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1. Scope

"Acta Orthopaedica Et Traumatologica" is the official journal of the Hellenic Association of Orthopaedic Surgery and Traumatology, first published in 1948. This revived edition of Acta Orthopaedica Et Traumatologica, published in English, aspires to promote scientific knowledge in Orthopaedics and Traumatology worldwide. It is a peer-reviewed Journal, aiming at raising the profile of current evidence-based Orthopaedic practice and at improving the scientific multidisciplinary dialogue. Acta Orthopaedic Et Traumatologica Hellenica presents clinically pertinent, original research and timely review articles. It is open to International authors and readers and offers a compact forum of communication to Orthopaedic Surgeons and related science specialists.

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

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

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Reference examples:

■ Journal article:

Trianafyllopoulos IK, Lampropoulou-Adamidou K, Schizas NP, et al. Surgical treatment of acute type V acromioclavicular joint dislocations in professional athletes: An anatomic ligament reconstruction with synthetic implant augmentation. *J Shoulder Elbow Surg* 2017; doi: 10.1016/j.jse.2017.05.032 Epub 2017 Jul 21.

or

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

■ Book chapters:

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

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LETTER FROM THE GUEST EDITOR

Dear Colleagues,

Spine problems have always been the focus of medical interest at any time, over time. Both, the investigation and the treatment of the complex diseases of the Spine were evolving at the same time with the general course of medical science and the technological development.

Looking back to ancient times we are surprised to find that, the study and the treatment of Spinal Diseases was of great concern to mankind, principle originated by the ancient Egyptians. The disease that particularly concerned them was tuberculosis which, among other problems, caused the destruction of the vertebrae. Consequence of this condition was the kyphoid deformity and often paralysis which resulted from the pressure exerted on the spinal cord.

Hippocrates of Kos, the father of Medicine, made the greatest contribution and sought to give a rational scientific interpretation of the existence of Spinal diseases and the therapeutic methods to be followed, thus removing any theocratic and metaphysical intervention,

In Greece, the first "Scoliosis and Spine Unit" was established in 1976 at the KAT Hospital under Dr.P.Smyrnis direction. Later,on 2006, HAOST aware of this special chapter of Orthopaedics, established an autonomous "Section of Spinal Diseases" which annually holds a Conference called "Annual Spine Conference N.Giannestras-P.Smyrnis" honoring with this title the pioneers surgeons who envisioned it and established the modern study and treatment of Spine Diseases. Since then, HAOST hosts in its Annual Conference also the Conference "N.Giannestras-P.Smyrnis"

A further development of HAOST Department, was the collaboration with the Greek Neurosurgery Society in order to create the "Greek Spine Society", which held its first Panhellenic Conference in 2007, incorporating in the annual Conference also the Conference of "N.Giannestras-P.Smyrnis".

Professor Nicos Papaioannou, distinguished friend and collaborator, former President of the "Greek College of Orthopaedic Surgeons" and current Chairman of the Editorial Board for the official magazine ACTA ORTHOPAEDICA ET TRAUMATOLOGICA HELLENICA, highly honored me by entrusting for the organization of publishing the first issue of the magazine for the 2021, exclusively dedicated to Diseases of the Spine.

Having in mind that the colleagues who express special interest in the subject of the Spine are excellent with a rich literary work as well as many Greek and international presences and distinctions, I tried to select the Authors combining the subject with geographical origin.

Most of the publications are reviews, which show that the authors want to present the current views on certain topics.

It is perfectly understandable that it is impossible to cover a varied subject like that of the Spine in a few pages, about 50-60 available for medical announcements. But even if that happens, this issue sends a strong message in the international community that the "Backbone Case" is in our country contemporary, absolutely substantiated and equal with the international scientific standards.

I hope that there will be in the future an opportunity for an upcoming issue to be dedicated to the Spine, so that other colleagues can have the possibility to participate.

