglund's deformity, calcified tendonitis**

### Introduction

Approximately 6% of the general population reports Achilles tendon pain during their lifetime (1) but only one third of them will develop AE (2). The condition can affect both male more than female population, young athletes, middle-aged long-distance runners and elderly patients with a tight heel cord. It is also found as clinical manifestation in metabolic bone disorders and in rheumatologic diseases such as ankylosing spondylitis.

### Anatomy

The Achilles tendon consists of the aponeuroses of the gastrocnemius, plantaris longus, and soleus muscles (3) and it is primarily composed of type I collagen, surrounded by a paratenon (4). The tendon inserts 2 cm distal to the posterosuperior calcaneal prominence with an anterior-posterior diameter of 5 to 6 mm with medial and lateral projections (5). The tendon's blood supply is primarily provided from an arterial plexus along the calcaneus, supplied by the fibular and posterior tibial arteries (6). Additionally, the tendon is surrounded by subcutaneous and retrocalcaneal bursae in order to reduce friction between its surface and the adjacent tissues (7). The sural nerve is in close proximity to the Achilles tendon, stretching across the lateral border of the sheath (3). Neuroma formation or other sural nerve disorders should be included in the differential diagnosis of AE.

### Pathophysiology

Achilles tendon degeneration is characterized by loss of parallel collagen structure, fatty infiltration, loss of fiber integrity, and capillary proliferation

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(8), manifested by increased thickness and abnormal appearance of the tendon. A tendon thickness over 6 mm has been used as a diagnostic criterion for AE (2). Nicholson et al (2007) developed a grading system for Achilles tendon pathology based on MRI findings, which guided selection of the optimal treatment option. The grading system was based on the tendon's diameter and the presence of degeneration within its substance: (I) grade I, anteroposterior diameter of 6 to 8 mm and non- uniform degeneration, (II) grade II, diameter of >8 mm with uniform degeneration of <50% of tendon width, and (III) grade III, tendon diameter >8 mm and uniform degeneration of >50% tendon width (9). The authors concluded that individuals with grade I disease were much less likely to require surgery (13%) than individuals with grade II and III pathology (91% and 70%, respectively).

The presence of bony spurs appears to be more common in patients with AE (65%-80%) (10) when compared to people without foot pain (25%-35%). Chimenti et al, found that on average, the spurs were significantly longer on the symptomatic side (12.9 mm) than the asymptomatic side (8.9 mm, P = .01) and controls (3.5 mm, P = .03) (11). All the above findings indicate that the size of the enthesophytes, rather than the presence of enthesophytes, may be a contributing factor to the development of symptoms in AE.

**Causative factors**

Predisposing conditions associated with AE include running on hard surfaces, walking gait abnormalities, which exert excessive pressure on the calcaneus and/or its ligaments and nerves, obesity and inappropriate shoes. It is also sometimes associated with gastrocnemius tightness and plantar fasciitis. Mechanical overloading may also contribute to AE symptoms. Running imposes loads of 4 to 6 times the force of body weight on the Achilles tendon (12) and approximately 8% strain along the entire length of the tendon (13). Although the load on the tendon is less with walking, this task still imposes approximately 7% strain along the tendon length (14).

The posterior-superior calcaneal prominence known as Haglund's deformity is mostly an idiopathic condition. Heredity also plays an important role since intrinsic foot anatomy, such as pes cavus, can often be a predisposing risk factor. Plantarflexion of the calcaneus leads to constant irritation of the overlying bursa, which is the main causative factor of redness and swelling associated with Haglund's deformity. Varus deformity of the hind foot represents another risk factor. The tendon protects itself by forming a bursa, which eventually.

Achilles enthesopathy may be also an expression of ankylosing spondylitis. Finally, fluoroquinolone antibiotics increase the risk of Achilles tendinopathy or tendon rupture especially in people over age 60.

**Clinical Presentation and diagnosis**

The diagnosis of AE is based primarily on past medical history, physical examination and radiographic findings. Patients typically report tenderness upon palpation of the terminal 2 cm of the Achilles tendon. A well-defined area of swelling and redness can often be seen at the posterosuperior aspect of the calcaneus. Ankle range of motion should always be assessed, since limited ankle dorsiflexion and plantarflexion weakness, are common findings in patients with AE. Lastly, pain that is aggravated by physical activity as well as stiffness that is associated with prolonged rest represent common complaints.

The lateral weight bearing radiograph reveals the presence of a bony prominence (Haglund's lesion) at the posterosuperior aspect of the calcaneal tuberosity, enthesophytes and intratendinous calcifications. (fig.1) Calcaneal bursal swelling and increased density in pre-Achilles bursa may also be present (fig.2) (15). The shape and lucency of the Kager triangle on radiographic imaging can also be used to assess the presence of retrocalcaneal bursitis (16).

Apart from the presence of the posterosuperior spur on the Achilles tendon, MRI findings may also include synovial thickening of the retrocalcaneal bursa as well as thickening and high signal at the site of Achilles tendon insertion. (fig.3) Ultrasound imaging can be also used to evaluate soft tissue changes such as tendon degeneration, neovascu-

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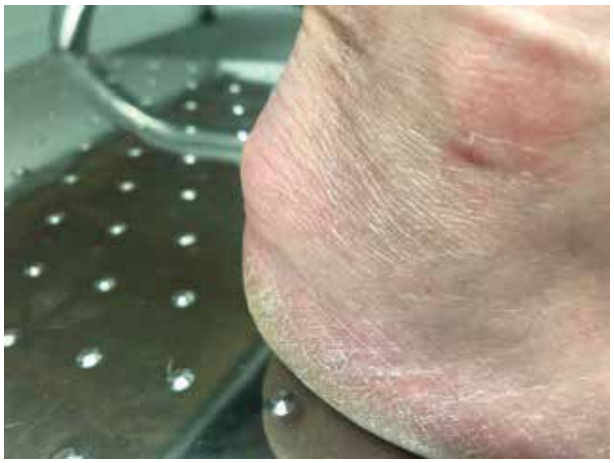

***Fig.1*** *A retrocalcaneal prominence may be either soft (retrocalcaneal bursitis) or hard (retrocalcaneal exostosis).*

larization, bursitis, paratendinitis, as well as bony changes namely enthesophytes and intratendinous calcification (11).

**Conservative Treatment**

*1.Eccentric Exercises*

Eccentric exercises such as open chain ankle dorsiflexion led to reduced pain and a higher level of patient satisfaction (Grade B recommendation). Closed chain eccentric exercises such as lowering the heel below the step, lead to less favorable clinical results with only 28% to 33% of patients with AE rating the intervention as excellent or good (Level IV evidence) (17). An alternative eccentric exercise program that utilizes a limited ankle range of motion with heel lowering to a past neutral standing position has been more successful for patients with AE. In a single case series study, Jonsson et al (18) had 67% (18/27) of patients reporting excellent or good results with pain rating decreasing from 72 to 33 on the VAS at 4 months (Level IV evidence).

Since 2010, 2 RCTs have compared traditional eccentric exercises to other treatment modalities such as extracorporeal shock wave therapy (19) and stretching (20). Traditional eccentric exercises do carry some therapeutic benefit, with an average decrease in pain ranging from 1.8 to 2.2 on the VAS (Level I evidence) at the 3 to 4months follow up (20). The modified eccentric exercise program also

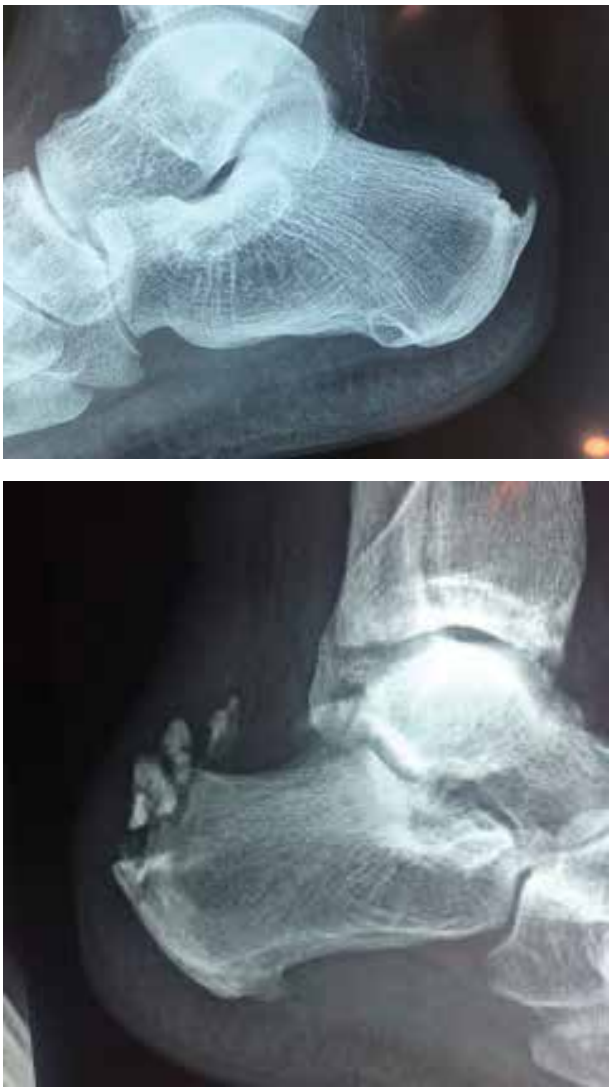

***Fig. 2*** *(a) Retrocalcaneal bony spur, and (b) Diffuse Achilles tendon intrasubstance calcification.*

reduces pain when performed alone (average 2.4 decrease at 12 weeks and 4.4 at 52 weeks, n=8) and when combined with a soft tissue treatment (average 2.9 decrease at 12 weeks and 3.9 at 52 weeks, n=7; Level II evidence) (21). A well-established exercise regime is the Alfredson's protocol that enhances tendon eccentric loading. (34)

*2. Extracorporeal Shock Wave Therapy*

A randomized controlled trial by Rompe et al in 2008, concluded that extracorporeal shock wave therapy (ESWT) was more effective at reducing pain and AE symptoms than a traditional eccen-

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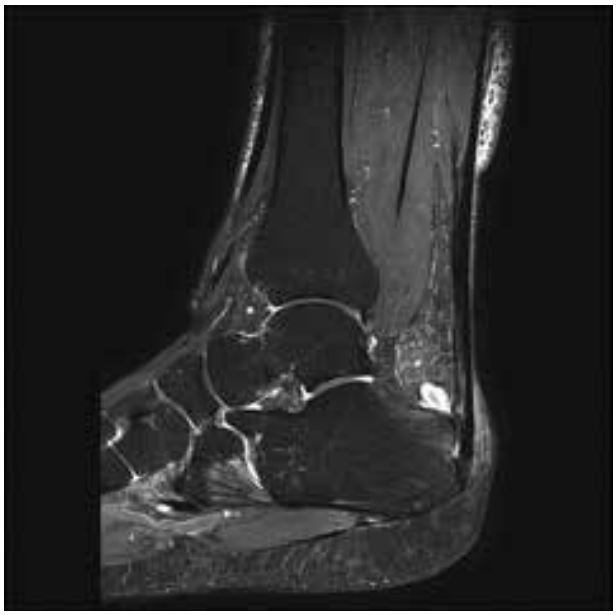

***Fig. 3*** *MRI T2 imaging showing retrocalcaneal bursitis and Achilles enthesopathy*

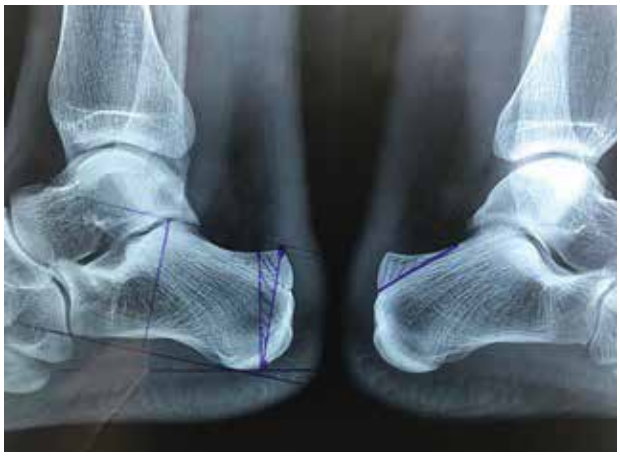

***Fig.4*** *The wedge osteotomy (left) and the oblique osteotomy (right).*

tric exercise program at 4 months (Level I evidence) (19). In 2006, Furia_reported that ESWT in conjunction with anesthetics lead to an average pain reduction of 5 points on the VAS compared to 1.4 points in the control group (Level III evidence) (22). More recently, a retrospective study found that ESWT resulted in a greater decrease in pain than a traditional eccentric exercise program at 6 months follow up (average decrease in VAS, ESWT: 3.9, Eccentrics: 1.6) and 18-month follow-up (average decrease in VAS, ESWT: 3.6, Eccentrics: 1.5; Level III evidence) (23). Wei et al, however, reported a relatively high prevalence of intolerable pain among patients undergoing ESWT that lead to discontinuation of treatment in 20% of the patients (23). Local anesthesia may help patients tolerate the treatment better, but it is unclear whether this adjunctive scheme affects patient outcomes. Two recent Level IV studies have also supported the use of shockwave therapy for IAT (24-25) yet the authors question the effectiveness for patients with enthesophytes. Based on the number of studies supporting EWST (22-24-19-25), this modality now has a Grade B recommendation.

*3. Orthotics*

Night splints are less painful and better tolerated than weight bearing calf stretches; however, if a patient can tolerate weight bearing exercises, then night splints may add no additional benefit. In a Level II study, night splints did not provide any additional benefit added to eccentric exercise in patients with non-insertional Achilles tendinosis (Level II) (26). The evidence regarding night splints and insertional disease is lacking. In another Level II study evaluating the outcomes of physiotherapy, the effect of night splints could not differ from the concurrent effects of other treatment components (20). As such, this modality has a Grade I treatment recommendation.

Insoles with heel lift or shoes with a heel lift are commonly recommended. Heel lifts can reduce the amount of tendon elongation (tensile strain) and compression (compressive strain) that occurs at the tendon insertion during walking (27).

*4. Local infiltrations*

According to Irwin's 2010 review, there are no studies on the use of corticosteroid or glucocorticoid injections specifically for IAT (28). Corticosteroid injections have largely fallen out of favor for treatment of tendinopathy at any location, and there is particular concern around the Achilles tendon for fear of contributing to further tendon degeneration and potential tear (30). In cases of isolated retrocalcaneal bursitis, corticosteroid injection may be considered, but care should be taken to avoid intra-

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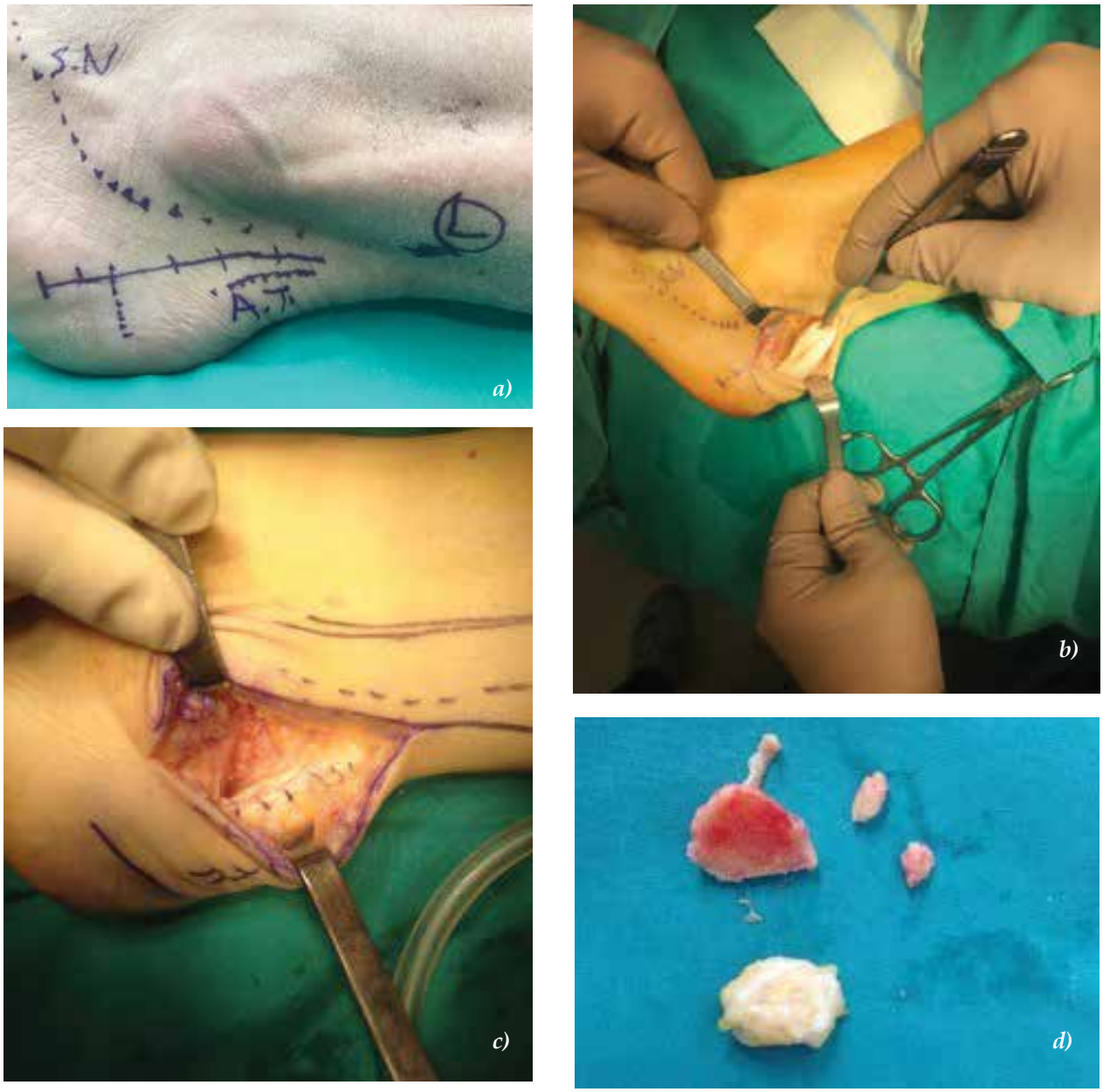


*Fig.5 (a) Incision and anatomic landmarks, (b) oblique retrocalcaneal excision and longitudinal split of the tendon, (c) excision of the calcification and repair of the tendon with interrupted sutures, (d) the retrocalcaneal prominence, the intrasubstance calcification and the retrocalcaneal bursa.*

tendinous injection.

Other potential types of injection include those targeting neovascularization, such as the sclerosing agent polidocanol or simple mechanical disruption with high volume saline and dextrose (prolotherapy). Sclerotherapy is poorly supported with only one study in literature evaluating the use of polidocanol in patients with chronic AE (Level IV evidence) (29). Although several small trials have studied these agents, most were not specific to AE and provide insufficient high-quality evidence to support their use in routine clinical practice (31). Quality evidence is therefore lacking regarding long-term efficacy of the agents for any insertional Achilles disease (Grade I recommendation).

Most studies using PRP have been in patients with

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TABLE 1.

| Proposed conservative treatment protocol for Achilles Enthesopathy in our dept. | |
|---|---|
| **Treatment** | **Effect** |
| • Alfredson's heel stretching protocol, applied daily for 12 weeks with 180 repetitions (34). | • A series of eccentric exercises, slow movements that focus on lengthening muscle contractions of the calf. |
| • Use of night splinting | • Plantar fasciitis and calf stretching. |
| • Use of shoe insoles | • Heel lift and reduction of Achilles enthesis tension. |
| • Dextrose prolotherapy outside the tendon and on the paratenon x1-2 times. | • Reduction of neovascularization and triggering of healing immune response |
| • Application of glyceryl trinitrate patches for one month. | • For local blood vessel dilation and healing enhancement |
| • Oral nutraceutical supplements for two months (35). | • Per os supplement based on methylsulfonylmethane, hydrolyzed collagen, bromelain, D-glucosamine, chondroitin sulfate, L-arginine, L-lysine, plant extracts of boswellia, myrr and turmeric, and Vitamin C |

midportion Achilles tendinitis (AT) or are mixed cohorts with controversial results. A 2012 prospective case series by Monto, found PRP to be effective in a mixed cohort of 30 patients with AT (8 insertional, 22 midportion) leading to satisfaction in 28/30 patients at 2 years (Level IV evidence) (32). However, both treatment failures in this study occurred in patients with AE (2/8) (32).

*5. Local glyceryl trinitrate patches*

There is no evidence to support the application of glycerol trinitrate patches in patients with AE. Conversely, Hunte and Lloyd-Smith concluded that the local use of a glycerin trinitrate patch was more effective than placebo in patients with chronic Achilles tendinitis in the first 12 and 24 weeks of treatment (33).

6. Adjuvant therapeutic modalities

Per os administration of nonsteroidal anti-inflammatory medications, iontophoresis, and cryotherapy may be useful if substantial inflammation is present. However, they do not act on therapeutic pathways.

In our department, an holistic conservative therapeutic protocol is initially recommended before any surgical treatment. Following a thorough clinical and imaging evaluation, the patient is instructed to follow the protocol for a period of 3-6 months. (Table 1)

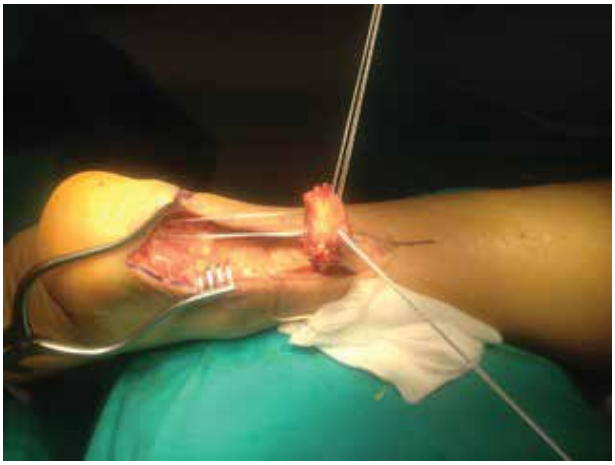

*Fig.6 Detachment of the Achilles tendon insertion for removal of large intrasubstance calcification and re-attachment to the debrided calcaneus bed with anchor and heavy sutures.*

**Surgical treatment**

If conservative treatment fails to provide adequate pain relief, surgery may be needed. In our department, we have established a certain protocol regarding the decision-making. In this protocol, surgical technique is based on the posterior morphology of the calcaneus and the intratendinous calcification of the tendon.

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- In cases of a localized heel bump (**retrocalcaneal exostosis**) an oblique excision of the posterior tubercle would be satisfactory. (Fig. 4)
- In cases of a global posterior heel bump (**Haglund's deformity**) the Keck & Kelly calcaneal wedge osteotomy is indicated. The wedge osteotomy has many advantages such as: (a) it tilts prominence forward away from the shoe, (b) it elevates the insertion of Achilles tendon and reduces equinus stress, and (c) it provides a straight orientation of Achilles tendon fibers at the calcanea insertion. (Fig. 4)
- In cases of additional **focal intratendinous calcification,** a longitudinal incision and split of Achilles tendon fibers may lead to the accumulated calcium. The calcified tissue is removed, and the tendon is sutured. The longitudinal incision has a minor risk for Achilles tendon rupture. (Fig.5)
- In cases of additional **diffuse calcification**, the tendon is fully detached from its calcaneal insertion, debrided and reattached with special anchoring techniques. (Fig. 6)

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REVIEW

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# Application of collagen-based scaffolds for the treatment of spinal cord injuries in animal models. A literature update.

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## ABSTRACT

This review compiles newer bibliographical data with regards to the application of collagen scaffolds for the purposes of treatment of Spinal cord injury (SCI) in animal models. SCI is regarded as one of the most devastating central nervous system (CNS) injuries, exhibiting an alarmingly rising incidence rate, indirectly connected with the expansion of global economy. The consequences of SCI are multidimensional: SCI injuries may result in permanent voluntary motor disfunction and loss of sensation, while incurring heavy economic and psychological burden as part of the treatment. Thus, it is of great importance that effective and suitable SCI treatment strategies are developed. Collagen-based scaffolds application is one of the most promising methods of SCI treatment. They come in a variety of forms, including hydrogel, sponge or guidance conduit serving as an instrument to administer therapeutic drugs and proteins to the SCI site. A number of relevant studies have been carried out fairly recently, exclusively using carefully selected animals that resemble human pathophysiology and surgical outcomes, without incurring cost-related, ethical or regulatory limitations. In mouse, rat and canine models having mainly undergone transection and hemisection, the stump connection, along with transplanted cell differentiation, elimination of glial scar, increased neuronal growth, decreased collagen deposition, behavioural recovery, improved electrophysiology and enhanced axonal regeneration are evident.

**KEYWORDS: Spinal Cord Injury, Animal Model, Collagen-Based Scaffold, Regenerative Medicine, Tissue Engineering**

**Introduction**

Spinal cord injury (SCI) is regarded as one of the most devastating central nervous system (CNS) injuries, exhibiting an alarmingly rising incidence rate, indirectly associated with the expansion of global economy [1-5]. The consequences of SCI are multidimensional: SCI injuries may result in permanent voluntary motor disfunction and loss of sensation, while incurring heavy economic and psychological burden []. Thus, it is of great importance that

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effective and suitable SCI treatment strategies are developed [1].

More specifically, SCI causes neurological disabilities as the CNS central axons or nerve fibres, more often than not, fail to regenerate [4,6] owing to chronic inflammatory response, demyelination and increased levels of proteoglycans [6]. In mammalian CNS, the leading cause behind the limitation of central axons to regenerate is glial scar formation, which inhibits axonal remodeling and regrowth [4,7]. Healthy glia cells are known to support neuronal function as well as signal transmission [8]. However, when SCI occurs, , the borders of SCI lesion are separated from healthy tissue by a glial scar densely populated by newly hypertrophic and proliferating astrocytes [4]. The mechanical trauma may well further progress, owing to recruitment facilitation and non-resident cell infiltration, both of which are known to jeopardise regeneration of myelin sheath and function of neurons, with glial scar constituting a physical and molecular barrier to the development of CNS axons [8,9].

Consequently, the majority of therapeutic strategies developed in recent years focus on eliminating the post-SCI inhibitors of regeneration. The strategies provide support and guidance towards regeneration of affected neurons by the application – among others – of neural scaffolds onto the SCI site [1]. The advanced tissue engineering technology has paved the way toward SCI treatment [3,10,11]. The extracellular matrices (ECM) allow living cell inoculation, growth and differentiation, promoting the regeneration of axons and fibers. The matrices are co-cultured with cells and are then transplanted in the SCI area [4]. This way, the extracellular matrix of the spinal cord can be successfully mimicked, as scaffolds are rich in glycosaminoglycan, a gap-filling polysaccharide of staunch structure [4]. However, excessive amounts thereof contribute to the uncontrollable development of extensive and grave glial scar. The most suitable solution to combat this issue shall be collagen [4].

Taking the above into consideration, there is indeed a great deal of attention regarding the characteristics of scaffolds, especially of the biomaterials these are made of. Wang et al. [12] stress the importance of the biocompatibility for cells, apposite porosity topography and permeability of scaffold materials. As aforementioned, collagen-based scaffolds are a popular choice when it comes to biomaterials used for SCI treatment purposes. Collagen is a protein found in abundance in the ECM, provoking minimal autoimmune response, promoting adhesion, proliferation, migration and differentiation of cells [13]. Collagen scaffolds come in a variety of forms, including hydrogel, sponge or guidance conduit serving as an instrument to administer therapeutic drugs and proteins to the SCI site [14].

This review constitutes a compilation of newer bibliographical data on collagen scaffolds, as applied for SCI treatment purposes in animal models, aiming to provide a fresh insight on the available bibliography.

## Discussion

This review has been compiled of articles and other bibliographical sources available on databases of strictly academic, peer-reviewed content. The search terms have been: "Spinal cord Injury, Animal Models, Collagen, Scaffolds, Tissue Engineering, Biomaterials, Regeneration Medicine". The results were filtered so that they were not published before 2014. Pieces of research not referring directly to animal models, SCI experiments and collagen scaffolds were also disqualified (Table 1).

## Pathophysiology of SCI

The spinal cord injury pathophysiology is often broadly categorized as either "acute impact" or "compression". Injury as a result of acute impact is essentially a spinal cord concussion. This mere concussion triggers a series of reactions localized in the grey matter, concluding to hemorrhagic necrosis. A grey matter hypoperfusion is usually the trigger of the series of events mentioned in this section. Occurring soon after the injury, reperfusion and increase in intracellular calcium are crucial for the injury outcome. The necrosis extent is analogous to the amount of initial force that caused the trauma, being also dependent on perfusion pressures, concomitant compression, pharmacological agents administration as well as blood flow. Mechanisms that

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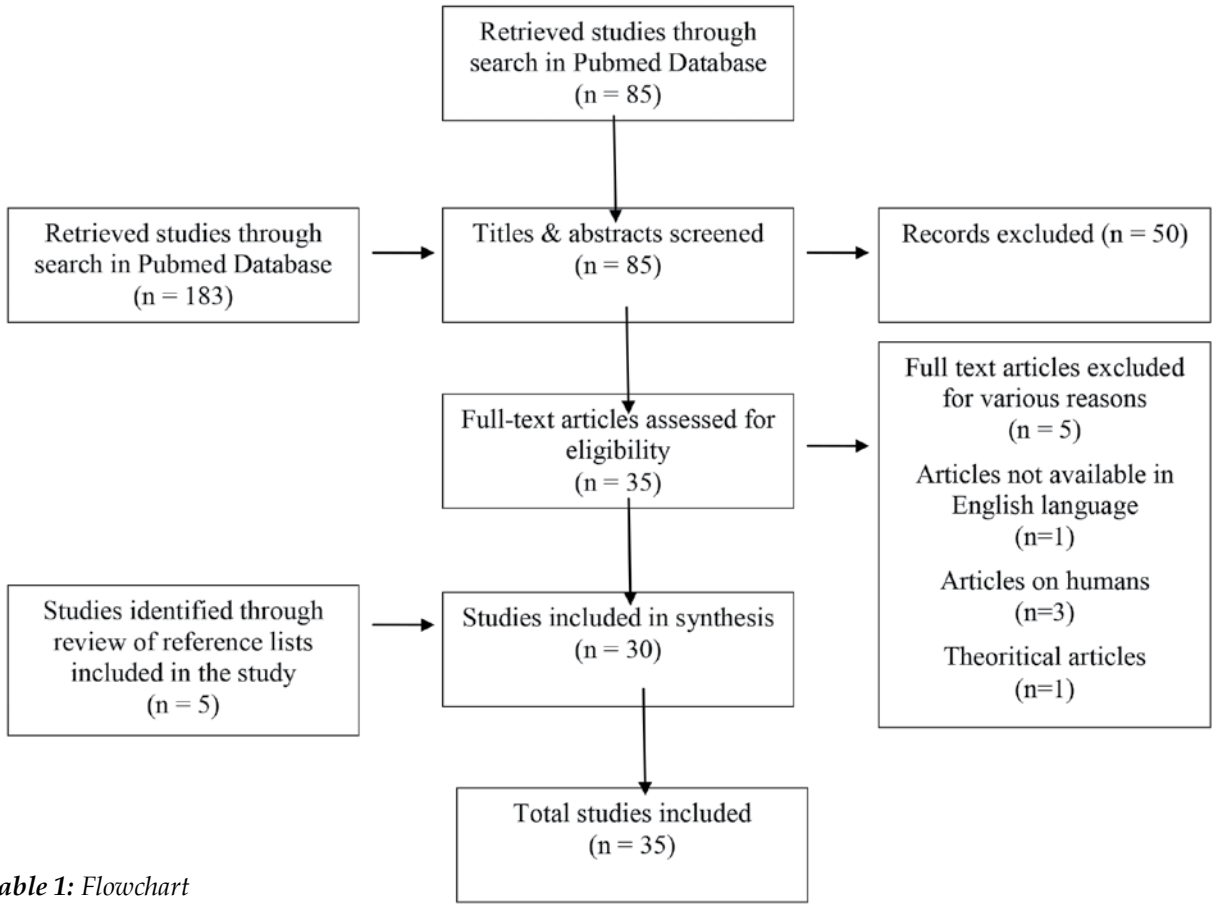


***Table 1:*** *Flowchart*

take place in the initial stages of the injury should be targeted for a better prognosis. Injury as a result of spinal cord compression occurs upon impingement of the spinal cord by a mass, resulting in an increase of the parenchymal pressure. The tissue response is gliosis, demyelination, and axonal loss. This occurs in the white matter, whereas gray matter structures are preserved. Rapid or a critical degree of compression will result in collapse of the venous side of the microvasculature, resulting in vasogenic edema. Vasogenic edema exacerbates parenchymal pressure, and may lead to rapid progression of dysfunction. Treatment of compression should focus on removal of the offending mass.

## Collagen Scaffolds for SCI Treatment

In line with the above, a number of Regeneration Medicine (RM) and Tissue Engineering (TE) studies prove the effectiveness of injected collagen hydrogels. Notably, Breenet et al. [14] examined injectable collagen hydrogels role in administering neurotrophin-3 into rat models that have undergone hemisection SCI. Others [15] discuss the positive results following the transplantation of collagen scaffolds loaded with stem cells in a mouse SCI model. In another study deploying canines with a "complete spinal cord transection, a linear ordered collagen scaffold was seeded with human mesenchymal placenta cells, demonstrating positive effects after transplantation [15]. Lastly, the team led by Jianwu Dai developed a collagen-based scaffold after ten years of research. It caused minimal side effects and exhibited increased therapeutic effectiveness. [16-18].

Li et al. [19-22] have also presented a series of outstanding pieces of research on regeneration and overcoming inhibitory factors after SCI. More specifically, they analyzed the delivery of proteins and drugs through scaffolds, to enhance post-SCI recov-

ery, mainly in animal models. Their oldest study mentioned in this review [19] refers to the construction of the CBD-EphA4LBD and CBD-PlexinB1LBD collagen-binding proteins, which help neutralize the ephrinB3 and sema4D molecules that inhibit neuronal regeneration. The proteins, administered with the use of collagen scaffolds, could promote outgrowth of neurities in vitro. Being immobilized by the scaffold itself, they were delivered by the transplantation of the latter into a rat that had sustained SCI, restoring locomotion.

In 2016, [20] the same group of scientists presented a porous collagen scaffold as means of neurotrophic protection, with seeded cerebellar granular neurons showing outgrowth in-vitro. Combined with Cyclic Adenosine Monophosphate (cAMP), the scaffold aided the repair of a completely transected spinal cord in a rat model.

In 2017, [21], Li et al reverted with another study, whereby they discussed the phenomenon of non-differentiation of endogenous Neural Stem Cells (NSCs) in rats with grave SCI. Cetuximab, a signaling antagonist, was administered via the implantation of Modified Linear Order Scaffolds (LOCS), increasing neurogenesis in lesions found in rats and, subsequently, dogs.

Most recently, Li et al [22] demonstrated that paclitaxel (PTX) reduced glial scarring attributed to SCI, by rescuing myelin-inhibited differentiation of NSCs. The cells were co-cultured with PTX and transplanted via a functional collagen scaffold into a complete T8 transection of spinal cord in a rat model. Improvement of sensation and locomotion was confirmed by Western Blot (WB) and mRNA-Seq results that showcased the ability of PTX to trigger neuronal differentiation via Wnt/β-catenin signaling pathway.

The effect of collagen-based scaffolds as a means of release of therapeutic substances was also discussed earlier by Snider et al [23], whereby the effectiveness was demonstrated using rat models to provide relevant evidence both during the acute and chronic SCI phase.

The importance of Animal Models in SCI studies

Sharif Al-Hoseini et al. [24], noticing the importance of using animal models in SCI studies, conducted a systematic review on "Animal Models of Spinal Cord Injury. The researchers categorized 2209 injuries according to level, outcome, animal species and purpose of study. Most of the reviewed studies examined drug effectiveness, while others simply observed pathophysiologic changes. Eighty one per cent of SCI sites involved the thoracic region, whilst contusion, transection and compression were the most common injury types induced. The majority (72,4%) of SCI assessments were conducted on rats, as the biological and behavioural outcomes, as well as the biomechanics and neuropathology of the rodents highly resemble those of humans. According to the study [24], rodents, in general such as mice or rats, are an optimal choice when it comes to preliminary SCI studies because of the low reproductory cost thereof and resemblance to human beings in terms of pathology and genomes. Cats are another popular choice in SCI studies, especially because of their larger size, compared to rodents, which allows easier surgical maneuvers. Another important preclinical model is the pig, which combines an intermediate size and greater resemblance to human physiology. Fish, lamprey and other vertebrates have also been deployed in novel SCI studies, owing to their unique regeneration capability. The study [24] continues to point out that the optimal choice for SCI studies would be the non-human primates and larger animals that actually represent human SCIs a lot better than other organisms. Notwithstanding the above, these primates are not ultimately deployed in such studies because of costly care, as well as regulatory and ethical considerations. As an alternative, canines can be studied in laboratory conditions after naturally-occuring SCI (e.g., due to accidents), causing less of ethical concern.

In 2021 [1], a systematic literature review has compiled a number of SCI studies conducted in animal models. Most importantly, as shown in Table 1, four studies [24-27] carried out between 2014 and 2016 have applied collagen-based scaffolds for the purposes of SCI treatment in mouse, rat and canine models. In these cases of transection and hemisection, stump connection, transplanted cell differen-

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tiation, elimination of glial scar, increased neuronal growth, decreased collagen deposition, behavioural recovery, improved electrophysiology and enhanced axonal regeneration were noted.

## Conclusions and perspectives

This review has aimed to compile the latest bibliographical data available with regards to the application of collagen scaffolds for the purposes of treatment of SCI in animal models. SCI is one of the most critical cases a patient and a surgeon may encounter, bearing significant economical and psychological implications, along with an increased rate during the recent years. Subsequently, novel ways of SCI treatment shall be developed.

Collagen-based scaffolds application is one of the most promising methods of SCI treatment. A number of relevant studies have been carried out fairly recently, exclusively using carefully selected animals that resemble human pathophysiology and surgical outcomes, without incurring cost-related, ethical or regulatory limitations. The results have been encouraging, with axonal regeneration, elimination of glial scar, as well as improved sensation and locomotion of animal models.

However, there is always room for improvement. May this review be the beginning of a new wave of research, suggesting minimally invasive, highly effective and biocompatible solutions that can actually improve the outcome and quality of life of every SCI patient.

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Zachariou D, Vlamis I. Application of collagen-based scaffolds for the treatment of spinal cord injuries in animal models. A literature update. *Acta Orthop Trauma Hell* 2022; 73(3): 254-259.

# ACTA

# YOUNG SCIENTISTS' PAGES

# Spasticity management in children and adolescents after spinal cord injuries

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## ABSTRACT

**Introduction:** Worldwide, the leading causes of death in childhood are injuries and violence. Spinal cord injury (SCI) is a potentially crippling injury which usually results in severe and permanent disability; however, it is relatively rare before the age of 15 years and accounts for only a low proportion of all childhood injuries. SCI and resulting spasticity may cause important loss of functionality. Despite its prevalence, spasticity as a syndrome in SCI patients is not always managed effectively. The aim of this study was to review the management of spasticity in children and adolescents with traumatic SCI. For this reason, a review of the current literature was performed following the PRISMA guidelines and using the online GOOGLE SCHOLAR database and the following keywords: spinal cord injury, pediatric population, spasticity, management of spasticity. Thirty-three studies were finally included in this review. **Results:** TENS (Transcutaneous Electrical Nerve Stimulation), FES (Functional Electrical Stimulation), muscle activation pattern during movement attempts, spinal manipulative therapy, non invasive brain stimulation, aquatic therapy or hydrotherapy, acupuncture, spinal cord stimulation and intrathecal baclofen therapy, Botulinum toxin A and selective dorsal rhizotomy appear to have a positive effect in reducing spasticity. However, the use of cannabinoids does not appear to have a specific effect on the pediatric population. Transplantation of bone marrow nucleated cells (BMNC) and multiple mesenchymal stem cells (MSC) appear to have an important role in treating SCI patients, however, more clinical trials are required.

**KEYWORDS: spinal cord injury, pediatric population, spasticity, management of spasticity**

## Introduction

Worldwide, the leading causes of death in childhood are injuries and violence [1]. Spinal cord injury (SCI) is a potentially crippling injury which usually results in severe and permanent disability; however, it is relatively rare before the age of 15 years and accounts for a low proportion of all childhood injuries [2]. The most common level of SCI in children under the age of 14 years is the upper cervical region, while in older children is the thoracolumbar region [3]. SCI and resulting spasticity may cause important loss of functionality [4].