Pr. George Sapkas, MD , PhD
Emeritus Professor of Orthopaedics

HISTORICAL ARTICLE VOLUME 72 | ISSUE 1 | JANUARY - MARCH 2021

History of scoliosis surgery in Greece

Constantinos Z. Zachariou

Former Director of Scoliosis and Spine Department of KAT Hospital, Kifissia-Athens, GREECE

ABSTRACT

This is a review of scoliosis surgery in Greece and its great development after 1975, which is linked with the establishment of Scoliosis and Spine Unit at KAT Hospital since 1975.
We focus particularly on the transpedicular screw that revolutionized surgery for scoliosis and the spine in general.
Spine surgery appears at the beginning of the 19th century with a simple access to the spine, without instrumentation, and mostly to treat conditions such as tuberculosis large-scale deformities and poliomyelitis only by debridement and graft-based spinal fusion.
The first scoliosis operation using metal devices was published in 1945 in the US by Paul Harrington, while the revolution of materials was made by the French Cotrel and Dubousset (1982) with the design of CD instrumentation, initially with hooks and later included the transpedicular screw (1986), which was originally used by the French Roy Camille and then by Magerl and Dick.
At the same time as the surgery the Greek orthopaedic since 1975 made so much progress that it does not fall short of foreign colleagues in technological equipment or in training and experience, shortly afterwards followed by neurosurgeons.
The trigger in surgery was given the working-shops lessons during the scoliosis symposiums on cadaver preparations where almost all the pioneers of the time taught.

KEY WORDS: history; scoliosis; surgery

Abstract

This review contains data and information from the records of the Scoliosis and Spine Unit and the later Department of Scoliosis and Spine of the KAT Hospital, as well as from the personal archive of Dr. C. Zachariou kept together with other files. Literature of the time was used as well as more recent one, from Greece and foreign.

The principal aims of Scoliosis symposia over time have been: Raising awareness and training of Orthopaedic surgeons in the issue of scoliosis, investigating and identifying as many children with scoliosis in Greece as possible, connecting Greek Orthopaedic surgeons with important personalities in orthopedics of the time to raise awareness for scoliosis and spine surgical procedures.

In Greece, the team in KAT first used fusion instrumentation for Scoliosis and spine surgeries. In this Unit, braces were designed (LCP, DDB, DTB, DLB, DKB) for conservative treatment of scoliosis/kyphosis and it was there that the idea for designing and constructing polyaxial hook, special for scoliosis. [1] [2]

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General Surgeons, Scoliosis and Spine

Orthopaedics up to the first twenty years of the 20th century had been practiced by general surgeons. In 1925, the Chair of Orthopaedics was established at the University of Athens, with first professor being Ioannis Chrysospathis (1873-1938) without however formal recognition of the specialty which took place in 1947 thereby separating it completely from general surgery. Athanasios Kontargyris was Professor (1892-1954). In the same year 1947, the Hellenic Society for Orthopaedic Surgery and Traumatology was founded (HAOST).

In 1983, inspired and pioneer by Apostolos Kavvadias, the College of Greek Orthopaedic Surgeons was founded, which undertook continuous training in Orthopaedics. [5][6][24]

Scoliosis surgery begins in 1911 when Hibbs in the U.S. began long vertebral fusion without materials with not good results due to failure to correct, prolonged recovery time, high rates of pseudarthrosis, and infections. [3][9][11][12]

Instrumented Scoliosis Surgery

Half a century after Hibbs, towards the end of the 50s, Paul Harrington assisted by and working together with John Moe, implemented initially the distraction and later the compression rod, with hooks for scoliosis induced by poliomyelitis and tuberculosis and then by idiopathic scoliosis, with better results that however did not resolve big issues such as pseudarthrosis, flat back, frequent fracture of devices, and dislodged of hooks. For this last point John Moe designed the lower part of the rod in such was as to end in a square shape to avoid turning of the rod that led to unhooking. [3] [5][6][9][15][11][20] [25][29][36]