Spasticity is a feature of upper motor neuron syn-

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drome and is a common but not an inevitable sequelae of spinal cord injury (SCI) [5]. The operational definition of spasticity used in this study includes the following items, on which there seems to be consensus in the literature: (1) increased muscle tone (the tonic stretch reflex): (2) increased tendon reflexes (the phasic stretch reflex): (3) increased exteroceptive reflexes (the flexor reflex): (4) pathologic radiation of reflexes (between spinal segments and over time). In general, spasticity is classified as a symptom of the upper motor neuron syndrome, characterized by an exaggeration of the stretch reflex secondary to hyperexcitability of spinal reflexes. Upper motor neurons originate in the brain and brain stem and project to lower motor neurons within the brain stem and spinal cord. The lower motor neurons are of two types, both of which originate in the ventral horn of the spinal cord: (1) alpha motor neurons project to extrafusal skeletal fibers and (2) gamma motor neurons project to intrafusal muscle fibers within the muscle spindle. In terms of pathophysiology, spasticity in SCI results when a lesion of the CNS interrupts the signals sent via the upper motor neurons to the lower motor neurons or related interneurons [4].

Immediately following a SCI, a period described as "spinal shock" exists whereby the patient presents with flaccid muscle paralysis and loss of tendon reflexes below the level of the lesion. Spinal shock has been reported to last from 1 to 3 days to a few weeks post-injury, after which there is gradual development of exaggerated tendon reflexes, increased muscle tone, and involuntary muscle spasms: the symptoms of spasticity. Symptoms of spasticity experienced by SCI patients following the period of spinal shock negatively affect quality of life through restricting activities of daily living [4].

Despite its prevalence, spasticity as a syndrome in SCI patients is not always managed effectively. This is likely due to the fact that the syndrome can have various presentations. It is recommended to take a step-by-step approach with a hierarchy of treatments [4]. The most conservative tactics are utilized first, with a progression from physical rehabilitation modalities, pharmacologic interventions, injection techniques, intrathecal baclofen, and lastly, surgery [4].

The incidence of pediatric traumatic SCI (0–17 years) in the United States has been estimated to be 17.5 per million-population. The median age at injury is 15 years and the most of patients are boys. No comparative studies have examined whether children with traumatic SCI have a better or worse prognosis than adults with SCI. There were no differences in survival in those injured at ages 0–4 versus 5–9 versus 10–15 years. Life expectancies for those injured before the age of 16 years are reduced compared to both the general population as well as persons with SCI injured at 16 or more years of age. The reasons for this increased mortality and reduced life expectancy are not clear but may be related to a longer exposure to SCI complications and secondary conditions, as well as consequences of developing SCI prior to achieving skeletal maturity [6].

**Differences between Pediatric and Adult SCI**

The child's cervical spine is characterized by ligamentous laxity, incomplete ossification of the vertebrae, anterior wedging of vertebrae, shallow angle of facets, and relatively underdeveloped neck muscles compared to teenagers and adults. As a result, forces on the head and neck can result in greater stretching of the ligaments and spine without resultant fracture but with injury to the spinal cord. Children with SCI experience some unique secondary complications such as scoliosis and head and neck bone mineral density and other complications such as autonomic dysreflexia require modifications in management due to pediatric physiology. Researchers are evaluating various modes of exercise in youth with SCI, attempting to lessen the impact of SCI on bone, muscle and metabolic health and manage resulting spasticity. The rehabilitation of children with SCI typically includes compensatory strategies and exercise, and new methods of exercise including functional electrical stimulation and activity-based locomotor training are being researched for efficacy in restoration of function [6].

The aim of this study was to review the management of spasticity in children and adolescents with traumatic SCI. For this reason, a review of the current literature was performed by following the PRISMA guidelines and using the online GOOGLE SCHOLAR database and the following keywords: spinal cord injury, pediatric population, spasticity, management of spasticity.

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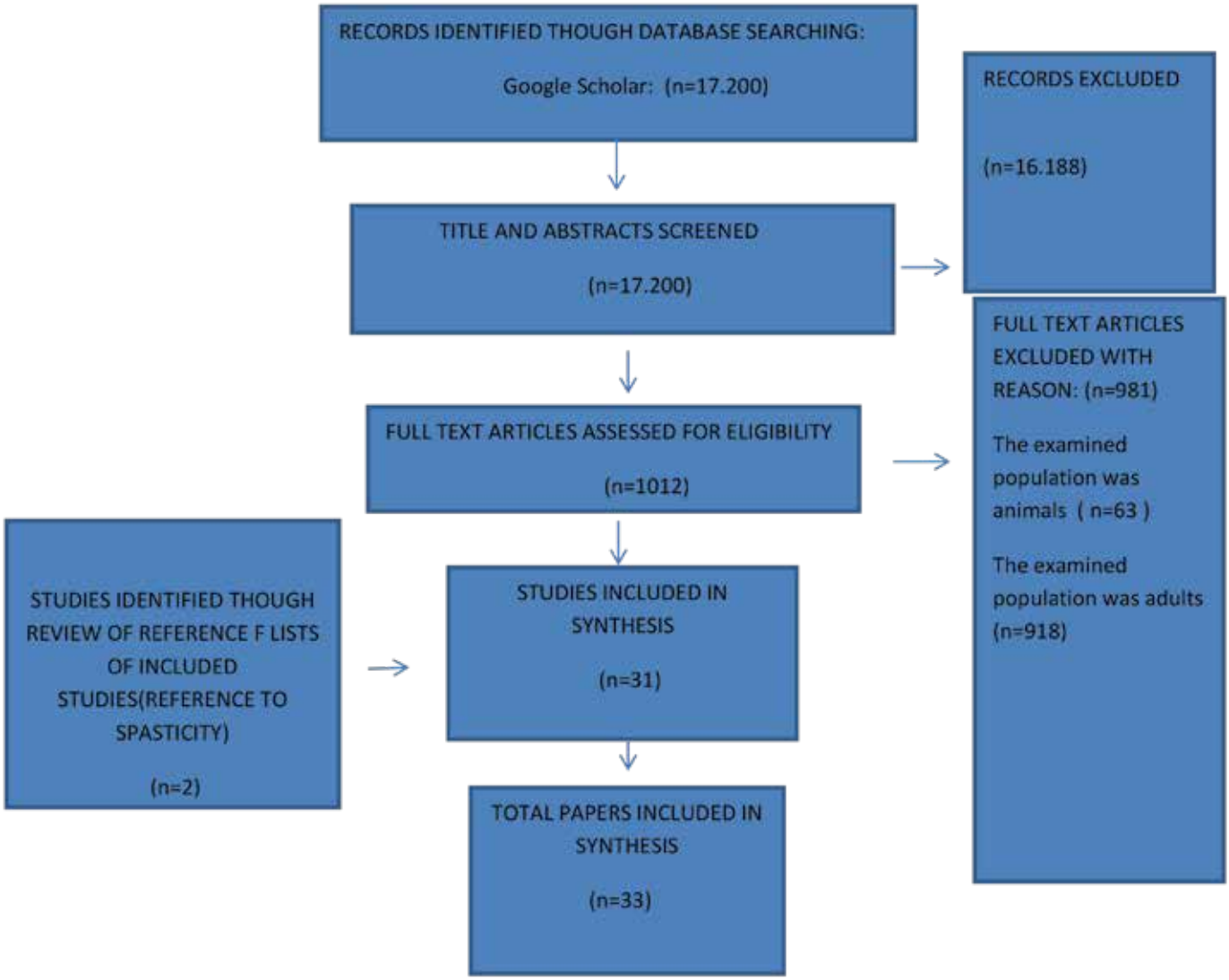
**TABLE 1: CURRENT REVIEW FLOWCHART**




Inclusion criteria in the review were: primary studies in pediatric population with traumatic SCI published in English language. Initial search resulted in 17.200 articles. After checking titles and abstracts, 16.188 articles were rejected for not meeting the inclusion criteria (studies concerning non traumatic SCI) and the remaining 1012 articles were assessed for eligibility. From them, a great number of articles were also excluded (n=981) due to the fact that they were studying SCI on either animals (n=63) or adults (n=918). Finally, 33 studies were included in the present review, with 2 of them being studies identified thought the review of the reference lists of already included studies (Table 1).

## Discussion

*Physiotherapy*

Transcutaneous Electrical Nerve Stimulation (TENS) is one of the most commonly used methods for the management of neuropathic pain in patients with SCI. This technique is used in combination with massage therapy in order to relief pain caused by spasticity. TENS is useful and safe and when added in long term

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rehabilitation programs can decrease pain to a significant level. In a recent study, a total of 60 patients with incomplete SCI and neuropathic pain were subjected to high frequency TENS (80 HZ). There were two sessions per day with each session lasting for 45 minutes. TENS was applied for four days in a week and all patients were followed for eight weeks. Pain intensity was measured by using VAS (Visual analogue scale). During the consecutive sessions of TENS application, pain intensity decreased in a linear fashion and there was a significant decrease in pain at the end of the treatment [7]. Furthermore, electrical stimulation improves muscle mass and strength, passive range of motion, upper extremity function and walking speed. In addition, positioning of the foot and ankle kinematics during walking, sitting posture and static/dynamic sitting balance may also be improved [8].A recent study showed that Functional Electrical Stimulation (FES) cycling may provide some functional improvement in chronic SCI (more than 2 years duration) after following a program of one hour FES cycling session 3 times per week for 16 weeks. The results showed that there were statistically significant improvements in total motor and FIM scores and spasticity level at the 6 months follow up [9].

Another method of physiotherapy to improve spasticity is muscle activation pattern during movement attempts. In a recent study, the activation pattern included training 2 times per week for 12 weeks on a lower body eccentric resistance (eccentric strength isometric and daily step physical activity). The results showed improvement with eccentric and isometric strength training while daily step activity remained unchanged [10]. In addition, locomotor training in children with SCI (15-18 years old) showed some benefit. Locomotor training included body weight supported treadmill or over ground training [11].

In a recent study, spinal manipulative therapy appeared to be safe and effective, offering pain relief as a result of myofascial release of paraspinal muscles (decrease spasticity) after a treatment with 13 physical therapies over a period of 5 weeks [12].

Non-invasive brain stimulation is also a way to promote motor and functional recovery following SCI. Non-invasive brain stimulation apart from repetitive transcranial magnetic stimulation and transcranial direct current stimulation was used in a research study aiming at motor and functional recovery of spasticity especially in upper and lower extremities following SCI. In the case that the residual corticospinal circuits could be stimulated appropriately, the changes might be accompanied by functional recovery or an improvement in spasticity[13].

In addition, a very important part of physical therapy can be the aquatic therapy or hydrotherapy. Hydrotherapy can be offered to patients with SCI in order to improve gait kinematics, cardiorespiratory and thermoregulatory responses and reduce spasticity [14]. Exercising in the water of a pool has been shown to improve mobility and quality of life and lessen spasticity and pain. It is highly effective in promoting overall recovery from SCI. However, more research is required to thoroughly investigate it and develop protocols and safety measures that will increase the variety of patients with access to aquatic therapy [15].

*Acupuncture*

Acupuncture has been used to resolve functional recovery problems after central nervous system injury. Researchers suggest that acupuncture has therapeutic potential to help improve limb movement function and decrease the severity of spasticity. Moderate quality evidence suggests that electro-acupuncture combined with conventional routine care (pharmacological/rehabilitation) can reduce spasticity and improve motor function and activities of daily living. In a recent study, 67 SCI patients with lower extremity spasticity were randomly assigned to electroacupuncture and control treatment groups. Electroacupuncture patients received 1-2 Hz for 30 min/day, 6 times/week for 2 months, whereas control received conventional pharmacology. After 2 months of treatment, electroacupuncture decreased lower extremity spasticity in SCI patients and was more effective than conventional therapy. Acupuncture acts on spasticity by breaking pain-spasm cycle, regulating activity of spinal motor neurons and regulating neurochemicals [16].

Pharmacological treatment

A few studies have examined the effects of cannabinoids on spasticity in the pediatric population. However, there is currently insufficient evidence to sup-

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port use of cannabinoids in treatment of spasticity in pediatric patients [17]. In a randomized controlled trial, 72 children and adolescents (8–18y), with spasticity due to traumatic injury were radomly assisted to receive THC (Tetrahydrocannabinol)/CBD (Cannabidiol) or placebo (2:1 ratio) for a period of 12weeks. Up to a maximum of 12 sprays/day, dependent on outcome and tolerance. No difference in spasticity between THC/CBD and placebo were found. Furthermore, were improvements in pain, though not to statistical significance. The posthoc analyses found difference in 12–17y [18]. Cannabinoid use should be discouraged outside well conducted clinical trials. As yet there are no long-term data on the effects of cannabinoids on neurodevelopmental outcome. Parents' reports describe potential cognitive benefits, though effects of the condition on cognition make the effect of CBD on the developing brain difficult to assess. The fact that in the majority of children spasticity results from neurodevelopmental abnormalities complicates the assessment of neurological effects of cannabinoids in pediatric population [17].

Medications such as baclofen that act on the central nervous system and botulinum toxin infusion causing muscle denervation, can be used against spasticity [19]. Baclofen is used for the relief of flexor spasms, clonus and concomitant pain [20]. However, intrathecal baclofen therapy (ITB) has been used in the treatment of spasticity in pediatric population with a delay in referral [21]. Often, only after a long time of failed medical therapy, the use of a baclofen pump is considered [22]. In a recent study, ITB had a dramatic long-lasting effect on spasticity (out of 30 patients, with age ranging from 5 to 23 years old, 20 reported effectiveness of ITB and 26 reported an improved quality of life). Despite the limitations of this study, earlier referral for ITB showed better results in treating severe spasticity. In a recent study, ITB showed very good reduction in spasticity and painful deformities caused by this condition in 80 - 97% of cases [23]. Spinal cord stimulation and intrathecal baclofen therapy are used for patients with severe spasticity after SCI [24].

Botulinum neurotoxin (BoNT) is one of the mainstays in the treatment of pediatric spasticity. It is known that BoNT is effective at reducing spasticity and improving range of motion, but it remains to be determined to what degree this translates into improved function, activity, and participation [25]. A recent study including 6 children with spastic diplegia, assessed the results of the combined use of Botulinum toxin A and electrical stimulation (ES) in treating spasticity. The outcomes were not significant at 4 weeks. The authors concluded that the addition of ES does not improve spasticity over any possible effects that BoNT/A therapy has when used alone [26]. Another study assessed the combination of botulinum toxin (BoNT) injections with virtual reality in the pediatric population for management of spasticity. The results showed that the VR intervention was well tolerated, and patients' guardians requested that it be used again in 9 out of 14 cases. VR was helpful in reducing BoNT procedure-related discomfort in the majority of patients. Challenges with VR setup, patient tolerance, and selecting viewing experiences were identified to guide further research and use of VR in a clinical environment [27].

*Orthopedic and neurosurgical treatments*

When conservative treatment fails to treat spasticity, surgical treatment such as upper extremity tendon transfers and nerve grafting/transfers can be used [28]. In addition, the selective dorsal rhizotomy technique can also be used for the management of spasticity in children and teens. Nowadays, rhizotomy is the most commonly performed operation to treat spasticity in children and is a reasonable option to consider for relieving spinal related spasticity [29,30]. A study with a 20-year follow-up by the Cape Town group, showed very good long-term outcomes in patients after selective dorsal rhizotomy. In a group of 14 patients, all but one had long-term control of their spasticity and good functional improvement that lasted into adulthood [23]. In another study, selective dorsal rhizotomy permitted the treated patient to acquire better ventral posture, abduction, and sitting posture [31]. Recently, the use of stem cells in treating and improving symptoms of neurological diseases has gained increased interest. The role of these cells in tissue repair by secretion of hormones and growth factors, induction of cell division and differentiation in local cells and stem cells in damaged tissue needs to be thor-

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oughly investigated [32]. The transplantation of bone marrow nucleated cells (BMNC) and multiple mesenchymal stem cells (MSC) have a very important role in treating SCI patients. In a recent study, a 15 year old girl with total spinal cord interruption was treated with BMNC and MSC transplantation followed by an intensive neurorehabilitation treatment. Within 2 years of treatment, the ASIA score improved gradually from A to C/D, and it reflected the sensation level change and the patient's ability to control the body trunk. Most importantly, the patient recovered some of the movement activities in lower parts of the body and gained the ability to stand in a standing frame and was able to walk with the support of hip and knee orthoses. The results were impressive; however, more clinical trials are required [33].

## Conclusion

Although the incidence of SCI in children is low compared to adults, there are important differences practitioners should be aware of. Age at injury and skeletal maturity are important factors when considering the child's functional goals and risks for long-term complications such as scoliosis and fractures. Quality of life is shaped by the child's physical health, the secondary complications of SCI the child experiences, and its active participation in the family and community. Physiotherapy and medication but also orthopedic and neurosurgical treatments can be especially helpful in improving spasticity and patients' overall quality of life. Each intervention separately and sometimes their combination can offer effective management of spasticity. Further research into innovative interventions will contribute to better spasticity management.

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# The effectiveness of acupuncture in patients with low back pain

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## ABSTRACT

The incidence of low back pain (LBP) has increased dramatically during the last 20 years. The usual management of LBP is conservative through pharmacologic and non-pharmacologic treatments. One of the non-pharmacologic treatments that are frequently used nowadays is acupuncture. Acupuncture is one of the oldest invasive healing techniques that were used worldwide, which aims to maintain the energy flow and function of the body and has therapeutic, cumulative and analgesic effects. A part of therapeutic acupuncture is electro-acupuncture, in which some of the points used in a treatment protocol are electrically stimulated. The purpose of this study was to review and assess the effects of acupuncture and electro-acupuncture in the management of LBP due to back related conditions. For this reason, a review of the current literature was conducted using the online databases PubMed, Scopus, Science Direct and PEDro and following the PRISMA guidelines. Article titles were searched by using the following keywords: acupuncture, dry needling and low back pain. Primary search on the online databases resulted in 1555 articles. Finally, 19 articles were included in this review. In conclusion, based on the results of different studies, acupuncture seems to be a safe and effective way of managing patients suffering from specific LBP.

**KEYWORDS: acupuncture, dry needling, low back pain**

**Introduction**

Low back pain (LBP) is conventionally defined as pain, muscle tension or stiffness localized below the costal margin and above the inferior gluteal folds, with or without associated leg pain (1). There are two different classifications of LBP. The first one relates to its cause and classifies LBP as non-specific (up to 90% of cases, when the pathophysiological source cannot be identified) or specific (when the pathophysiological source can be identified). Patients with specific LBP are usually diagnosed with lumbosacral muscle strains/sprains (70%), lumbar spondylosis (10%), disk herniation (5% to 10%), spondylolysis (less than 5%), vertebral compression fracture (4%), spondylolisthesis (3% to 4%), spinal stenosis (3%) or with a prior unsuccessful surgery in the back region. The second classification is related to the duration of its symptoms, and classifies LBP as acute (lasting less than 6 weeks), subacute (lasting from 6 weeks to 3 months) or chronic (lasting more than 3 months). (2)

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Most often, LBP is managed conservatively with pharmacologic and non-pharmacologic treatments (psychological therapies, multidisciplinary rehabilitation, spinal manipulation, **acupuncture**, massage, exercise and related therapies, and various physical modalities). (3) Rarely LBP is managed with surgical treatment. In fact, surgical treatment is a subject of controversy for doctors and therapists and its indications are constantly redefined. However, sometimes the symptoms and pathology are so severe that surgery cannot be avoided. (4)

The purpose of this study was to review and assess the effects of acupuncture and electro-acupuncture in the management of LBP due to back related conditions. For this reason, a review of the current literature was conducted using the online databases PubMed, Scopus, Science Direct and PEDro and following the PRISMA guidelines. Article titles were searched by using the following keywords: acupuncture, dry needling and low back pain. Inclusion criteria to the study were: randomized controlled trials assessing the effects of acupuncture or electro-acupuncture in the management of specific LBP. Non-randomized controlled trials, study protocols, reviews, case reports and studies published in non-English language were excluded from the review. Primary search on the online databases resulted in 1555 articles. After screening of titles and abstracts, 1390 articles were excluded as inappropriate. From the remaining 165 studies, 147 were rejected for various reasons, leaving 18 studies for analysis. Subsequently, a scan of the articles' reference list was performed to check for more eligible articles to be included in this study. Following the above procedure, 19 articles were finally included in this review. **(Table 1)**

## Discussion

Acupuncture is a holistic, blood-free and drug-free method, which uses special thin needles placed in specific parts of the body for the therapeutic restoration of reversible functional diseases, syndromes or symptoms. It is one of the oldest invasive healing techniques used worldwide. (5) The "biomedical" acupuncture is the "western" version and the historical development of the traditional Chinese acupuncture. Although the therapeutic mechanism is common, there are important differences. Medical acupuncture is based on the western clinical examination, the contemporary diagnostic approach of the patient, the universally accepted medical terminology, and its mechanisms of action are based on physiology, neurophysiology and follow the rules of biomedical science. In contrast, traditional Chinese acupuncture is based on the concept of vital energy (qi) flowing throughout the body through multiple channels (meridians). Meridians connect the internal organs with the skin and provide channels-paths of communication between the various organs, tissues and cells of the body. They are divided into primary (6 Yin and 6 Yang) and secondary (56 meridians) and are bilateral for each organ. (6)

Apart from body acupuncture, there are also other types of acupuncture, which either involve different parts of the body or the treatment is not performed exclusively by needles. These types include auricular acupuncture (7), electro-acupuncture (EA), acupuncture in combination with moxibution (8) (9) (10), cranial acupuncture, laser acupuncture, oral acupuncture, nasal acupuncture (rhinoacupuncture), acupuncture of the vagina, acupuncture of the periosteum, acupuncture of the foot etc.