The need for new treatment methods, for neglected cases after Harrington, prompted several researchers to design new devices and methods to treat scoliosis. For instance, Eduardo Luque with the type L angled rod at one end, and then John Dove with the Hartshill rectangle and then D.S Drummond with interspinous wires**.** These last three methods used wire to support the rods [6][8][9][26][27][29][36]

At the end of the 1970s and the beginning of the 1980s, the French Yves Cotrel and Jean Dubousset revolutionized scoliosis surgery with two rods and hooks, that with appropriate manipulations achieved 3D correction. Also, the two Frenchmen defined the concept of strategic vertebrae which until this day is the basis for preoperative and intraoperative planning of scoliosis surgery. [11][14][15][16][17][25]

The CD system soon incorporated transpedicular screws (1986), which were the essential multi-tasking tool for the 3D segmental correction with ''derotation maneuvers'' whereby the pre-angled rod in scoliosis, rotated to a kyphosis position. [17][18][19][38]

Transpedicular screws

The Frenchman Roy Camille at the beginning of 1970 used transpedicular screws for his own plates. In 1977, F. Magerl used transpedicular screws for external fixation, while Walder Dick in 1984 for internal fixation using Schantz screws paving the way for transpedicular devices that until now dominate and offer support for all three vertebral columns.

In the US, in 1982 Arthur Steffee designed his own symmetrical plate with transpedicular screws.

[4][9][11][12][30][33][34] [40]

In the 1990s, almost all companies adjusted their production to include the transpedicular screw, which succeeded strong fixation and fusion of all three columns. At the same time, other screws appeared: fixed, multiaxial, cannulated, fenestrated, etc. Transpedicular screws were combined with plates or rods or artificial connectors (ligament) or buckles. [29][39][38][40]

Systems of anterior correction of scoliosis: after the non-instrumented Dwyer procedure emerged (1988) the Kostuik- Harington system mostly for kyphosis and fractures, then Zielke for scoliosis with a derotation mechanism. [9][12][13]

The study of material biomechanics developed rapidly with multiple research papers (H.F. Farfan 1978, White and Panjabi 1988) providing solutions and suggestions for the proper application of new methods of spine surgery and as regards the difficult part of application on scoliosis. [11]12] [41]

The use of intervertebral protheses later with the study of spine biomechanics provided greater stability in the systems used.

Initially the Swiss USS (Universal Spine System), the

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Figure 1

Figure 2

French CD- Somafor-Danek (Medtronic), Moss- Miami, Texas Scottish Rite Hospital etc. started manufacturing transpedicular screws and as time went by the number of companies supplying transpedicular devices increased which are currently estimated at one thousand, worldwide. [14][17][18][25]

In the early 1990s (and previous efforts) the Interoperative Neurophysiological Monitoring (INDP) was developed which helped a lot to reduce neurological small and large complications. For twenty years (1970-1990) the "Stagnara wake-up test" was the only way to intraoperatively monitor the neurological complications of scoliosis procedures. [4][9][21][25]

At this point I must mention Dr Konstantinos Papadopoulos, pioneer in Greece, member of the European Neurological Society, the International Society of intraoperative Neurophysiology (ISIN) and elected member of the Educational Committee of ISIN. [1][2]

Navigation Systems: Although it has more than twenty years that was used there are still doubts about its generalization. Today there are several types and already, we are in the third generation with 3D technology. We do not ignore the fact that this method has several skeptics due to prolonged surgery time, limited scope especially for scoliosis, kyphosis, or kyphoscoliosis and for an increased rate of radiation for the patients, doctors and for the staff of the surgery room. Recently, increased rates of neurological complications have been reported in the literature perhaps by the widespread of the method. .[9][11][12] [42] [43] [48][44]]

Pioneers

The international literature of the time is full of articles on scoliosis and spine surgery. Among the leading pioneers of instrumented surgery for the spine and scoliosis, we can mention from France: R. Camille, then Y. Cotrel and J. Dubousset, Daniel Chopin, C. Mazel, P. Stagnara (wake up test), in Switzerland: Fr. Magerl, W. Dick, E. Morscher, in the US: the great J.H. Moe, R. Winter, A.D. Steffee, and many others such as J.E. Lonstein, K.D. Leatherman, D.S. Bradford, H. Farfan (biomechanics studies) W. Fielding, E. Simmons, J. Kostuik, R.W Gains, M. Zindrick, A. Vaccaro, L.G. Lenke, in Canada: Max Abie, J.P. Kostuik, In S. Africa: G.F. Dommisse (research on Adamkiewicz arteries of spinal cord), Koos Louw, in Italy: A. Ponte (spinal osteotomies), St. Boriani, in Germany: C. Zilke (anterior procedure), J. Harms, in Sweden:, A. Nachemson, C. Olerud, in Britain:, despite the fact that there were no pioneers in this field many engaged in scoliosis and spine surgery, such as R. Owen, Mc Master, M. Edgar, R. Dickson, J.K Webb (its great contribution to the studies of materials of A.O.) an exception was M.A. Mehta with the experimental work that gave us the prognosis of infantile scoliosis based on the rib-vertebra angle. [1][2] (Figures 1 and 2).

The Greek Actuality/Reality

ALL pioneers and researchers, from almost around the world, who have been mentioned above, ALL those people, were our first teachers in theory and practice.

ALL played an active role, some many times, in the Scoliosis and Spine Symposia, not just as speakers but mainly as trainers. [1][2]

What is the situation in Greece during this period of development and revolutionizing management of scoliosis and spinal surgery in the world? How did we learn scoliosis?

We found our teachers and instructors. We took

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Figure 3

advantage of our guests as much as possible both in our country and in their own hospitals in their country where we went. [1][2][5][6][7] (Figure 3).

Greece: Symposia and First Scoliosis operations in Greece

In 1975 Panagiotis Smyrnis was appointed as director of the 5th Orthopaedics clinic of KAT. Georgios Chartofylakidis was Professor of Orthopaedics at the University of Athens. At that time, in Greece orthopaedic surgeons operated without instrumentation on disc herniated discs, they performed laminectomies (only the spinous process or part of the lamina, not wide procedures) for decompression or also inflammation mainly tuberculosis.

Panagiotis Smyrnis intense interest in the news coming from America, P. Smyrnis's friendship with Professor G. Hartofylakides and Nikos Giannestras (1908-1978) who was an orthopaedic in America, Cincinnati-Ohio and was involved in diseases and foot surgery, and later scoliosis attracted interest in school screening. In 1973 they start at the PIKPA Hospital of Penteli a gathering of a few doctors (5-6) who discussed about scoliosis. Speakers were N. Giannestras and Professor K. McElroy (Columbia NY).

In the following year, 1974, the same gathering took place on the same topic, but added the first scoliosis operation using distraction instrumentation (Harrington), which was brought by N. Giannestras from the States. Speakers: N. Giannestras, Professor R. Roaf (Liverpool) and the Frenchman Ives Cotrel (marking the start of the friendship between P. Smyrnis and Cotrel). This gathering was later counted as the 1st Scoliosis Symposium, which would be repeated every year until this day, when we have reached the ''44th Symposium N. Giannestras- P. Smyrnis''.