Nowadays, acupuncture is an important preventive and curative treatment for a variety of problems. According to the Neuronal Theory of Acupuncture, the needle is an exogenous stimulus, which follows the same path as all sensory stimuli. After its placement on the skin, fat tissue, muscle, bone or in kinetic or aesthetic fiber and peripheral ganglia, follows the rule of neurons (transduction). It is then transferred to the processing center, where it is modified according to the prevailing conditions and previous experiences (modulation) and finally, it is transferred to the cortex, where it is expressed as a sense (perception). The results of this theory are two distinct actions of acupuncture: acupuncture analgesia, for the inhibition of mainly acute pain, and acupuncture therapy, which is being used in the daily clinical practice for chronic pain syndromes. (11)

As mentioned above, EA is a type of acupuncture, in which some of the points used in a treatment protocol are electrically stimulated, achieving continuous, intense and controlled stimulation parameters. EA increases the effectiveness of traditional acupuncture and expands its range. The main indication for EA is

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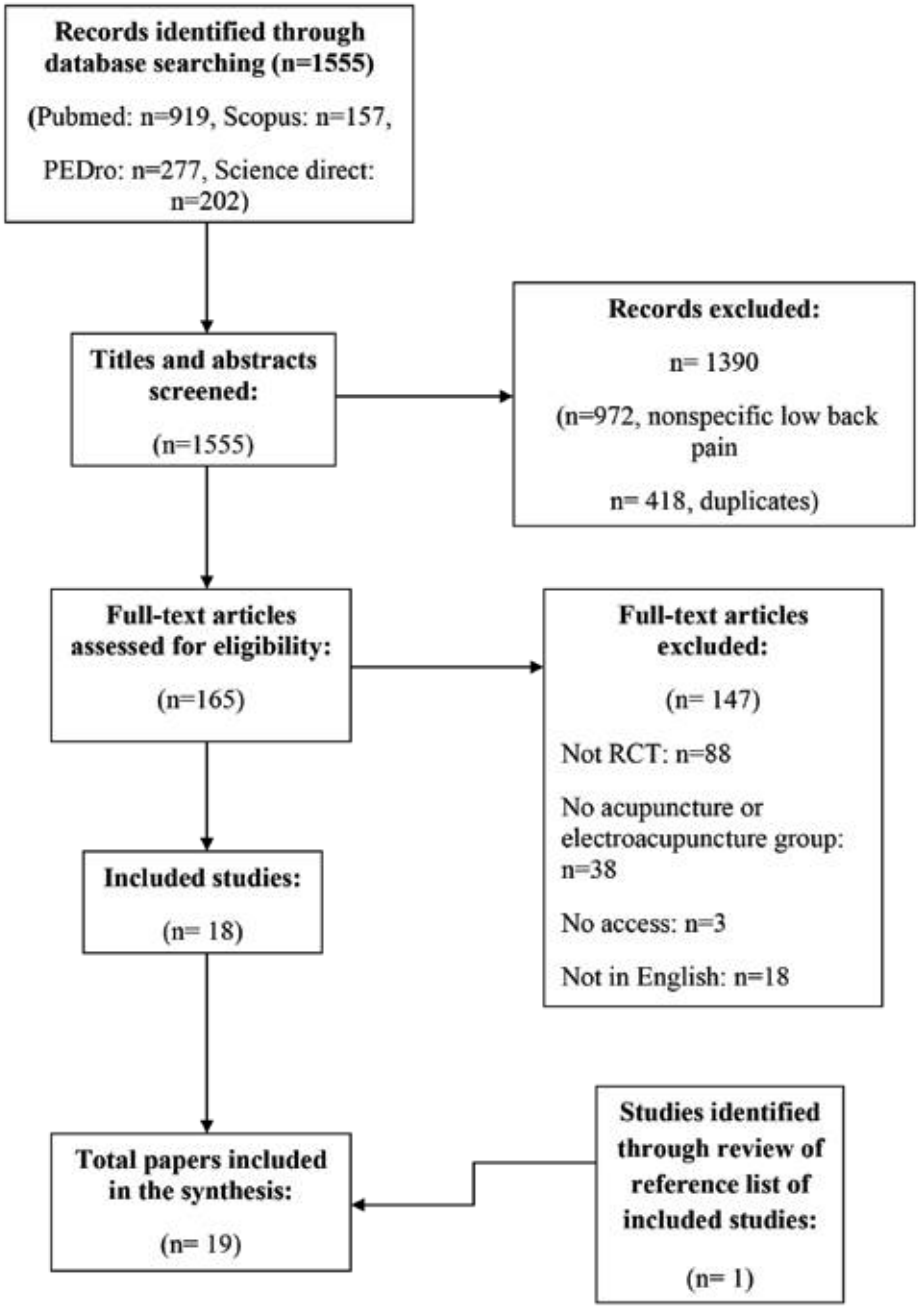
**Table 1: Flowchart**




acute (frequency of 150-220 Hz for 20-30 minutes) and chronic pain (frequency of 1-5 Hz for 15-20 minutes). EA is also selected to achieve analgesia before or after surgical repair of vertebral injury (200-3000Hz, high intensity 500-700mA and explosive pulse or pulse scan of different frequencies, while the irritation begins 20-30 minutes before the operation and continuous during it). (11) It can be applied bilaterally, at symmetrical acupuncture points or at ipsilateral points of an area or a part of the body. Acupuncture points are divided into 3 major categories: points with an aesthetic substrate (for analgesia), points with a muscular substrate (for therapy), and points with a neural substrate (intense sensation de-qi and contraction of more than

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one muscle). It is important to mention that the World Health Organization (WHO) has compiled a list of the main indications of acupuncture. LBP, sprains, sciatica and postoperative pain (among many others) are included in the list of diseases, symptoms or conditions for which acupuncture is considered to be an effective treatment. (12)

The randomized controlled trials that were included in this review assessed the effectiveness of acupuncture and EA in the management of specific LBP by comparing these two techniques to each other and to other treatments as medication, conventional therapies and other forms of acupuncture.

*Acupuncture*

In a recent study, involving 58 patients with discogenic LBP, researchers compared acupuncture and conventional therapy. Pain intensity was significantly reduced in both acupuncture's (P<0.001) and conventional therapy's groups (P<0.001). Moreover, LBP kept reducing during the follow-up period. However, the reduction in pain intensity (P=0.006) and degree of disability (P=0.002) was significantly greater in the intervention group, acupuncture. (13) Another study by Wang et al, including 132 patients, compared the effectiveness of acupuncture and sham acupuncture in the treatment of LBP and sciatica before and after surgery for lumbar vertebral protrusion. Acupuncture proved to be more effective than sham acupuncture, with longer duration, both before and after surgery. It is therefore believed that acupuncture may be a good alternative to medication for the treatment of LBP and sciatica before and after surgery in patients with lumbar disc protrusion. (14) A study by Gu et al, including 60 patients, compared warm needling and acupuncture in chronic LBP. It was noticed that after treatment, VAS scores of both groups decreased significantly and the differences between the groups were statistically significant (both P<0.05), with better results in the warm needling group. (8) A study by Guo et al, including 108 patients, examined the effectiveness of triple needling in combination with moxibustion and Tanbo-plucking tender points compared to acupuncture and moxibusion for Third Lumbar Transverse Process Syndrome (TLTPS). The difference in the overall improvement rate was statistically greater in the intervention group. (9) A study by Zou et al, compared warm needling and acupuncture in the treatment of TLTPS in 60 patients. Upon completion of treatment, VAS scores in both groups decreased significantly (P<0.01), indicating that both methods effectively reduced pain. However, the VAS score in the warm needling group was significantly lower than in the acupuncture group, showing a better effect. (10) A study by Huang et al, including 46 patients, evaluated the efficacy and safety of acupuncture for discogenic sciatica by comparing two groups, one of acupuncture with one of sham acupuncture. It was noticed that the mean VAS scores for sciatica in both groups decreased gradually over the four-week treatment period, with the reduction in the acupuncture group being greater than in the sham acupuncture group. The differences between the two groups in the mean VAS score for LBP were greater than 5 mm at weeks 4, 16 and 28, with no significant statistical significance. (15) A study by Kim et al, including 34 patients, examined the safety and efficacy of a comprehensive 4-week treatment program for inpatient with severe symptomatic LSS in South Korea. MT1 team received Mokhuri Chuna (mobilization and relaxation of the lumbar spine and back muscles), side manipulations, medication and daily acupuncture. In the MT2 team all the other interventions were the same as MT1 group, except medication. In the CMT group, oral medications, epidural steroid injections and physiotherapy, were given. Three months after the treatment, there was no difference between the VAS of the groups for low back and leg pain. Six months after treatment, there were significant differences between groups in VAS for back pain between MT2 and CMT (P=0.001) and VAS for leg pain between MT1 and the CMT group (P=0.01) and between the MT2 group and CMT (P=0.003), indicating that medication could be replaced by other methods. (16) Another recent study, including 72 patients, compared the efficacy of point-toward-point acupuncture in residual back pain after percutaneous kyphoplasty, in chest function and quality of life in patients with osteoporotic fracture, to pharmacological and injectable treatment. After treatment and at the follow-up visit, the VAS score was significantly reduced in both groups (both P<0.05). However, VAS was significantly lower in the intervention group proving it is more

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effective for pain relief. (17) Another clinical trial, performed on 408 patients, studied the efficacy and safety of integrated TCM therapy for LDH and, therefore, to confirm its clinical effect, compared to a conservative treatment program. Eventually, both groups had a significant reduction in VAS, however the intervention group had a significantly greater improvement. Six months after the intervention, compared to the initial measurements, the changes in the VAS remained significant in both groups, but the difference between the groups was not significant (P=0.091). These findings suggest that integrative TCM therapy may be a beneficial complementary and alternative therapy for patients with LBP due to LDH. (18) A study by Yu et al, including 80 patients, studied the clinical effects of acupuncture treatment for LDH, comparing aligned acupuncture to vertical acupuncture. After treatment, VAS scores decreased in both groups. The difference in the treatment group before and after treatment was statistically significant (P<0.05) and it was also statistically significant between the two groups, after treatment (P<0.05). In contrast, in the control group, the difference was not statistically significant (P>0.05), proving that pain improvement was better in the treatment group than in the control group. (19) Finally, a study by Kim et al, including 50 patients, studied the effectiveness and safety of acupuncture in patients with symptomatic lumbar spinal stenosis, compared to conventional therapy. Eventually, there was a significant difference in favor of the intervention group for both LBP (at 3 months) and sciatica (at 6 weeks and 3 months). Overall, 39% of the people who received acupuncture said they were satisfied with their treatment, while in the control group this percentage was only 14%. (4)

*Electro-acupuncture*

A recent study by Zhang et al, involving 100 patients (22 men and 78 women), compared the effectiveness of EA and moderate-frequency electrotherapy in sciatica and LBP. Back pain was more reduced in the EA group (P=0.05) and a statistically greater reduction in sciatica was also noticed (P<0.001). (20) In a study by Giles et al, EA, medication (tenoxicam with ranitidine), and spinal chiropractic were compared in the management of chronic (>13 weeks) spinal pain syndromes. The results of this study, despite its shortcomings, indicate that in patients with chronic spinal pain syndromes, chiropractic, if not contraindicated, is more effective than acupuncture and medication. (21) Another study by Wu et al, including 295 patients, examined the clinical effect and change in the thermogram through EA compared to medication, in people with acute lumbar strain. After the treatments, the improvement rates in the EA group and in the medication group were 71.4% and 42.6% respectively (P<0.01), proving that EA has significantly better results. (22) A study by Inoue et al, including 17 patients, investigated the effectiveness of EA of the spinal nerve root using a selective spinal nerve blocking technique to treat lumbar and hip symptoms in patients with vertebral stenosis. Eventually, the 17 patients who received EA, all showed significant improvement over time in LBP, lower extremity pain , lower limb numbness and continuous walking distance (p<0.01 for all parameters). (23) A study of the same author, including 9 patients, investigated the effectiveness of pudental nerve EA for LBP and sciatica in patients with lumbar spinal stenosis, one week after conventional acupuncture treatment in this area. Finally, 6 out of 9 patients reported that their sciatica decreased after treatment, 4 out of 9 reported that the aesthetics of the area increased, and 4 out of 5 increased their continuous walking distance. However, no one showed more than 30% improvement in LBP. Therefore, it is believed that pudental nerve EA is effective only when acupuncture has not previously had a significant effect on the patient. (24)

*Acupuncture vs Electro-acupuncture*

A recent study by Miao et al, including 73 patients, compared the effectiveness of EA and acupuncture in LBP due to TLTPS Eventually, pain decreased in both groups, but the reduction was greater in the EA group. (25) Another study by Wu et al, compared the effectiveness of acupuncture with qi-guiding to EA in the treatment of LDH. Eventually, the difference in the overall outcome between the two groups was not statistically significant, proving that both treatment protocols can be effective in treating LDH. The recovery rate in the intervention group was significantly higher than in the control group. (26) A study by Chen et al, including 180 patients, assessed the clinical effect of

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treating LDH by needling the points on both sides of the impaired lumbar vertebrae, while randomly dividing patients in three groups. In the treatment group, basic and auxiliary acupuncture points were selected, combined with hydro-acupuncture, EA and chiropractic. The acupuncture team received acupuncture and medication. The last group received only medication. In the end, there was statistically significant difference between the effectiveness of the intervention group and the other two groups. Also, in the intervention group there was no deterioration of any patient after half a year. (27)

Based on the results of the studies mentioned above, it becomes obvious that acupuncture is really effective in patients with specific LBP. Indeed, in the majority of the studies, acupuncture's efficacy was superior to other interventions that were applied. Positive results were mostly obtained by a combination of acupuncture techniques, i.e. warm needling, EA, triple needling plus moxibusion plus tanbo plucking, aligned acupuncture, etc. Regarding the etiology of LBP, it seems that some interventions are superior to others in certain pathologies. Specifically, it was noticed that for Lumbosacral muscle strains/sprains and Triple Transverse Process Syndrome, warm needling, EA, chiropractic spinal manipulation and triple needling plus moxibustion had the best results. For disc herniation, EA, acupuncture, and a combination of "acupuncture, hydro-acupuncture, EA, manipulation" are recommended. Moreover, for spinal stenosis, "Mokhuri Chuna, acupuncture, and/ without herbal medication", EA and acupuncture showed better results. Last but not least, acupuncture, point-to-point acupuncture and EA were shown to be very effective in managing LBP before and after surgery. Thus, acupuncture may be an effective alternative to oral medication for the management of LBP before and after surgery in patients with lumbar disc protrusion. In fact, in many cases, surgery can be avoided by using alternative therapies.

However, further examinations and longer follow-ups are necessary, due to the chronicity of the diseases being studied, so that the results are more reliable. Objective measurement of the patients' symptoms must also be ensured, as pain is subjective and affected by social conditions and high expectations. It's really important to ensure that enough follow-ups will be made, to test the durance of the therapies' effectiveness. A sufficient number and homogeneity in the sample size of the studies should also be secured. Finally, more studies examining the effect of acupuncture without the simultaneous application of other treatments, as well as studies comparing the types of acupuncture with each other, would be very useful.

***A Conflict of interest***

*The authors declare no conflicts of interest.*

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# Wheelchair design for patients with spinal cord injuries

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## ABSTRACT

Wheelchairs are the most common means of transportation for people with spinal cord injury (SCI). The needs, requirements, functional capabilities and personal preferences of the SCI patient should be clarified in order to obtain a wheelchair that will satisfactorily meet its particularities and will enjoy maximum comfort. The purpose of this study is to review the designs of wheelchairs used in the rehabilitation of patients with SCI. In the PUBMED electronic database, a search was performed with the use of the following keywords: "wheelchair" AND "spinal cord injury" AND "design". Inclusion criteria were studies evaluating wheelchair design in patients with SCI. The search revealed 573 papers. After checking titles and excluding papers, 48 studies were left for the present review. The proper design of wheelchair is vital to the quality of life of SCI patient. The design characteristics of the seat, the backrest, the wheels, the footrests, the cushions and other accessories may help SCI patients increase their independence and functionality and prevent from pressure ulcers.

**KEYWORDS: Orthotics, Wheelchair, Spinal Cord Injury**

**Introduction**

Patients with spinal cord injury (SCI) suffer from a loss of mobility and sensation below the level of the injury. Some patients with incomplete injury below T12 have the ability to mobilize independently and self-care indoors and / or outdoors. However, in many cases, independent mobilization is impossible as the SCI causes problems that significantly affect patients' functionality. Their functional outcome depends on many factors such as the age of the patient, the level of the lesion, the type of lesion (complete or incomplete), the maintaining motor and sensation function, the body type, etc. The most important of these patients' problems are severe lack of mobility, loss of balance, spasticity as well as chronic pain and increased fatigue. These are the most important factors that lead patients to become partially or completely dependent on the use of wheelchair for travel and performing functional activities, as they have difficulty or are unable to move comfortably, easily and without assistance.

Wheelchairs are the most common means of transportation for people with SCI. The first wheeled device is found in China and Greece around the 6th century BC. Later, around 525 AD, the first wheelchairs for people transportation appear in Greek and Chinese works of art. In 1655, Stephen Farfler, a paraplegic

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watchmaker, made a self-promoted three-wheeled chair. In 1783, John Dawson in Bath, England, invented a wheelchair with two large wheels at the rear and a small wheel at the front, surpassing all other wheelchairs invented by the early 19th century. In 1900, the first radial wheels were added to wheelchairs. In 1916 the first motorized wheelchair was built in London. In 1933, the first folding, lightweight steel wheelchair was invented by Harry Jennings and Herbert Everest who had broken his back in an accident [1-2]. Since then, the evolution of technology and the seasonal trends have contributed to the construction of wheelchairs from different materials and different designs in order to meet different needs [3].

Wheelchair-dependent SCI patients use the power and function of their upper limbs for the manual push of the wheelchair and the performance of functional activities such as moving from their chair and movement of paralyzed body areas to avoid pressure ulcers [4]. Transportation is necessary daily as patients have to move to and from the bed, bathtub, toilet, car seat, etc. They are one of the most important and determining factors for community involvement and quality of life [5]. The number of daily transports varies widely, with some studies reporting a low average of 8 transfers per day, others estimating numbers that are closer to 20 transfers per day. Taking all these into consideration, the identification of the most suitable wheelchair is a difficult process and must be performed by the rehabilitation team. More than 55% of wheelchair has been found to be inappropriate for SCI patients [6]. The needs, requirements, functional capabilities and personal preferences of the SCI patient should be clarified in order to obtain a wheelchair that will satisfactorily meet its particularities and will enjoy maximum comfort.

The purpose of this study is to review the designs of wheelchairs used in the rehabilitation of patients with SCI.

## Materials and Methods

In the PUBMED electronic database, a search was performed with the use of the following keywords: "wheelchair" AND "spinal cord injury" AND "design". Inclusion criteria were studies evaluating wheelchair design in patients with SCI.

## Results

The search revealed 573 papers. After checking titles, 507 articles were rejected. Among the 67 publications evaluated, 18 were excluded as they did not mention wheelchair design or did not involve SCI patients, leaving finally 48 studies for the present review.

### *Goals of the wheelchair design*

Choosing the right wheelchair is of paramount importance, as the right type provides every possible facility in the daily life of SCI patients. The wheelchair should be designed in a way that it can be used easily and safely by SCI patients providing comfort, stability and ergonomics. It should be flexible and easy to move both indoors and outdoors or at the patient's workplace. Additional goals include the possibility of adjusting the individual sections, the installation of removable covers to be washed and the use of ecological and recyclable materials [7]. The right choice of wheelchair makes the SCI patient more autonomous, sometimes relieves him of the need to rely on other people and increases his engagement with activities [8].

### *Wheelchair design characteristics*

#### Seat

A proper wheelchair should provide a comfortable seat, good support for the back and the entire musculoskeletal system. This also helps in better breathing, easier swallowing and reducing pain along with the prevention of pressure ulcers [9-10]. The seat must be detachable from the main frame in order to be washed or cleaned [11]. Standard seat sizes are not suitable for every person and every type of disability. The seat of the wheelchair should be designed in order to allow ventilation of the patient's body, easy access, the possibility of aligning the backrest to allow physical therapy, the folding of the seat for easy transport and easy storage. It is important to calculate correctly [12-13]:

- The width of the seat, as it should be spacious for the hips, but not so spacious for the hands to reach the wheels.
- The depth of the seat should prevent lower limb vasoconstriction.
- The height of the seat should be adjusted to the body type of each patient to offer support and free-

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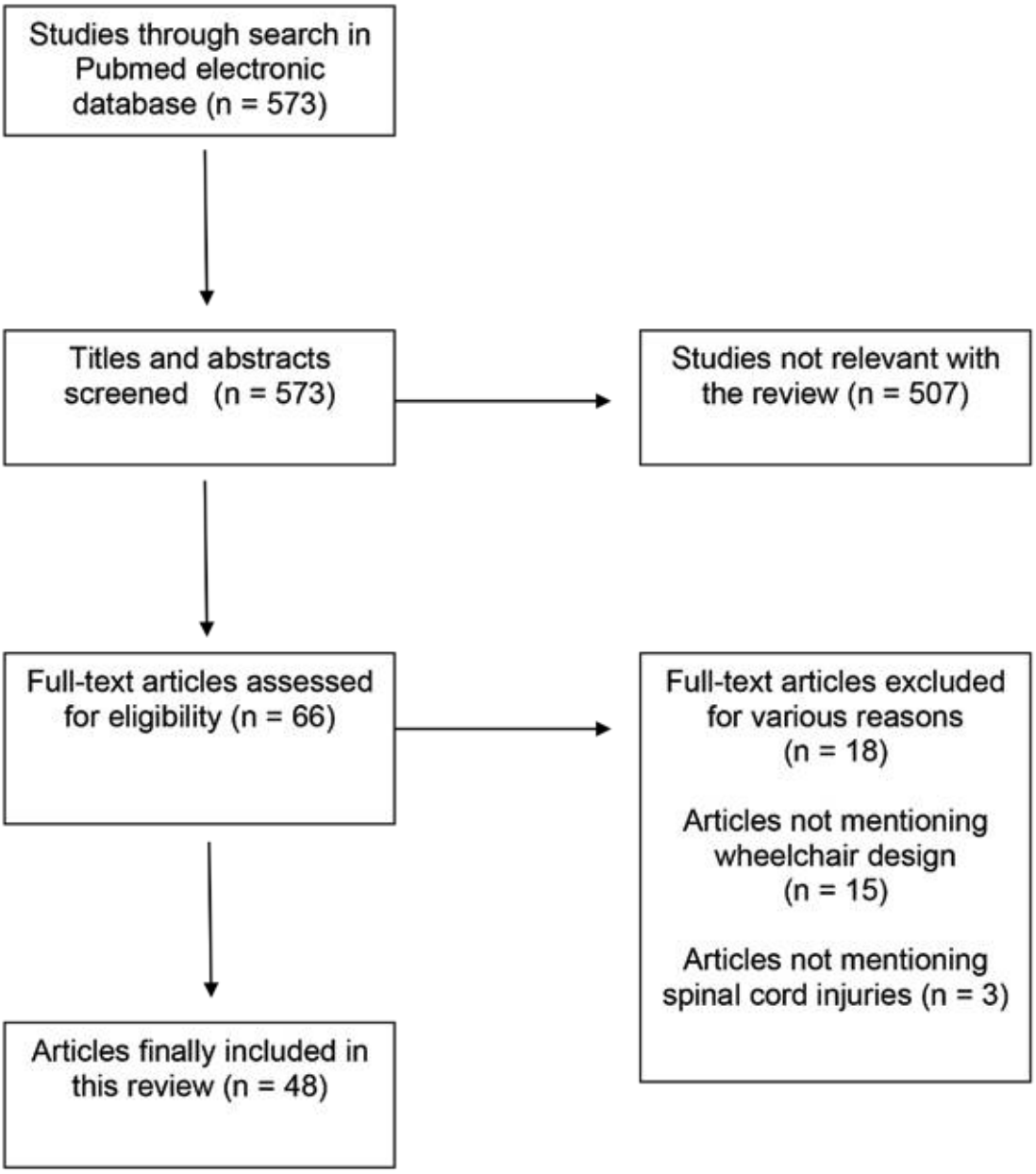
Fig. 1 Study Flowchart.




dom. A lower seat position has been associated with greater upper limb motions

Adding weight to the wheelchair can affect stability, and therefore packages or backpacks ideally should be located underneath the seat of the chair [14].

*Backrest*

The wheelchair backrest is manufactured by a flexible material stretched between the two side frames which are fixed with respect to the seat. The backrest should be high enough to support the spinal curves without inhibiting motion, yet not so low that the scapulae can hang over the back of the wheelchair and cause discomfort [7, 15]. A right detachable backrest may improve upright posture, functionality and wheelchair propulsion skills [16-17]. Changing wheelchair tilt with an inclinable backrest may be beneficial in relieving the pressure at ischial tuberosities and sacrum, by

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changing the intensity and direction of skin pressure, providing protection from pressure ulcers [18-21].

*Footrests*

The footrests are an essential and integral part of a wheelchair as they provide support to the feet and create a sense of security for SCI patients as they themselves may not control their feet. The type and length of the footrest must be determined by the type of use. In any case, the height of the feet should prevent the legs from hanging down and on the other hand it should not push upwards to create a slope in the pelvic area [22].

*Cushions*

Protective pads and soft, flexible cushions are important for relieving pressure and the prevention of pressure injuries [23-27].Cushions are also important for stabilizing the pelvis and providing postural support [28]. Therefore, patients with SCI should use an appropriate, regularly cleaned cushion for their wheelchairs [29].

*Wheels and tires*

The basic type of wheelchair has two 24-inch diameter rear wheels and two 8 inch caster wheels in the front. The tires may be pneumatic, semi-pneumatic, or solid. Solid rubber tires are suitable for use on smooth surface and indoors. The semi-pneumatic and pneumatic tires are more suitable for rough surfaces and outdoor use as they provide shock absorption. Tire pressure affects wheelchair durability. Pneumatic tires provide a smoother ride and their shock absorber action may increase the life duration of a wheelchair under proper inflation [30-31].

*Wheelchair accessories*

The use of the table is essential as it allows the patient to dine, read and more. The table should not obstruct the patient with its position, so it should be folded or detachable. Ergonomic hand rims improve SCI patients' symptoms, functionality and independence [32]. Wheelchair arms should be light and detachable, providing support and facilitating the transfer into and from the wheelchair. The rear axle should be moved forward incrementally, provided the wheelchair user feels stable [14, 33]. Wheelchair rear-suspension systems may improve wheelchair mobility by providing comfort at higher speeds, and by minimizing the seat forces and head accelerations experienced by the SCI patients [34].

*Types of wheelchair*

Wheelchairs are classified into the following types: Manual wheelchairs (simple type wheelchairs, special type wheelchairs), electric wheelchairs, lightweight wheelchairs, scooters, standing power wheelchairs, bath-toilet wheelchairs and sea wheelchairs

The standard manual wheelchair has two side frames linked by a cross-bar that is pivoted about its intersection and a flexible and foldable seat and backrest, two large driving wheels at the rear, and two caster wheels at the front. Manual wheelchairs may be used by patients with paraplegia who have the ability to move the upper limbs or by patients who use the wheelchair occasionally [35-36]. Repairs completed on the wheels and casters were the most frequent repairs to manual wheelchairs [37].

*Simple-type wheelchairs*

Simple wheelchairs may be used at almost every type of disability. They include (a) wheelchairs with large rear wheels (intended for outdoor use), (b) wheelchairs with medium rear wheels (suitable for both outdoor and indoor), (c) wheelchairs with small rear wheels (recommended only for indoors) and (d) special types [38-39].

The first type is a wheelchair with two large wheels at the rear and two smaller ones at the front. It is used outdoors as it is more flexible, easy to use and offers the patient the opportunity to put it at an angle, so that he can climb stairs and pass over obstacles. Many times a second, auxiliary frame is applied to the main frame of the wheelchair, which smoothens the weight distribution and prevents the overturning of the wheelchair [39]. Various anti-rollback devices may assist manual wheelchair users to ascend ramps and inclines [40].

The second type is a wheelchair with two medium wheels at the rear and two smaller ones at the front. These wheelchairs are ideal for movement inside or outside the house, but always with the help of an attendant since the patient cannot move alone. Moving

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around a house is easier, but it puts a lot of restrictions on transportation and is not practical, especially when it comes to obstacles [39].

The third type is a wheelchair with 4 small identical wheels at the rear and at the front. These wheelchairs are ideal for indoor use only, as the size of the rear wheel does not allow them to move outdoors. Patients with this type of wheelchair need the help of an attendant in order to move, while there are usually no extra amenities. Their big advantage, however, is their extremely small width, which allows them to fit even in very narrow spaces [39].

Special categories of simple wheelchairs may offer greater comforts and include folding wheelchairs, wheelchairs with braking assistance, wheelchairs with separated backrest, recliner wheelchairs, wheelchairs with retractable sides, wheelchairs with retractable footrests [41].

*Special-type wheelchairs*

They are wheelchairs for specialized uses, specially designed for SCI patients with sports disabilities, who have lower backrests and extra features, mainly to offer safety and balance during use. Most of them have a reclining backrest, reinforced mechanisms and many practical adjustments that ensure complete comfort and cover every need. They are reinforced with large inflatable rear wheels, inflatable front wheels, folding or fixed frame, with brakes, adjustable backrest and seat, removable and adjustable footrests and push handles [39].

*Electric wheelchairs*

Electric wheelchairs are designed to be used by SCI patients who cannot move wheelchairs manually or who would have to waste too much energy doing so. This involves patients with very limited mobility of the upper extremities and especially in cases of quadriplegia and SCI above C7 level. It moves with two motors with battery lithium 12V, speed up to 10 km/hr and carrying capacity up to 100 kg [42-43].

The electric wheelchair has a high backrest, with specialized head or hand controls, with front wheels, with detachable legs, either with high support in the gastrocnemius area or with support at the height of the heel, with a seat and with cushions [43-44]. Electric wheelchairs allow tilt and recline maneuvers, redistributing loads away from coccyx and ischium, preventing ulcers [45]. However, using a motorized wheelchair has certain disadvantages, such as potential weight gain, increased rate of electrical failures and repairs, deconditioning and increased cost. Electric wheelchairs are also associated with decreased transportability and increased maintenance [6, 46-48].

*Lightweight wheelchair*

The standard lightweight wheelchairs are manufactured by most companies as a variant of the standard models. They are wheelchairs with a light frame and accessories that contributes to easy movement. They are wheeled with brakes, manufactured by light alloy frame (aluminum, titanium or magnesium) with adjustable center of gravity, angulated seat and backrest, removable 24-inch rear wheels and footrests, swinging detachable footrests and with high support in the gastrocnemius area. Its maximum weight is up to 12 kg without rear wheels, about the 2/3 of the standard model. Lightweight wheelchairs, generally preferred by patients with paraplegia, they may be easily placed in cars and contribute to increased mobility and freedom of movement, independence and enhanced socialization [49].

The sports wheelchair is a very lightweight wheelchair, with a weight less than 12.5 kg and is designed for intense use in sports activities with wheelchairs. Its frame is disassembled and stored in a special box [50]. Development of this lightweight, high-performance, sports chair has led to racing among wheelchair users and has made playing sports from wheelchairs practical and enjoyable. These wheelchairs have also been found useful in non-competitive recreation, such as camping and mountain climbing. Recently, ultralight wheelchairs have been manufactured by titanium and aluminum, improving the efficiency of propulsion [30, 44].

*Scooters*

They are designed for SCI patients with incomplete lesions who can walk, but also who have very good control of the body. They are dynamic, electric-powered systems, with four or three wheels, folding seat and they are driven by steering wheel. Their main feature

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is their rotating properties, facilitating entrance and exit of rooms [51].

*Standing power wheelchair*

The standing power wheelchair is an important aid that helps patients with incomplete SCI and inability to walk to stand in an upright position with the help of a controller by simply pressing a button without the need for adjustments or external assistance. These wheelchairs offer the user the ability to automatically–and safely–move from a sitting position into a standing one [52].

Bathroom - Toilet wheelchair

It facilitates SCI patients as it has a toilet bowl, soft seat, removable or folding legs, solid wheels, lifting and fixed arms, brakes on the rear wheels and in some cases a special waterproof lining suitable for bathing.

Sea wheelchairs

They are specially designed wheelchairs for easy rolling in the sand, waterproof and durable.

*Dangers from improper wheelchair designs*

The right wheelchair can help prevent injuries related to balance and instability. There are possible dangers from wheelchairs which are not properly fitted in SCI patients. The pelvis and spine can be misplaced in the wheelchair and at a later stage there is an increased chance of serious health problems (such as fatigue, pain, infections, tissue damage, respiratory problems and permanent injuries). Simple wheelchairs provide limited options and do not effectively serve everyone's personal needs. Heavy wheelchairs are not suitable for all body types. It may burden the SCI patient and keep him / her away from activities, locations and people. Proper position of the SCI patient in the wheelchair is important, so as not to create pressure ulcers and deformations, and the patient to gain maximum stability for independent activity [53].

## Conclusions

The choice of the proper wheelchair is of paramount importance in SCI patients, as the right type provides every possible facility in the daily life. The wheelchair should be designed in a way that it can be used easily and safely by SCI patients providing comfort, stability and ergonomics. The right type of wheelchair makes the SCI patient more independent, sometimes relieves him of the need to rely on other people and increases his engagement with activities.

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# Epidemiology and management of spinal cord injury in children and adolescents

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## ABSTRACT

Pediatric spinal cord injury (SCI) is a rare condition with significant long-term consequences affecting both children's and their caregivers' lives. Leading causes of pediatric SCI are motor vehicle accidents, falls and sport accidents. Patient assessment and management should be based in pediatric physiology and be adjusted to age. The maturity process brings up many unique challenges and complications such as scoliosis and hip dysplasia that have been reported to be common problems after sustaining a SCI in young age. Decreased mobility, autonomic dysreflexia, neurogenic bladder and neurogenic bowel have also all to be managed throughout the child's growing and maturity process. Rehabilitation and management of pediatric SCI patients aims in facilitating independence to meet peer lifestyle and successful transfer into adulthood. The present study is a literature review aiming to summarize the current knowledge on the rehabilitation and management of the secondary complications of pediatric onset SCI. A literature research was performed using the PubMed and Google Scholar online data bases and the following key words: "spinal cord injury," "pediatric", "children", "epidemiology", "management" and "rehabilitation". Following the PRISMA guidelines, 27 articles were finally included in this review. Caring for children or adolescents with SCI presents many unique secondary health complications and should be based on normal life milestones.

**KEYWORDS: spinal cord injury; pediatric; epidemiology; management**

## Introduction

Spinal cord injury (SCI) is damage to the spinal cord that leads to a medically complex condition with life-changing impact on the affected individuals. [1,2] As in SCI in adults, the degree of impaired mobility and secondary health complications in pediatric population SCI depends on the severity and the location of the injury in the spinal cord. However, children through all life stages until the completion of adolescence and the transition into adulthood have different, and sometimes unique, health complications from those occurring in adults. Age at injury, skeletal maturity and the ongoing dynamic developmental physiology throughout childhood and adolescence are factors to be considered in the rehabilitation approaches of SCI pediatric population. [1, 2, 3, 4] Life expectancy after SCI continuous to increase; however, patients that sustain SCI in an age younger than 16 years are

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noted to have reduced life expectancies compared to older ones. This fact is supposed to be the result of longer exposure to SCI complications and maximizes the need of long-term patient monitoring to prevent such complications. [1, 3]

Child's typical developmental motor milestones, communication and socialization skills are the main domains to consider adjusting the assessment and caring to patient's age. Depending on age at injury, certain skills may have never been achieved previously and they are taught for first time. Furthermore, undeveloped communication skills may present as barriers in the assessment and management of pediatric SCI patients and a more understandable language or the help of the caregivers may be required. [1] For example, assessment with the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) is recommended for children over 6 years old based on several large-scale pediatric psychometric studies. [4] Children younger than 6 years old are not able to fully understand the directions given for the sensory examination and distinguish between normal and reduced sensation. [3,5]

The present study is a literature review aiming to summarize the current knowledge on the rehabilitation and management of the secondary complications of pediatric onset SCI. Following the PRISMA guidelines, 27 articles were finally included in this review as it is seen in Table 1. [8] Starting from year 2010, a literature research was performed by using the PubMed and Google Scholar online data bases and the following key words: "spinal cord injury," "pediatric", "children", "epidemiology", "management" and "rehabilitation" with Boolean operators. Animal studies, case reports, case series involving less than 10 participants, and studies involving participants with congenital spinal injury (e.g. spina bifida) or cerebral palsy were also excluded. Original and review articles written in English concerning SCI in children and adolescents (less than 18 years) were reviewed for epidemiological data, rehabilitation and secondary complications. Studies in adults were included if they had separate reporting for participants less than 18 years old. Studies in adults with pediatric-onset SCI were also excluded.