In the following year 1975, Harrington tools and materials arrived in Greece, which was donated to the emerging Scoliosis & Spine Unit of the KAT Hospital, the American-Hellenic union of the US of course via N. Giannestras. In this 2nd symposium two scoliosis operations were performed, and the first school screening took place in Athens which was later published. (Figure 4)

Next step, in 1976, was to establish the "Scoliosis and Spine Unit" within the E' Orthopaedic Clinic of the KAT Hospital, where P. Smyrnis was director. The effort was not easy, as the reaction of the other Directors of KAT Hospital were excessive and aggressive. However, Professor G. Hartofylakides whose prestige

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Figure 4

and influence, after embracing Smyrnis's views on the immediate need for Greece to move forward on the issue of scoliosis and spinal surgery, took down any objections and arguments of the other Directors of the KAT.

In the 1978 Symposium, a Great absentee was Nikolaos Giannestras. He died a short while beforehand, leaving a large legacy, the continuation of the Symposia and the education of Greek orthopaedic surgeons. [1][2][7]

School Screening in the province

In parallel with the symposia, a great responsibility and obligation was shared by all members of the Smyrnis team (Antoniou, Valavanis, Zachariou, Alexopoulos, Kollitsidas, Tsafantakis, Siderakis, Voutsinas, Alexopoulos, etc.) to prepare and organize screenings in Athens and mainly in province areas to examine school populations for deformities and other conditions, starting with the island of Evia, where the entire school population was examined, totaling 11,000 students (1976). In this excursion was initially supported by the Athens University team at KAT (Soukakos, Sapkas, Daoutis). In total in Greece around 600,000 children were examined. [1][2] (Figure 5).

Research to discover deformities in school had taken place in Greece, but only the KAT Unit and the University in Ioannina much later (after 1980) led by Professor Panagiotis Soukakos had the knowledge and experience to deal with them.

Professor Panagiotis Soukakos returning from the States to the University Orthopaedic clinic in Athens (1975), professor G. Chartofylakidis founds in the clinic a spine department and appoints P. Soukakos as its head. P. Soukakos worked together with G. Sapkas, D. Kores, and others.

The annual Scoliosis symposia ''N. Giannestras, P. Smyrnis'' were organised every year with an ever-increasing interest by orthopaedic surgeons, seeing in the lecture theatre mature and experienced orthopaedics that started showing an interest on scoliosis and the spine.

I can remember K. Giotis, N. Triantafyllou, G. Nikolakakos, E. Fragαkis, Ap. Kavvadias, V. Petropoulos, D. Dimitriades, Kampouroglou, E. Dretakis, K. Kamperoglou, Artzimanoglou (not frequently), I. Demetriou, I. Karadimas, N. Antoniou, S. Theodorou and many others. (Figures 6, 7).

Doctors' interest on the Symposium was great that it could no longer be accommodated in the KAT Hospital amphitheatre and we were constantly looking for larger spaces. The highlight series was the 14th, 15^{th,} and 16th symposia, which took place in the grand lecture theatre of the Athens College, which was almost full of orthopaedic surgeons, pediatricians, radiologists, physiotherapists, etc. but also important speakers and trainers among pioneers of Europe and the USA. [1] [2] (Figure 8).

A small parenthesis

Opening a parenthesis, I want to mention, the events that I cannot forget and so many years concern me: For the many efforts made by well-known University Orthopaedics from time to time, the scoliosis symposiums should be interrupted, stopped, forgotten....

We remember the great effort made spent to invalidate the symposia actually even organising a ''Para-conference'' (side-meeting), with the front *of the the*

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Figure 5

Figure 6

Hellenic Society for Orthopaedic Surgery & Traumatology (HAOST) and its Department of Spine and Disorders for two consecutive years in 1988 and 1989, the first on the cervical spine and the other one on spinal Diseases, without any success, as the symposia of 1986,1987,1988,1989 were the most populous and most successful, in particular the workshops with cadaver. (Figure 9).

This effort did not stop when the "side-meetings" stopped. [1][2]

At this point let me quote from a book by a professor in orthopaedic surgery and member of the DSD on the contribution of the symposia, which he sums up in three lines: "*Since 1973, the organisation of an annual scientific meeting has started on spine surgery, with participations from around the world, which later was named "N. Giannestras-P. Smyrnis" and continues to be organised incessantly until this day.* Fortunately, allies of the Scoliosis and Spine Unit were Professors G. Hartofylakides, P. Soukakos and G. Sapkas. [1][2][5][6][7] (Figure 10).

Conservative Treatment of Scoliosis

The team at the KAT Scoliosis and Spine Unit did not limit its work to the successful organisation of the Symposia only; we were not satisfied with the conservative treatment using only a Boston brace and we were constantly seeking something different, something lighter and powerful.

The workshop of Giannis Maragoudakis with Nikos Vastatzidis as lead technician was our afternoon retreat for ideas and studying. It was there that P. Smyrnis designed the LCP (Limited Contact and Pressure) brace, Antoniou and Zachariou designed DDB (Dynamic Derotation Brace), and G. Valavanis DTB, DLB (thoracic and lumbar). All braces were used at the outpatients of the KAT hospital. (Figure 11).

DDB was presented in the SRS Meeting in Bermuda 1986 and it has been used ever since. T. V. Grivas pre-

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Figure 7

sented the brace of the KAT (DDB) who, as he says, the impressions were incredibly good, as evidenced by the international literature. [1][2]

KZ series Hook

Apart from designing scoliosis braces, the doctors at the Scoliosis and Spine Unit, had also contributed to the design of devices such as the SpineSwiss polyaxial hooks.

In a visit to S. Africa to the laboratories of SwissSpine (Antoniou and Zachariou), I described the idea of developing a polyaxial hook. In a few weeks, a polyaxial hook was presented to us, and this series was named in our honor as we were told "KZ Series Hooks" and was used in many operations of scoliosis Surgery worldwide. We used this series in our scoliosis surgery.

Our thoughts have also been focused on research, led by Giannis Valavanis, where his discussions about various patents with various medical materials manufacturers were continuous.

We should also remember that the logos of the Scoliosis and Spine Unit, the Department of Spine Disorders and the Hellenic Spine Society were designed by G. Valavanis. Very recently his patent is about to be released in Israel.

Instrumented scoliosis and spine surgery in Greece

After Harrington instrumentation, we used the Luque sublaminar wires, and then the Hartshill rectangles by John Dove, and the interspinous wires (Drummond/Wisconsin method). Application of the CD system followed.

At the same time, the training of all the executives of the Smyrnis team (D. Antoniou, J. Valavanis, c. Zachariou) in the newer methods was a priority since the needs began to become pressing.

Greece: First application of Transpedicular Materials

In 1986, much earlier compared to Europe, as the transpedicular screw had just emerged, we asked from Synthes to bring the Dick/internal fixateur system to Greece for the treatment of spine fractures. We had been trained in this system (1984 Antoniou, Valavanis and 1985 Zachariou) and after supplied cadavers (spinal) from the Athens mortuary, we did our own studies and after considering ourselves ready for these operations, we proceeded.

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Figure 8

Figure 9

On 5/10/1989, Dr. C. Zachariou together with two trainee doctors (G. Georgiou, S. Papastefanou) operated a female patient, 52y, with incomplete paraplegia with an incredibly good result. This was the first application of the transpedicular screws in Greece, which was immediately also applied for scoliosis that require much more care [1][2] (Figure 12).

As the transpedicular screw dominated thanks to many advantages, we used most known transpedicular devices of the time, (Medtronic, DuPuy-Moss-Miami, Isola, Acromed, Synthes, Aesculab, Stryker, Scientix, Internal Fixateur/Dick, etc.).

I would give the following advice to all young doctors wishing to apply a surgical procedure: "Surgery can never be learnt from the various brochures of companies, no matter how impressive they may be".