## Discussion

*Epidemiology*

It is estimated that every year, around the world, between 250.000 and 500.000 people sustain a SCI. [6] It is most likely to occur in young individuals between the ages of 16 and 30 years (47% of all injuries) and the elderly (≥ 60 years old). Estimates reflect a consistent trend toward older age at time of injury. [6, 9] Children younger than 15 years old represent less than 10% of SCI cases. [3, 11] In more detail, incidence of pediatric SCI has been reported to be 5.27 per million per year between 1988 and 2014 in Spain (internal registry of the Spinal Cord Injury Unit) [12], 17.5 per million per year between 2007 and 2010 in the United States (Nationwide Emergency Department Sample) [9], and 5.99 per 100,000 per year between 1998 and 2008 in Taiwan (National Health Insurance Research Database) [13]. Studies with cut of age at 15 years old reported incidence ranging from 0 to 3.1 per million between 2000 and 2015 in Ireland (National Rehabilitation Hospital) [14] and 3.8 per million per year between 2000 and 2010 in Australia (Royal Children's Hospital). [15]

Pediatric patients are associated with higher risk of cervical SCI (approximately 80%) and SCI without radiological abnormality (SCIWORA) because of the underdeveloped anatomic characteristics of their spine. [3, 6, 16] The most common cause of pediatric SCI are motor vehicle accidents (MVA), while other common causes are falls and sports injuries. [9, 12, 13, 14, 15, 17, 18] Young children also sustain SCI through medical or surgical causes. [10,14] Sports accidents that result in SCI are more frequent in children older than 10 years old, with the higher rates being reported in the 10-13 years old age group. [17, 18] Other reported causes in adolescents include violence, firearm and self-inflicted injuries. [9, 15]

Males and females under 5 years of age seem to have the same risk sustaining SCI, while as the age at the time of injury increases males have a higher risk. [9, 10] This is probably due to males' increased risk behaviors especially during adolescence and young adulthood such as motorcycle riding, diving and involvement in violence/gunshots. [12, 13] The incidence of pediatric SCI has shown a downward trend in recent years. [9, 12, 14] This is probably related to road safety strategies

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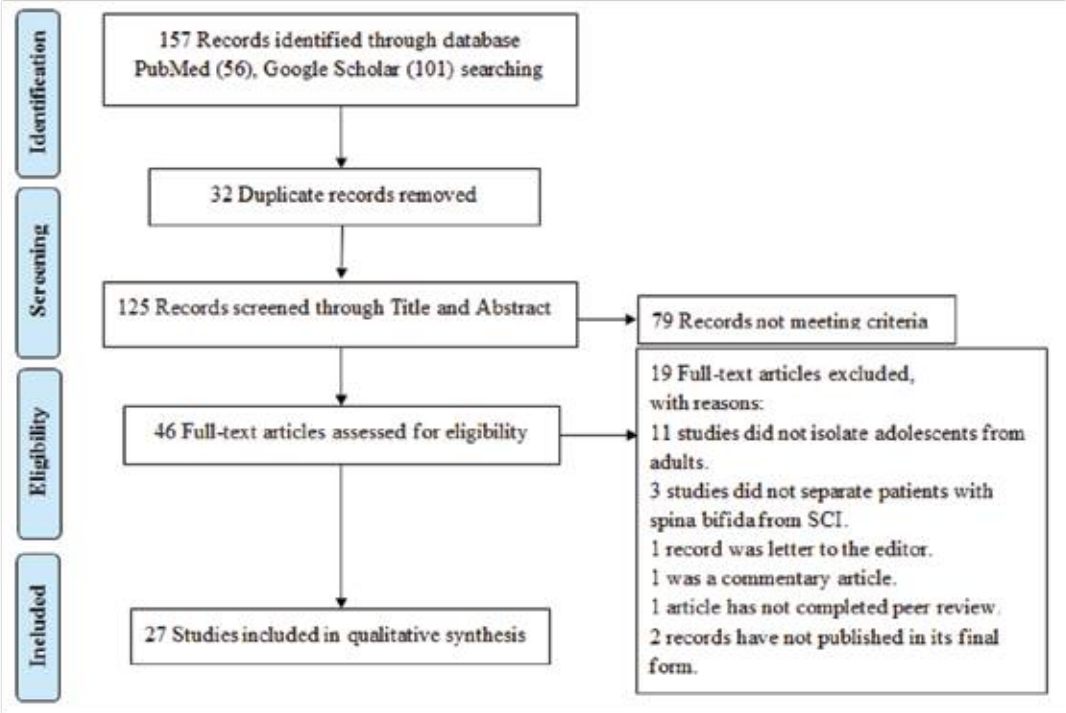


**Table 1**.Flow chart

having a positive impact in traffic incidents. [12, 14] Mortality rates are higher in children with SCI associated with cervical injury and MVA. [6, 9]

SCIWORA

Forces acting on the head and neck can result in great stretching of the spinal ligaments without resultant fracture but with injury to the spinal cord known as SCI without radiographic abnormalities (SCIWORA), which is more common in children under 8 years old. [3, 7] A multicenter retrospective study conducted in France between January 1988 and June 2017 included 37 patients (30 patients with SCIWORA, 2 patients with severe cranial trauma and 5 patients with obstetric trauma). Among SCIWORA patients, 50% of injuries were caused in MVA and 36.6% in sports accidents. Younger aged children sustained SCIWORA during MVA and children older than 7 years and adolescents during sport accidents. [16] Similarly, MVA and sports accidents were the main causes of injury among 297 SCIWORA patients included in the 2012 dataset of Healthcare Utilization Project KID (HCUP-KID). In more detail, it was reported that children with SCIWORA under the age of 3 years usually were involved in MVA (38%) and falls (23%), while the main cause for SCIWORA in adolescents were sports accidents (57%) and MVA (19%). In all age groups, cervical spine was the most common location of injury. Upper cervical spine injuries, located between C1 and C4, were most common in the youngest patients (aged 0-3 years) while SCIWORA in adolescents often occurred by injury in the lower cervical and thoracic spine. [19]

*Conservative and surgical treatment of pediatric SCI*

The majority of pediatric cases with SCI are managed conservatively and surgical intervention is chosen if needed depending on the type of spine trauma and the age of the children. [6, 11] There is low evidence for using instrumentation in pediatric SCI, but there is literature that supports their safe and effective use in pediatric spinal deformities. Based on that literature, surgical stabilization is suggested in unstable pediatric trauma to protect neural elements [11] Although there are pharmacological treatments for adults who

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sustained SCI, there is no evidence regarding the use of these treatments in children with SCI. [20, 21] However, studies investigating possible complications after high-dose steroid treatment in children with SCI reported no significantly high rates of complications. [20, 22]

*Neurological Recovery*

Neurological and functional outcomes after SCI in pediatric patients seem to be better when compared to the outcomes in adults. Although existing evidence is not significant enough to prove that, some studies reported good neurological recovery after SCI, with incomplete lesions having the best prognosis and complete lesions improving over time. [21] In a retrospective, multi-center case control study, each one of the 32 adolescents with SCI was matched to 2 adults according to neurological level of injury, initial AIS grade and total Spinal Cord Independence Measure (tSCIM). There were no statistical differences in respect to AIS conversion, but there were statistically significant higher final tSCIM scores in the adolescent group indicating higher functional improvement than adults. [2]

*Ambulation - Gait training*

In pediatric population with SCI mobility varies depending on age and impairment. The means used for mobility are evaluated and revised as needed during child's growth. The type of power or manual wheelchair needed depends on child's age, level of injury and functional status, environment, and child's and family's preferences. [24] Children about 1 year old should be encouraged to use a power or manual wheelchair to facilitate independence and limit the use of a stroller. Scooters are not considered an appropriate choice for most children and adolescents with SCI. [24] Among 131 children with SCI under 5 years of age using a wheelchair 98% were independent in propulsion, 3% exclusively used power wheelchairs, 85% exclusively used manual wheelchairs and 12% used both power and manual wheelchairs. Manual wheelchair use was initiated at a median age of 3 years and 5 months and power wheelchair use was initiated at a median age of 2 years and 11 months. [10]

Orthotics, assistive devices and locomotor training (LT) is an option for household and community ambulation. [24] In a recent study, the walking ability of 48 ambulant children with SCI was measured using the WISCI score (ability of a person to walk 10m after a SCI from the most to the least severe impairment). The authors reported that 60.41% of patients had WISCI score 20, which means that more than half of children aged between 2-18 years were walking with no help (device, brace, physical assistance), and 14.58% had WISCI score 12, which means that patients walked with two crutches and two ankle foot orthosis. [18]

Recovery of walking is dependent on the age at the time of injury, the level of injury, and the completeness of neurologic impairment. [23] Younger children have better prognosis for recovery. Indeed, children injured at the age of 5 years or younger are approximately seven times more likely to walk than older ones. [23] Individuals with incomplete lesions are more likely to recover ambulation compared to those with complete lesions. [23] Children with paraplegia are more likely to ambulate than those with tetraplegia. [23, 24]

Two recent systematic reviews reported improvement in ambulation when a variety of LT interventions were initiated in children during the chronic phase of their injury. [5, 23] Furthermore, after the LT there were positive results for gait speed, distance and participation. [5, 23] An additional benefit resulting from upright mobility and LT is the reduced risk of developing hip dysplasia or severe scoliotic curves. [10, 23] At present, there is neither official guideline for LT or knowledge of its long term effects in the pediatric population due to lack of evidence. [5] The progression of LT depends on the segmental control and the ability of the participant to independently maintain proper trunk, pelvis, and lower extremity postural alignment. [5] Factors like increased walking speed and distance, decreased BWS, decreased manual assistance and ambulation over ground promote a more functional gait pattern. [5, 24]

Functional electrical stimulation (FES) and neuromuscular electrical stimulation (NMES) are used to promote muscle activity in adults. [3, 24] Although there is not much evidence about the use of them in children, a randomized study including 30 children with SCI aged from 5 to 13 years old reported improved muscle volume after NMES, improved muscle

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volume and strength after FES cycling and no differences after passive cycling. [3]

*Scoliosis*

Children with SCI have high risk for developing scoliosis due to their on-going musculoskeletal growth. [3, 18, 21, 25, 26] Age at time of injury is the most important predictor for spinal curvature progression. [3, 25, 26] Patients who sustained a SCI before the adolescent growth spurt has take place have increased risk for developing scoliosis. [3, 11, 21] Indeed, children who sustained an injury under the age of 14 years are in great risk of developing scoliosis within 10 years past the injury. [25] The secondary complications of neuromuscular scoliosis often include pelvic obliquity, skin breakdown, pulmonary compromise, and functional decline. [26]

The management of trunk deformities is conventionally focused on progression prevention by bracing and realignment of the spine in the wheelchair, with close follow up at least until trunk growth plateaus. [11] Curves less than 40° have been shown to respond well to bracing [26]. Bracing in neuromuscular scoliosis with Cobb angles less than 20° delays surgical correction and in angles less than 10° may prevent scoliosis progression [3, 11]. However, thoracolumbar sacral orthosis (TLCO) treatment is reported to impair daily activities. [3, 11, 26] Tolerance in bracing is even more difficult in the presence of hyperhidrosis or in warm environments. [26]

Activating the trunk muscles and improving Segmental Assessment of Trunk Control (SATCo) scores reflective of greater trunk control may reduce the risk and incidence of scoliosis. The SATCo is a new reliable and validated pediatric measurement instrument used to assess and measure improvements in trunk control regardless of chronicity, severity and level of injury in children with SCI lacking independent sitting or impaired sitting control. [27]

Although there is very limited evidence concerning the results of surgical treatment of spinal deformity following SCI [11], children who sustain a SCI before the age of 12 years have a 3.7 times increased possibility to undergo spinal fusion. [3, 26] Surgical treatment of neuromuscular scoliosis is indicated only in patients older than 10 years and in cases where Cobb angle is greater than 40-45°, there is rapid progression of the curve, or functional problems exist [1, 3].

*Hip subluxation*

Hip subluxation and dislocation is the second most common orthopedic complication in children who sustain a SCI before the age of 10 years, affecting about 90% of these patients. [1] This complication may occur no matter if spasticity is present or not. [1] A recent review concluded that children under the age of 5 years with complete SCI and paraplegia have a significantly increased risk to develop hip subluxation. [10] Hip surveillance and orthopedic surgery are suggested. [1] Among 146 injured children less than 5 years old, 57% presented hip dysplasia and only 8% had surgery. [10] An abduction pillow or pommel can be useful to support hip abduction in supine and sitting position respectively. [24]

*Autonomic dysreflexia*

As seen in adults, pediatric patients with T6 or higher SCI are at risk of developing autonomic dysreflexia (AD). However, this life threatening complication is more difficult to be recognized in children due to their inability to express symptoms of AD. This is especially true in children younger than 5 years which rarely show any symptoms. [1] Measurement of blood pressure (BP) provides a reliable diagnosis of AD. A 15 mmHg increase of BP above baseline in children and a 15–20 mmHg increase of BP above base line in adolescents are considered to be signs of AD. [3] However, normal BP values vary with age, and are also related to body mass index (BMI) and type of SCI. Indeed, as the child grows BP increases and children with paraplegia and incomplete injury tend to have higher BP than non affected children. [3]

Removal of the inciting factor and monitoring of BP and heart rate is the initial management of AD. Bladder distention and fecal impaction are the main causes of AD. [1, 3] AD may also appear during surgical procedures. [3] Medications recommended for children are nitroglycerin and nifedipine and they are used when the systolic BP exceeds 120 mmHg in children younger than 5 years, 130 mmHg in children 6–12 years, and 140 mmHg in adolescents. [3]

*Urology*

Management of neurogenic bladder in pediatric SCI

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patients aims in preservation of renal function, prevention of life-threatening complications and promotion of continence which correlates with the child's self-esteem and participation. [1] A recent study, including 127 children under the age of 5 years who sustained a SCI and had no bladder control, reported that 82% of children were on an intermittent catheterization program and became independent at a median age of 8 years and 4 months. [10] Clean intermittent catheterization (CIC) is the appropriate management of neurogenic bladder in children over 3 years old. The goal of CIC is for children to obtain complete independence by the age of 5 to 7 years old, given there is adequate hand function. Children with inadequate hand function should gain independence in verbal direction of care. [1] Furthermore, children with poor hand function may benefit from a continent catheterizable urinary conduit, known as Mitrofanoff procedure. [1, 28] Urodynamic studies (UDS) in children with SCI may include uroflowmetry, electromyogram, and cystometry and should be performed for the first time after the spinal shock has passed (at least 3 months after the injury). Follow-up UDS is necessary as children with SCI will need long-term evaluation as they grow and bladder function may change over time. [28]

Normal urine output is age-dependent and should adjust according to the child's growth. [3, 28] Bladder capacity in children is calculated as follows: (age + 2) × 30 = Bladder Capacity (in milliliters/cubic centimeters). [28] Bladder capacity in children with SCI has been found to be less than expected. A normal adult-size bladder does not develop approximately until the age of 10. [3, 18] Inadequate bladder capacity may result in need for impractical frequency of catheterization or incontinence. [3] Management of incontinence with oral anticholinergic medications usually is effective [3]. Studies in small patient groups have reported that daily intravesical oxybutynin and onabotulinumtoxin A injections into the bladder detrusor increased bladder capacity, but there are no specific guidelines about the administration in children with SCI. [3, 28] Studies regarding long term effects from the injections showed improvement in capacity up to 10 months and less improvement over time. [28] When conservative management fails augmentation cystoplasty can be performed. [3, 28]

Urinary tract infections (UTI) are a common problem and may require treatment when there are symptoms such as fever, chills, AD, or exacerbation of spasticity. [28] Bacteriuria is present in 70–76% of children who use clean intermittent catheterization method to empty their bladder. [28] Prophylactic antibiotics for asymptomatic bacteriuria are not recommended. [28] UTIs increase the risk for urinary stones formation and may lead to pyelonephritis and sepsis. [28] In a recent cross-sectional retrospective study, including 76 pediatric patients with traumatic and non-traumatic SCI, it was reported that approximately 43% of patients suffered from Upper Urinary Tract (UUT) deterioration. Iatrogenic trauma to the spinal cord, presence of abnormal radiological lower urinary tract findings, absence of CIC and antimuscarinic drug treatment, maximum detrusor pressure (maxPdet) greater than 70 $cmH_2O$ during the storage phase and bladder volume ratio less than 0.7 constitute causes of UUT deterioration in children with SCI. [29]

*Neurogenic Bowel*

Neurogenic bowel dysfunction is common after SCI. The assessment for bowel dysfunction and neurogenic bowel management and rehabilitation in children with SCI are similar to those in adults. Neurogenic bowel might be the result of upper or lower motor neuron injury. [1, 3] Children aged from 2 to 4 years old are recommended for bowel programs. The bowel program is usually a tailored treatment plan that includes consideration of diet, physical activity level, oral or rectal medications and scheduling of bowel care. [1, 3]

In conclusion, study of the epidemiology and etiology of pediatric SCI may help in creating prevention strategies and education campaigns about safety of children and adolescents. Caring for children or adolescents with SCI presents many unique challenges such as the management of the secondary health complications. Furthermore, management of pediatric SCI should be based on normal life milestones, on changing objectives in each developmental stage, and on using appropriate strategies to facilitate adjustment and maximize independence across the spectrum of physical and emotional maturity levels.

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# The effects of Clinical Pilates exercises on patients with chronic low back pain: a systematic review

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## ABSTRACT

LBP can be characterized as a common disorder, with serious complications to a patient's life, as seen in clinical practice. The aim of the present study was to perform a systematic review of all the previous studies, in order to examine and clarify the impact of Clinical Pilates exercises on CLBP and to investigate any benefits of Pilates to CLBP patients. Eighteen randomized controlled trial articles were included. Each Pilates exercise regime was heterogenic, concerning its frequency and duration. Clinical heterogeneity was apparent in the RCT studies, a fact that was proven by the contrasting conditions, frequency, and duration of either the Pilates or the normal intervention. The study's outcomes indicate that Pilates as a therapeutic exercise method is exceeding typical intervention for pain relief up to an extent. Even though it was observed that Pilates-based regime combined with typical exercise regime can enhance pain relief process, it is should be noted that it is not the norm. Pilates exercise can be characterized as fairly more effective comparing typical physiotherapy treatment as far as disability reduction is concerned, and can provide equal advantages to minimal intervention.

**KEYWORDS: clinical Pilates, chronic low back pain, physiotherapy, systematic review.**

**Introduction:**

Low back pain (LBP) can be characterized as a common disorder, with serious complications to a patient's life, as seen in clinical practice [1] . The prevalence of LBP is at about 60% to 70% in developed countries · the prevalence of LBP in children and adolescents is lower than in adults, however the percentages are increasing rapidly [2,3]. In Europe, 30% of the adult working population, that is 44 million people, is suffering from LBP, whereas in Greece, 44% of the adult working population has manifested LBP related to working conditions [4].

LBP as a condition can be defined as either chronic or acute, concerning the duration of the syndrome. The European guidelines for physical therapy treatment suggested a further division of the LBP syndrome into three types: specific spinal pathology, nerve root pain/ radicular pain and the third type and most commonly manifested, chronic nonspecific LBP [5] . To be diagnosed with chronic LBP (CLBP), patients should report pain in the posterior lumbar region lasting for over 12 weeks or back pain existing for 7 to 12 weeks

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[6] . Nonspecific CLBP prevalence and high relapse ratios often generate disability and affect the patient's quality of life greatly [7,8].

Recently, patients suffering from CLBP have been exposed to Pilates exercise regime as a rehabilitation program (9), since Pilates is a mind-body intervention focusing on core stability and posture improvement and is widely used as an assistance in treatment of various diseases. Pilates as an exercise regime was developed in the early 20th century by Joseph Pilates. Joseph Pilates described his exercise routine as a controlled regime, emphasizing in the quality and precision of movements, resulting in improved strength and flexibility, and as a final step, improved overall health. However, there is only limited evidence in the literature supporting that the use of Pilates can decrease back pain and enhance the functionality of nonspecific CLBP patients [10,11]. Systematic reviews comparing Pilates exercises to placebo or habitual daily activities have revealed that Pilates exercises relieve pain but do not reduce disability [6,12], whereas other reviews have shown that Pilates cause no improvement to disability and/or pain [13] . However, there have been systematic reviews that proved the effectiveness of Pilates exercises in relieving pain and reducing disability, compared to placebo or habitual daily exercises [14].

Nevertheless, there have been several systematic reviews in which Pilates did not show significant improvement in comparison with other forms of exercise [13–15]. The evidence of the studies is not consistent, since in another review, it was found that Pilates actually reduced disability effectively in comparison with other types of exercise [12] . The result discrepancies of these studies may be caused by the selection size of the randomized controlled trial (RCT) articles, which were comprised by low-level evidence. Furthermore, it was concluded that in some systematic reviews, meta-analyses were performed, and results were misleading, in spite of the existing clinical heterogeneity [14]. To date, conclusions made from several studies concerning pain-relief and disability treatment effects for patients suffering from LBP with Pilates exercise regime and with other types of exercise showed considerable differences [16]. There is no extensive literature on the recommendations for Pilates exercises to patients with CLBP, including various Pilates exercise regime, for instance Pilates mat exercises or Pilates equipment exercises [17]. Consequently, the aim of the present study was to perform a systematic review of all the previous studies, in order to examine and clarify the impact of Clinical Pilates exercises on CLBP and ultimately, to investigate any benefits of Pilates to CLBP patients.

**Methods:**

The MEDLINE/ PubMed and Google Scholar data bases were used in search of related key words, for instance "Chronic Low Back Pain (CLBP)" and "Clinical Pilates". Various relating and appropriate for our research articles were found, after our search with the keywords. Our literature research completed in January 2022 and its main focus was on recent publications, concerning the impact of Clinical Pilates exercise regime on chronic low back pain.

A systematic literature review was conducted according to the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) database [18,19].

*Study inclusion criteria:*

In this review, we included only randomized controlled trials. Only double-blind studies examined in order to avoid any partial evaluations of the impact of treatment in the studies. The target population was male and female adults suffering from chronic low back pain. The articles should be written exclusively in English and the whole text should be accessible; also, we chose articles that were recently published and presented clinical results of the RCTs that were conducted.

*Study exclusion criteria:*

The excluded reviews were those failed in the above-mentioned criteria: they were not written in English, with no access to the whole review text, they did not perform a randomized controlled trial, the main topic was not chronic low back pain and they did not evaluate the impact of Clinical Pilates therapeutic exercise regime.

The full papers were read and any papers not meeting the inclusion/exclusion criteria were removed.

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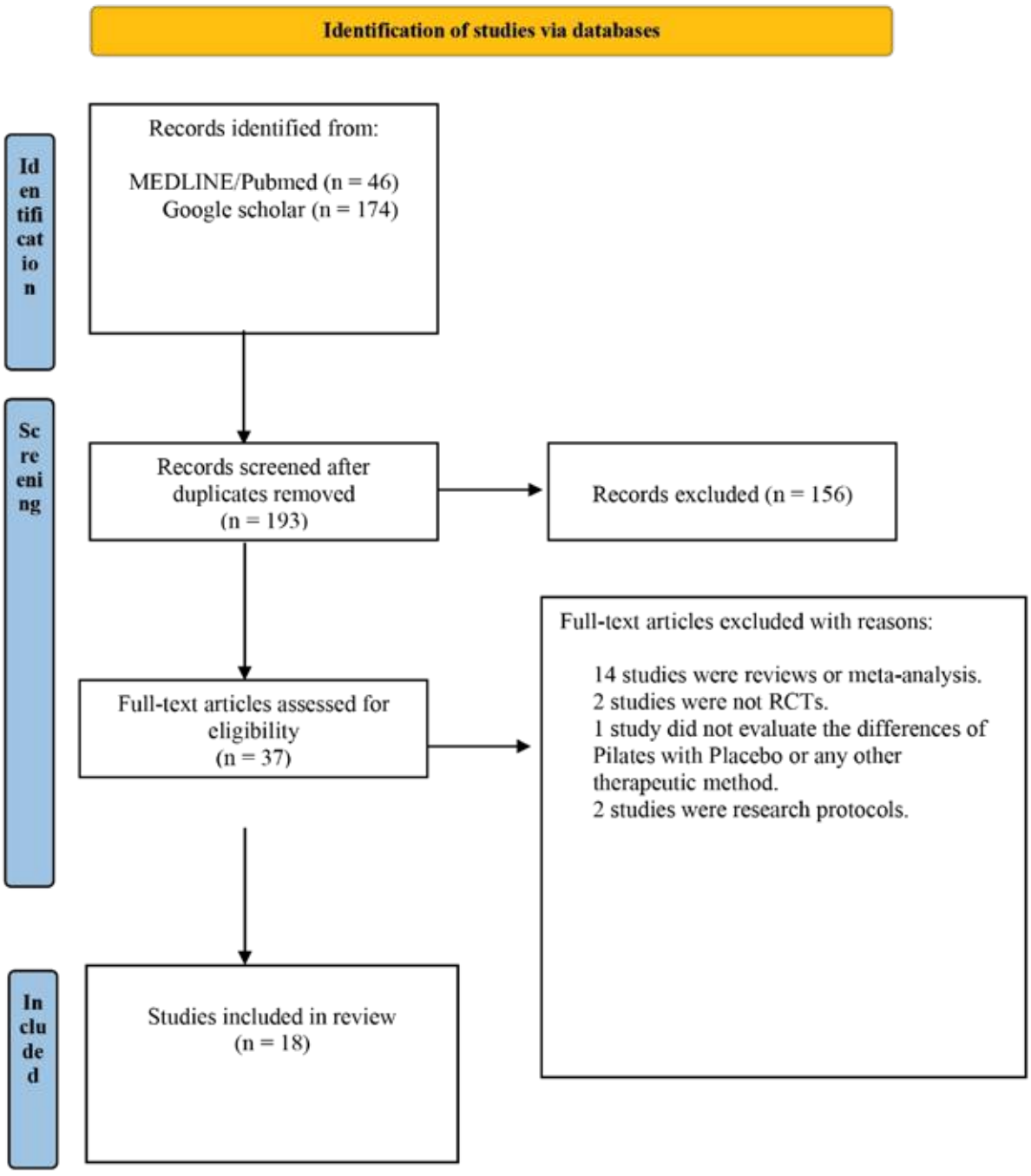
Figure 1 Flowchart




Data was extracted from the papers and entered into a table for later analysis.

**Results**

The initial electronic database search resulted in a total of 220 articles of these, 18 were considered for inclusion in this review (Figure 1).

The current study was consisted of 1249 subjects in total, with their age ranging from 18 to 65 years old. Each Pilates exercise regime was heterogenic, concerning its frequency (once to three times per week) and duration (thirty to sixty minutes). Clinical heterogene-

ity was apparent in the RCT studies, a fact that was proven by the contrasting conditions, frequency, and duration of either the Pilates or the normal intervention, which consisted of home exercise training, use of Pilates equipment, administration of nonsteroidal anti-inflammatory drugs, follow-up sessions and overall evaluation of the outcomes over certain periods of time (Table 1). Each session lasted for equal amount of time, mostly for sixty minutes, involving Pilates Mat exercises and Pilates Studio equipment exercises [20–24]. In their study, Rydeard et al. performed specific rehabilitation exercise programs, influenced by the original Pilates exercise regime [25]. Seven trials performed co-interventions, comprising physiotherapy treatment, analgesic intake and home exercise training as an experimental design [22,24–28]. In their study, Gladwell et al., performed Pilates exercise regime as an additional treatment to the drug treatment [28] .

All the above-mentioned studies and their subjects presented a considerable improvement concerning pain [20,21,23–34]. Da Luz et al, Marshall et al., Natour et al. and Rydeard et al. reported a significant improvement in patients' disability [21,25,27,34]. Four of the above-mentioned studies [22,35–37] reported no significant difference among Pilates and another intervention. The study by Mostagi et al. was conducted by typical physiotherapy exercises program, for instance stationary cycling, stretching exercises, spinal mobilization exercises and trunk muscle strengthening [36]. Wajswelner et al. conducted their study using a typical exercise regime including stationary cycling, leg stretching, upper body weightlifting, resistance band exercises, and an overall floor exercise regime [37]. The study conducted by Gagnon et al. performed mat exercise regimes for lumbar stabilization operated by a team of sport trainers, physiologists, and physical therapists [22] . The studies by Gagnon et al. and Wajswelner et al. reported considerable amelioration to both the Pilates and the intervention groups ($p=0.004$ and $p<0.01$ accordingly) in their final measures, implying that Pilates exercise regime can be effective, but not equally effective to a typical exercise program [22,37] . However, the study conducted by Mostagi et al. reported no considerable improvements in either groups at the end of the trial session, even though the general exercise group reported a slight clinical but not statistical amelioration [36].

**Discussion**

The aim of this study was to review high-quality RCT studies and present update evidence on the effects of Pilates on patients suffering from nonspecific CLBP. In two high-quality RCT articles comparing the effects of Pilates over various exercise regimes on patients suffering from CLBP, the Pilates exercise regime was included in a typical equipment training session. In their study, Wajswelner et al. concluded that a Pilates influenced training session, lasting for 12 to 14 hours, showed no statistical advantage over a typical therapeutic exercise for patients suffering from CLBP [37]. This conclusion was also proved by the study of Pereira et al, thus suggesting that Pilates exercise regime and lumbar stabilization exercises provide equal effects on patients' functional enhancement and pain relief [13]. Marshall et al. investigated a longer Pilates exercise session (up to 24 hours) and concluded to the fact that Pilates did show statistical advantage for functional enhancement and pain relief for patients suffering from CLBP compared to exercises with stationary cycling. Pilates-influenced exercise routine and typical therapeutic exercise routine showed related outcomes to the study by Wajswelner et al., possibly due to the fact that both regimes focused on trunk exercises, particularly in extension, rotation and flexion. Marshall et al. argued that both exercise groups, either Pilates-influenced exercise regime or stationary cycling regime had equal psychological effects on patients with CLBP, indicating that the psychological factor cannot be considered as a cause for statistical discrepancies on functional enhancement and pain relief [34].

The post-trial follow up periods of each study differed, likewise the results of the longer periods differed. Miyamoto et al. observed that any group discrepancies were not statistically significant after the period of time of six months, while in contrast, Wajswelner et al. observed that any amelioration in the final outcomes of the studies was still valid at 24 weeks [33,37].

Another considerable conclusion of this specific study was that any significant progress to a patient's

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TABLE 1.

**Description of included studies**

| Study | Year | Population | Intervention | Time period | Results |
|---|---|---|---|---|---|
| Bhadauria et al. (Comparative effectiveness of lumbar stabilization, dynamic strengthening, and Pilates on chronic low back pain: randomized clinical trial) | 2017 | 44 patients were assigned into three groups (n=12). Group A was about Lumbar stabilization, Group B about Dynamic strengthening and Group C did Pilates exercises. | All three groups performed different exercise regimes. Group A completed 16 lumbar stabilization exercises. Group B completed 14 exercises for core strengthening; Group C: focus on activating the powerhouse | 3 weeks | A reduction of pain, an improvement in the range of motion and core strength was shown in all three groups. In spite of that, lumbar stabilization was the most effective form of exercise for patients suffering from CLBP. |
| Borges et al. (Pilates exercises improve low back pain and quality of life in patients with HTLV-1 virus: A randomized crossover clinical trial) | 2014 | 22 patients were infected by HTLV-1. 11 patients was divided into group A (Pilates-control), treated with Pilates exercises. The second group, Control-Pilates group, consisted of the rest 11 patients. | Group A did Pilates exercises immediately, whereas the Control-Pilates group did not change their lifestyles for 15 weeks, up to the point when they started the Pilates program.<br><br>The groups exchanged their activities after 30 sessions. The Pilates exercise regime consisted of 60′ sessions, twice a week. It was taught by trained personnel. | 30 weeks | An important decline in pain intensity, together with an amelioration in almost of the domains of the SF-36 after treatment with Pilates exercises was documented. |
| Cruz-Diaz et al. Comparative effects of 12 weeks of equipment based and mat Pilates in patients with Chronic Low Back Pain on pain, function and transversus abdominis activation. A randomized controlled trial | 2017 | 98 patients Were divided in the Mat Pilates Group (n=34), Equipment-based Pilates Group (n=34) and control group (n=30) | The Pilates group exercised twice a week of approximately 50 min, together with physical therapy treatment sessions. The Control group did only physical therapy treatment sessions. | 12 weeks | The Pilates regime was proven effective in ameliorating pain, disability, core activation and kinesiophobia. The equipment-based Pilates exercises showed better and faster results, contrary to Pilates Mat exercises. |
| da Fonseca et al. (Laboratory Gait Analysis in Patients With Low Back Pain Before and After a Pilates Intervention) | 2009 | 17 patients (Low-Back Group) were divided into either the Pilates group (n=8) or a no-Pilates group (n=9). | The Pilates group did an exercise program with 15 sessions in total, 2 sessions per week for 1 hour and no-Pilates continue usual physical activity but no treatment apart from medications. | 7-8 weeks | The weight-acceptance rate and push-off rate were quite declined in the right lower limb for the low-back group rather than of the Pilates group. The Pilates group showed improvement after the intervention in the increased middle support force for the left lower limb at a faster walking pace. The low-back group did not show the same improvement. |

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| da Luz et al. Effectiveness of Mat Pilates or Equipment-Based Pilates Exercises in Patients With Chronic Nonspecific Low Back Pain: A Randomized Controlled Trial | 2014 | 86 patients with LBP were randomly assigned into two groups: a Pilates Mat group (n=43) and a Pilates equipment-based group (n=43). | The sessions lasted 1 hour and were administered twice a week Both groups completed their sessions twice a week for 1 hour. | 6 weeks | After a course of time of six months, an important difference in the disability and kinesiophobia of the patients allocated in the Pilates equipment-based group was noted (p<0,01). No other difference was noted in the findings. |
| Franco et al. (Is Interferential Current Before Pilates Exercises More Effective Than Placebo in Patients with Chronic Nonspecific Low Back Pain? A Randomized Controlled Trial) | 2017 | 148 patients with CLBP were randomly assigned into two groups: active IFC + Pilates and placebo IFC+ Pilates | Each group was treated for 30′ with active or placebo IFC for 2 weeks; afterwards, 40′ of Pilates exercise was added to their routine for 4 weeks. The treatment had a duration of 18 sessions | 6 weeks | As far as pain pressure, disability and pain threshold are concerned, no significant differences were observed in both groups. However, an important difference was observed between baseline and a 6-month-follow up in the analysis of the intragroup for all findings except pain pressure and pain threshold in the place IFC+ Pilates group. |
| Gagnon (Efficacy of Pilates Exercises as Therapeutic Intervention in Treating Patients with Low Back Pain) | 2005 | 12 patients who were introduced for physical therapy with LBP were randomly divided into two groups: the traditional lumbar stabilization exercise group (Group A) (n=6) and the Pilates exercise group (Group B) (n=6). | Group A completed traditional lumbar stabilization exercises for 30-45′, whereas group B completed a Pilates Mat regime for 30-45′. | The duration was 6.6 weeks for Group A and 7.3 for Group B. | The Pilates group showed improvement in measures of pain, function and core strengthening; equal measures showed the lumbar stabilization group. |
| Gladwell et al. (Does a Program of Pilates Improve Chronic Non-Specific Low Back Pain?) | 2006 | 49 patients suffering from CLBP were assigned in two groups, the Control group (n=24) or the Pilates group (n=25). | The Control group did not change their lifestyles or the pain relief routine. The Pilates group completed six one-hour sessions per week. | 6 weeks | The Pilates group showed an improvement in general health levels (p<0.05), sports functioning (p<0.05), proprioception (p<0.05), flexibility (p<0.05) and lower pain levels (p<0.05). The Control group did not show any improvement. |
| Marshall et al. (Pilates Exercise or Stationary Cycling for Chronic Nonspecific Low Back Pain: Does it Matter?) | 2013 | 64 patients suffering with LBP were randomly divided into two groups, the Pilates group or the Stationary Cycling group. | The Pilates group completed three supervised sessions for 50-60′ per week, whereas the Stationary Cycling group completed three supervised sessions for 50-60′. | 8 weeks | The Pilates group showed improvement in disability after 8 weeks (d=0.62, p=0.018). After training, pain was significantly lower in both groups (p=0.05), however, it was lower for the Pilates group (p=0.05). |

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| Miyamoto et al. (Different doses of Pilates-based exercise therapy for chronic low back pain: a randomised controlled trial with economic evaluation) | 2018 | 296 patients received advice about their condition and were randomly divided into four groups (n=74). The first group was the Booklet Group (BG), the Pilates Group 1, exercised one a week, (PG1), the Pilates Group 2, exercised twice a week, (PG2) and the Pilates Group 3, exercised three times a week, (PG3). | All patients exercised individually, with ground exercises, for one hour. PG1 patients completed six treatment sessions, once a week. PG2 patients completed 12 treatment sessions, twice a week and PG3 patients completed 18 treatment sessions, three times a week. | 6 weeks | All Pilates groups improved relating to pain, in contrast to the BG group. Among the Pilates groups, PG2 improved in a significant way concerning pain and disability, compared with PG1. |
| Miyamoto et al. (Efficacy of the Addition of Modified Pilates Exercises to a Minimal Intervention in Patients With Chronic Low Back Pain: A Randomized Controlled Trial) | 2013 | 86 patients suffering from non-specific CLBP received an educational booklet about low back pain and were randomly divided into two groups. The Pilates group (n=43) was assigned to complete 12 sessions over six weeks, the non Pilates group did not follow any exercise regime. | The Pilates group completed two Pilates Mat sessions for 60'every week. The No Pilates group received the educational booklet and physiotherapy advice twice per week. | 6 weeks | The Pilates group showed improvement in terms of pain, disability and general recovery, contrary to the No Pilates group. However, the improvement was only statistically important for a six-month period. |
| Mostagi et al. (Pilates versus general exercise effectiveness on pain and functionality in non-specific chronic low back pain subjects) | 2015 | 22 patients were divided into two groups. The Pilates group (n=11) and the General exercise group (n=11). | Both groups exercised twice a week, for 60', in a private session. | 8 weeks | Functionality was improved for the General exercise group during the study (p=0.02 at the end of the study and p=0.04 at the follow up). Also, flexibility was improved for the General exercise group at follow up (p=0.01). The Pilates group showed no significant improvement during the study. |

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| Natour et al. (Pilates improves pain, function and quality of life in patients with chronic low back pain: a randomized controlled trial) | 2015 | 60 patients suffering from non-specific CLBP were randomly divided into two groups. The Experimental group continued their medication treatment with NSAIDs and Pilates sessions. The Control group continued their medication treatment with NSAIDs, with no Pilates exercising. | Both groups completed Pilates sessions for 50′ twice per week. The patients were adviced to use 50mg of sodium diclofenac every 8 hours when needed. | 13 weeks | Pain was significantly improved for the Pilates group (p=0.001), functionality (p=0.001), vitality (p=0.029) and general quality of life (p=0.046). Also, the Pilates group took fewer medication than the Control group (p=0.010). |
| Quinn et al. (Do patients with chronic low back pain benefit from attending Pilates classes after completing conventional physiotherapy treatment?) | 2011 | 29 patients suffering with CLBP who had completed physiotherapy treatment sessions and had core instability and residual pain. The patients were divided into two groups, the Pilates group and No Pilates group. | The Pilates group completed supervised mat sessions for 60′ once a week and five home exercise sessions for 15′per week. The No Pilates group did not complete any exercise sessions or treatment. | 8 weeks | The Pilates group showed a statistical improvement in pain (p=0.047) compared to the No Pilates group. However, this improvement cannot be characterized as clinically significant. There was not an important difference in disability in both groups at follow up (p=0.301). Lumbopelvic control improvement was shown in the Pilates group. |
| Rajpal et al. (A Study on Efficacy of Pilates & Pilates & Mckenzie Exercises in Postural Low Back Pain- A Rehabilitative Protocol) | 2008 | 40 female patients with postural CLBP were divided into two groups; the Pilates group (n=17) and the McKenzie group (n=15). | The Pilates group completed daily home exercise regime (ten repetitions with 10′′ hold) for over four weeks. The McKenzie group completed daily postural correction exercise regime (fifteen-twenty repetitions, three times a day). | 4 weeks | No significant improvement was shown in both groups. The Pilates group did not show any important improvement during the 0-15 days period (0.805); however, during the 15-30 days period, the Pilates group improved (p=0.001). The McKenzie group showed no important improvement during the 0-15 days period (0.452); yet, during the 15-30 days period, the McKenzie group improved significantly (p=0.001). Therefore, both groups improved as a whole, but the Pilates group showed greater improvement than the McKenzie group. |

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| Rydeard et al. (Pilates-Based Therapeutic Exercise: Effect on Subjects With Nonspecific Chronic Low Back Pain and Functional Disability: A Randomized Controlled Trial) | 2006 | 39 physically active patients with CLBP were randomly divided into two groups. The Intervention group (n=21) completed Pilates sessions, while the Control group (n=18) received the traditional treatment, that is a consultation with healthcare specialists and doctors. | The Intervention group completed Pilates sessions for 60′ three times a week and home exercise regime for 15′, in total 13 hours of exercise. The Control group did not exercise. | 4 weeks | Functional disability (p=0.023) and average pain intensity (p=0.002) were lowered significantly in the Intervention group than in the Control group. The ameliorated disability levels in the Intervention group were sustained for up to 12 months, together with treatment intervention. |
| Wajswelner et al. (Clinical Pilates versus General Exercise for Chronic Low Back Pain: Randomized Trial) | 2012 | 87 patients with LBP suffering for over 3 months were divided into either the Pilates group (n=44) or the General exercise group (n=43). | The patients exercised at the clinic for 60′ twice a week for 6 weeks total, together with home exercise for 60′ once a week. The total exercise regime was 12-14 hours. | 6 weeks | From the 87 patients, the 96% completed the 6-week intervention and the 60% completed the 24-week follow up. There was no significant difference at six weeks, for both groups. Also, no significant difference was shown at the 12-week and 24-week follow ups. |
| Yang et al. (Pilates-based core exercise improves health-related quality of life in people living with chronic low back pain: A pilot study) | 2021 | 39 physically active patients suffering from non-specific CLBP were divided into two groups: the Control group (n=20) and the Experimental group (n=19). | The Control group completed Pilates sessions for 60′ twice a weak. The Control group was given advice and information regarding LBP, specifically about posture, stretching exercises and lifestyle adjustment. Also, they had access to medical consultations and traditional medical care, involving injections and physiotherapy treatment sessions, but no Pilates sessions. | 8 weeks | The Experimental group showed an improvement in the quality of life, relating to health, rather than the Control group. The trends regarding pain showed a preceding pain reduction for the Experimental group, lasting until the end of the study, over the Control group. |

condition with Pilates exercise compared to typical treatment and physical activity is not possible at 24 weeks. This finding was based on research evidence by one high quality RCT investigating the extending effect of Pilates exercise [23]. However, in the specific RCT, the participants ended their Pilates training regime at 6 weeks, thus it is unknown if an extended lasting effect may have been found if the groups concluded their regime for more than 6 weeks, as recommended [38].

The findings of systematic reviews are parallel to those of another review concluding that a statistically considerable decrease in pain was achieved by Pilates exercise regime compared to no Pilates exercise regime [15]. This specific review analyses that the improvement caused by Pilates can only be considered as short

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term but clinically substantial. As far as functional capability is concerned, the findings of the two reviews are in contrast with other systematic reviews, since these reviews showed a statistically considerable amelioration in functionality in the short term [12,13,15]. This discrepancy may be because meta-analyses of some reviews, together with variable grouping of comparing treatments, was not in the appropriate manner [38]. However, the measure range of functional recovery in RCTs in the current study is not statistically considerable [39,40].

It is worth mentioned that not all RCTs included in the current study are consisted to the effectiveness of Pilates exercise regime in comparison with typical treatment and exercise routine (24,28,30). The contrasting results may be clarified by the variable methodological quality of the RCTs of the study. Moreover, any contrasting result may occur on the grounds that the sample sizes were small or there were co-interventions within the RCTs. Four of the RCTs that did not present statistically considerable data were underpowered with small sample sizes, thus any treatment alterations may have not been as easily detectable [24,32,34].

Additionally, any alteration in the outcome of the RCTs may be attributed to the fact that the groups completed altered Pilates exercise regimes, for instance exercise sessions that happened more than once a week, often using specialized Pilates equipment, thus producing RCTs with statistically substantial results [16,25,26,29]. Therefore, it is advisable to perform equal Pilates exercise regimes of the RCTs that produced statistically considerable results as a way to maximize the treatment outcome.

Since the present data is limited, it is challenging to conclude on the short-term effectiveness of Pilates exercise on people suffering from CLBP comparing to other forms of exercise. This is based on the fact that statistically considerable advancements in pain and disability have been reported in one high quality RCT [34], not in other high quality RCTs [37. However, it is commonly believed among high quality RCTs that pain and functional ability in patients with CLBP will be improved with Pilates exercise or other types of exercise at 24 weeks [34,37].

Therefore, Pilates exercise is unclear whether it can provide higher advancements in pain and functional ability when compared to other forms of exercise, at best in a long-term period. The findings of this review are equal to those of past systematic reviews, since that advancements in pain and functional ability from Pilates exercise regime in contrast with other types of exercise have not been characterized as statistically critical [12,13,15]. However, in the current review, it is agreed that there could have been alterations in the short term.

There has been a statistically critical alteration in the outcome when Pilates exercise was contrasted with a definitely dissimilar exercise, that is cycling [34]. However, no discrepancy was observed when Pilates exercise was in contrast with lumbar stabilization exercises [22,35–37]. We propose that any future reviews should examine the relative effectiveness of Pilates exercise over other forms of exercise.

This review consisted of only high-quality RCTs and therefore, few articles comparing the effects of Pilates exercise and other types of exercise on patients with CLBP were included· likewise, few articles comparing the effectiveness of Pilates Mat exercise regime over Pilates equipment regime were included. Several limitations were noted throughout this review. The first limitation was that even though the selection criteria of this review were equivalent to several studies, the results might have a bias as a consequence of the discrepancies in the ability to participate in each original RCT. The second limitation involved the publication bias since we reviewed studies only with English keywords at two databases. Another limitation that was encountered was that since this review pinpointed on the effects of Pilates exercise on specific health conditions and health enhancement, further information about the quality and quantity of Pilates Mat exercise and Pilates Equipment exercises was not described.

## Conclusion

In the current study, we conducted a systematic review of clinical trials that used Pilates as a rehabilitation method for treatment of patients suffering from CLBP. The majority of these clinical trials concluded that Pilates can be an effective method towards achieving a reduction in pain and disability. The outcomes of the current study indicate that Pilates as a therapeutic exercise method is exceeding typical inter-

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vention for pain relief up to an extent. Even though it was observed that Pilates-based regime combined with typical exercise regime can enhance pain relief process, it is should be noted that it is not the norm. Pilates exercise can be characterized as fairly more effective comparing typical physiotherapy treatment as far as disability reduction is concerned, and can provide equal advantages to minimal intervention. The low methodological quality of the studies that were reviewed, as well as the diversity of the physiotherapy treatments demonstrated an estimate bias of the effectiveness towards disability and pain. Therefore, it is advisable to consider Pilates as a rehabilitation program for patients with CLBP, even though its ideal application is not clear at present. Any future studies investigating the topic of the therapeutic effect of Pilates should conduct placebo-controlled trials, with larger sample sizes, with intervention protocols capable of being comparable and make provisions for longer follow-up terms in order for any outcome to be considerable.

**Abbreviations**

LBP, low back pain; CLBP, chronic low back pain

*The authors declared no conflicts of interests.*

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# Adult Scoliosis: Therapeutic Approach and Spinal Pain Management

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## ABSTRACT

Advancing adult scoliosis may lead in deterioration of patients' overall health and progressive disability. It can be a quite complex disorder to manage; however, nowadays there are several conservative and surgical therapeutic approaches. The aim of this study was to review the current literature concerning the therapeutic management of patients with adult scoliosis and the management of spinal pain that the majority of these patients experience. The review of the current literature was carried out by using the online PubMed database and the following keywords: ("adult" [MeSH Terms] AND ("scoliosis" [MeSH Terms] AND ("pain" [MeSH Terms] AND ("conservative treatment" [MeSH Terms] AND ("spinal fusion" [MeSH Terms]. The primary search recovered 3.941 publications. In the initial screening of abstracts and titles, 3,902 articles were excluded because of either irrelevant titles or not matching content. From the remaining 39 studies, in which the full text was assessed, 12 were rejected due to particular reasons. Finally, 27 studies were included in this review. In conclusion, a variety of therapeutic approaches for adult scoliosis exist. The type of treatment depends on various factors and has to be personalized. The prevailing aspect is that patients with moderate scoliosis should seek conservative treatment first, as long as there isn't any serious deterioration in their symptoms and quality of life. Conservative management should be exhausted before any decision for surgery is taken.

**KEYWORDS: adult, scoliosis, pain, conservative treatment, spinal fusion**

## Introduction

Scoliosis is described as a three-dimensional malformation of the spine. The typical method to measure the deformation of the spinal curvatures is the Cobb technique. A Cobb angle of ≥10 degrees clearly marks the presence of scoliosis [1, 2, 3]. Scoliosis can be classified into structural and non-structural or functional. Structural scoliosis is by far the most common type of

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scoliosis and it is characterized by a stiff lateral curvature of the spine that includes a component of rotation as well. The spinal deformation is permanent unless treated. The most common types of structural scoliosis are neuromuscular, congenital, adolescent idiopathic and degenerative or "de novo". Non-structural is the type of scoliosis that involves a non-permanent lateral curvature of the spine without spinal rotation. Non-structural or functional scoliosis is caused mainly in response to an underlying painful condition as muscle spasms, osteoid osteoma of the spine or appendicitis in order for the patient to maintain an antalgic position. Another common cause of functional scoliosis is leg length discrepancy. If the patient bends forward or is lying down the curve is most likely to disappear. In addition, during a radiographic assessment the curve can be corrected with lateral bending to the opposite side. Treating the underlying cause corrects this type of scoliosis [4].

Adult scoliosis can stem from different causes and has two basic types: adolescent idiopathic scoliosis that keeps evolving during adulthood and degenerative or "de novo" scoliosis that affects adults without scoliosis history and often manifests after the fourth decade of life. The yearly increase of the scoliotic curve is 1.6 degrees for degenerative and 0.24 degrees for idiopathic scoliosis [11]. Degenerative scoliosis is a result of the degeneration of spinal components such as facet joints and discs that occurs with aging and usually affects the lumbar and thoracolumbar spine [4-7]. A sufficient number of studies mention the high incidence of scoliosis in the adult population. Indeed, in the elderly population from the age of 60 years and over the incidence may be as high as 68% [5, 7-13]. Neuromuscular scoliosis can be due to central or peripheral neurologic conditions that have an effect on the developing spinal column. It can also develop from conditions that affect muscle tissue like arthrogryposis, muscular dystrophy and Duchenne myopathy. All these conditions can lead to muscular imbalance and atrophy of the spinal muscles. Aging is a major cause of deterioration of this condition [14, 15].

There are several similar symptoms between the different types of adult scoliosis. The leading symptom is back pain that mainly derives from insufficiency and contractions of the spinal and postural muscles. In addition, back pain can derive from the lack of equilibrium in the frontal or sagittal plane and the subsequent degeneration of spinal components such as the articular facets and the intervertebral discs [1]. Another cause of back pain could be the lack of lumbar lordosis [3, 11]. Although it has been shown that pain is not directly related with the scoliotic curve's magnitude and location, lumbar and thoracolumbar curves have increased risk to cause pain [3]. Patients with degenerative scoliosis experience back pain in a percentage of 40-90% [11]. Often, the pain can be detected along the side of the convexity [16]. Back pain is associated with lumbar radiculopathy in 47-78% of cases [1, 7, 16]. In addition, patients with adult scoliosis after the 6$^{th}$ decade of their life may also develop symptoms of spinal stenosis and myelopathy [4].

Treatment of adult scoliosis includes conservative and surgical methods of management. Pain management and improvement of physical ability and quality of life is always an important goal for any type of treatment. However, surgical treatment has different indications from conservative treatment. Stopping further development of the spinal deformity and restoring or avoiding feature neurologic defects are the main indications for surgical treatment [1]. Traditionally, patients with curves ≥45-50$^{o}$ are in need of surgery, usually spinal fusion [2]. However, when there are no disabling symptoms the first choice is usually conservative treatment [5]. Conservative treatment typically consists of oral medications (non-steroidal anti-inflammatory drugs, opiates, amitriptyline, gabapentin, pregabalin), epidural injections, nerve blocks, physiotherapy, specific scoliosis and stabilization exercises and soft or rigid bracing [5, 6, 9, 17, 18, 19, 20].

The aim of this study was to review the current literature concerning the therapeutic management of patients with adult scoliosis and the management of spinal pain that the majority of these patients experience.

## Discussion

A review of the current literature was carried out by using the online PubMed database and the following keywords: ("adult" [MeSH Terms] AND ("scoliosis" [MeSH Terms] AND ("pain" [MeSH Terms] AND ("conservative treatment" [MeSH Terms] AND ("spinal fusion" [MeSH Terms]. Inclusion criteria to the re-

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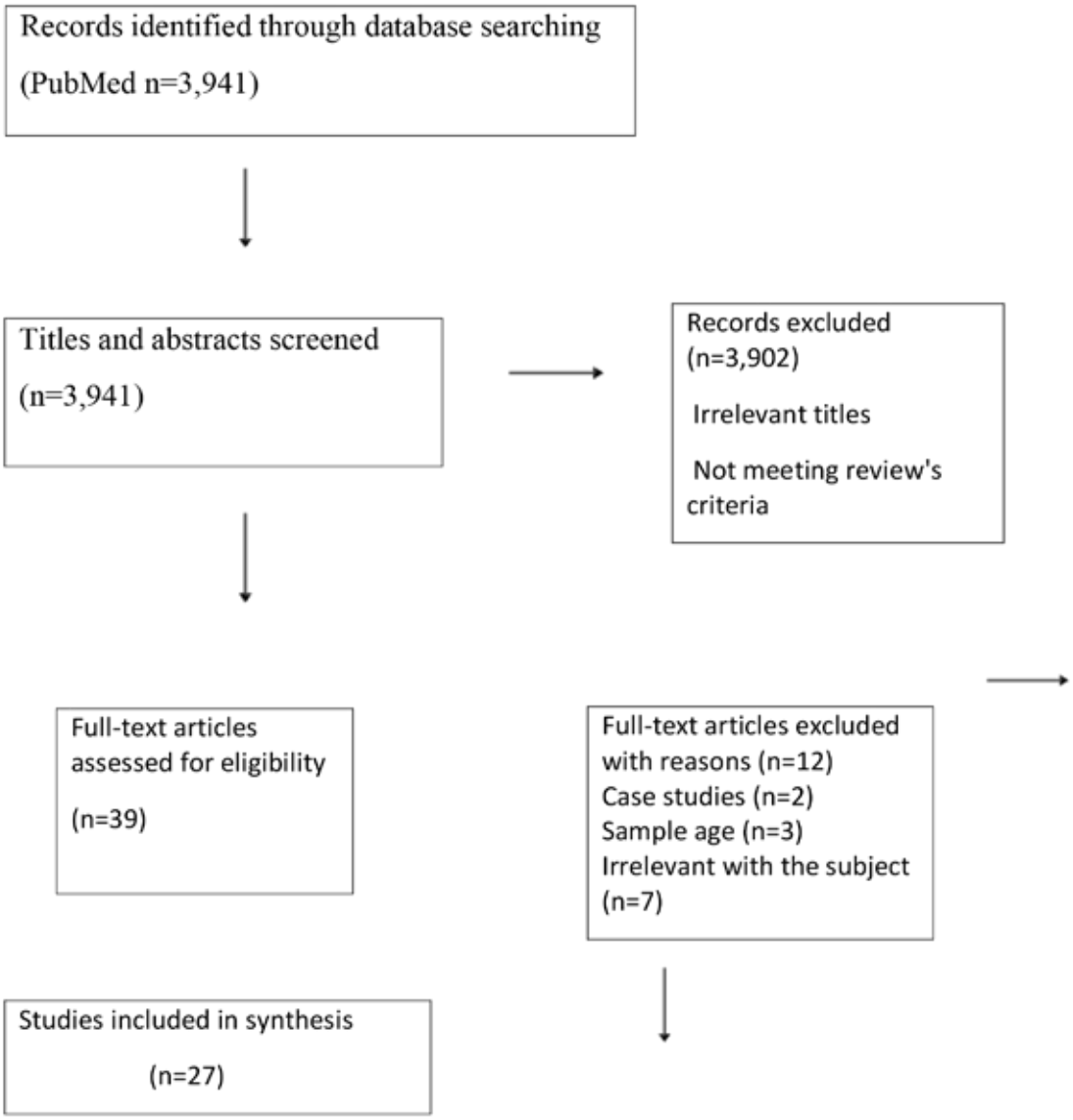


(Table 1. Flowchart)

view were: studies from 2010 and on, review articles, systematic reviews, randomized controlled trials, prospective and retroprospective studies, pilot and cohort studies related to the therapeutic approach of adult scoliosis and spinal pain management. Articles in other than English language were excluded. The primary search recovered 3,941 publications. In the initial screening of abstracts and titles, 3,902 articles were excluded because of irrelevant titles and not matching content. From the remaining 39 studies in which the full text was assessed, 12 were rejected due to particular reasons. Finally, 27 studies were included in this review (Table 1).

**Bracing**

Bracing is a treatment modality that seems to be used more and more as it is a non-invasive and inexpensive method to treat scoliosis. However, this conservative option is more popular and preferred in adolescence and childhood. Even though, in a recent study, adult

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patients suffering from idiopathic or degenerative lumbar scoliosis that were prescribed a custom-molded lumbar sacral orthosis (LSO) which had to be worn for at least 6 hours daily, showed a crucial deceleration of angular value ($p<0.0001$) [6]. In another study, adults with scoliosis suffering from chronic non-specific low back pain related to loss or reduction of lumbar lordosis seemed to benefit from lumbar bracing [3]. Furthermore, according to a recent review study, soft or rigid spinal bracing (with wearing prescription varying from 2 to 23 hours per day) used as monotherapy or in conjunction with physical therapy, led to moderate or significant pain relief as well as function improvement in patients with adult scoliosis. However, observations concerning the Cobb angle were various; curve magnitude improved moderately or significantly or progressed slower or not at all. Despite that fact, there were also cases that bracing didn't seem to affect the curve's progression [7]. In another recent study, peak scoliosis brace was found to be beneficial in reducing pain in adults with idiopathic scoliosis. After a four-week period of using the brace for 2-4 hours per day, 75% of patients noted some improvement regarding worst pain and leg pain and 65% noted improvement in chronic low back pain; however, the results were not statistically significant [13].

**Exercising**

Adults suffering from scoliosis with no critically important neurological symptoms or perdition of quality of life could manage their condition to a great degree by following an appropriate exercising program. However, there are certain limitations because exercising is recommended mainly in patients with adult idiopathic scoliosis (ADIS). On that note, several protocols of exercising have been studied such as asymmetric spinal stabilization exercises (ASSE), scoliosis specific exercises, SEAS (scientific exercise approach to scoliosis), Pilates method, Schroth technique as well as a multidisciplinary program that except of the physical training includes a psychological therapy. In a recent study, patients who followed a personalized program that depended on the curve's type and aimed in strengthening the muscles on the concaved zone of the scoliotic curve showed a significant improvement in Cobb angle mainly in prone position [17]. In another study, ADIS patients were assessed after a mean of two years of performing SEAS. The results showed a progress of scoliosis in less than 68% of the patients. In addition, there was an improvement in angular value ($p<0.05$) unrelated to the curvature's magnitude and location and unrelated to the age, gender and duration of treatment [18]. Furthermore, Schroth technique seems quite helpful when the curve's angle is 10-30$^{o}$ and the exercise protocol is performed for at least 6 months in a row [19]. Moreover, a rehabilitation program for ADIS patients consisting of specialized exercises and cognitive behavioral therapy (CBT) seemed to be superior from a general physiotherapy program [20]. In another recent study, ADIS patients that followed the same program for 20 weeks seemed to have a significant improvement in domains like pain, disability, kinesiophobia, catastrophizing and quality of life. However, regarding the clinical deformity, there was improvement but not clinically significant. The benefits of this approach were present for one year at the minimum [21]. Similar benefits have been reported in women with thoraco-lumbar scoliosis that followed a therapeutic intervention based on Pilates Method. In these women, scoliosis angular values decreased by 38%, stretchiness improved by 80% and pain was critically decreased by 60% [22].

**Operative approach**

Surgery is usually considered when all conservative measures have failed. When the patient is not satisfied with their current condition and their symptoms insist and cause deterioration of their quality of life, surgical options have to be discussed considering all the benefits, the disadvantages and the possible complications. The type of surgical technique used depends on patient's age and clinical condition and on surgeon's preference.

The main goals of surgical treatment are pain reduction and improvement of deformity principally on the sagittal plane. Spinal fusion, using pedicle screws with or without the use of cages and grafts, through a posterior or/and an anterior approach is the most commonly used surgical technique. Surgical treatment appears to have better results than conservative treatment. According to a recent study including 49 patients operated for degenerative scoliosis, on the eight years fol-

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low up 23% of patients had excellent results, 29% had good, 34% had good enough and 14% had inadequate results. In addition, pain was improved in the visual analog scale (VAS) from 7 to 2 and Cobb angle was improved approximately by 12º [1]. Similar results have been reported in another study including patients over 75 years old who underwent spinal reconstructive surgery. On the two years follow up, all patients had a significant improvement in radiographic evaluation and in Health-related quality of life (HRQOL), as well as in pain and disability. In contrast, conservatively treated patients did not show any improvement ($p>0.05$) [12]. Moreover, in another recent study, patients with symptomatic lumbar scoliosis who underwent spinal fusion, had better results than patients who followed a conservative protocol with physical therapy, facet injections, oral administration of different medications (non-steroidal anti-inflammatory drugs, opioids, gabapentin) and nerve root injections for back and leg pain management. At the two years follow up, Oswestry Disability Index (ODI) and Scoliosis Research Society-22 Score (SRS-22) were more improved ($p<0.001$) in the operative group [23]. Even though patients that chose to proceed with surgery were in worse clinical condition than those who preferred the conservative approach, at the two years follow up they showed a significant improvement in domains like pain, disability and quality of life [24, 25].

**Pharmacological Approach**

Adults with scoliosis often suffer from persistent back or leg pain that can lead to disability. Constant pain is usually managed with a combination of oral medications as non-steroidal anti- inflammatory drugs, antidepressants and opiates administered for only a short period of time [26]. Indeed, narcotic analgesics, muscle relaxants and tricyclic antidepressants can be useful in pain management, especially of night pain. Gabapentin seems to be beneficial in managing neurogenic pain and it seems to be well tolerated by elderly population [27]. However, all these drugs come along with side effects such as gastrointestinal dysfunction and acid-peptic disease and must be used with caution. Moreover, focused epidural, facet injections or nerve root blocks can be used both for diagnostic and pain-relieving reasons because they can help patients localize the source of their pain [5, 9].

In conclusion, a variety of therapeutic approaches for adult scoliosis exist. The type of treatment depends on various factors and has to be patient specific. The prevailing aspect is that patients with moderate scoliosis should seek conservative treatment first, as long as there isn't any serious deterioration in their symptoms or quality of life. Conservative management should be exhausted before any decision for surgery is taken. The surgeon has to assess the benefits and risks of such decision taking into consideration patient's best interests.

***Conflict of interest***

*The authors declare no conflict of interest.*

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