Training of foreign doctors

Professors and curators from neighboring states, Bulgaria, Romania, Northern Macedonia, Serbia were sent from hospitals working in the Scoliosis Department of KAT hospital, to be trained in surgical technique for scoliosis and other spinal disorders. [1][2]

With the recognition of the Scoliosis and Spine Unit in the KAT by the Ministry of Health enables Greek trainees to be trained in the Unit for a semester.

Epilogue

Until 2003 scoliosis was surgically treated only in Athens by the Department of Scoliosis and Spinal Disorders of the KAT Hospital that covered the whole of Greece; later, in Ioannina, Professor P. Soukakos in Athens University G. Sapkas and much later in Patras at the Agios Andreas Hospital P. Korovesis, since 2003, in University of Thessaloniki T. Christodoulou at the Papanikolaou Hospital, since 2005; later in Crete A. Chatzipavlou with Pavlos Katonis and D. Dimitriades with J. Hager at PIKPA of Penteli mainly for neuromuscular scoliosis.

The Symposia were organized by doctors of the Scoliosis and Spine Unit of the KAT Hospital (P. Smyrnis, Antoniou, G. Valavanis, K. Zachariou, later also M. Tsafantakis, A. Bountis, etc.), our secretary Rena Klonari, nurses etc. [1][2]

In 1992 organization was taken over by same people under auspices of the newly established Scoliosis and Spine Department of the HAOST, while in recent years (2006) it is held within the annual Conference of the Hellenic Spine Society, which was established in 2006 by Orthopaedic Surgeons and Neurosurgeons, including other specialties such as Pediatricians, Radiologists, Physiatrists etc.

Hellenic Spine Society (HSS)

The issue of establishing a Greek Spine Society was from time to time discussed by Orthopaedic Surgeons without reaching any conclusions.

In 2004 in the Scoliosis and Spine Symposium in Samos, the President of the Symposium, Thomas Patsiouras, raised the matter in the General Assembly for discussion and to reach a final decision.

There were many Professors, Directors, registrars, orthopedists, where the trend and the current were, to answer, NO we do not want the HSS with neurosurgeons.

I spoke almost last, I do not know why and how, listening to the arguments of everyone and I said that ''each one of us is making their own story and the fear

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Figure 10

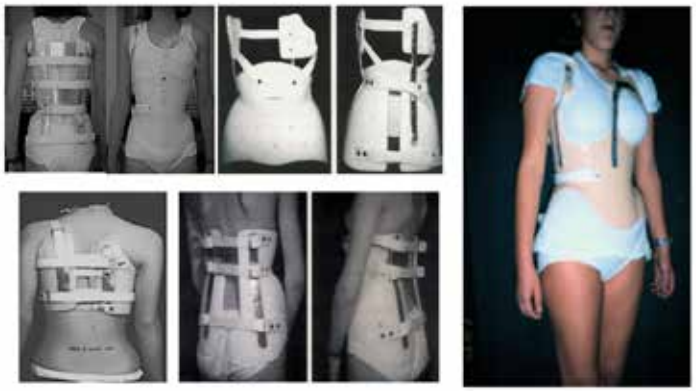

Figure 11

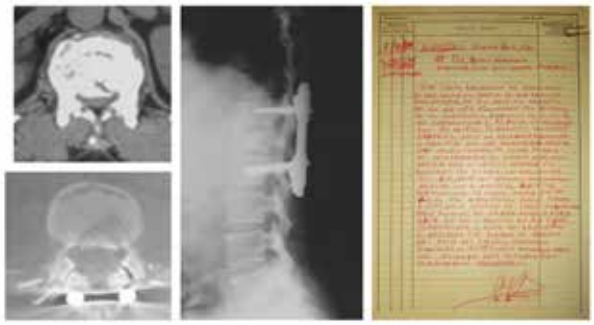

Figure 12

Figure 13

Figure 14

that we will be overshadowed by neurosurgeons depends on everyone's training and experience; we cannot shut our eyes to progress, when in Europe similar Societies have been in place for years".

I think that George Sapkas was the first one to agree and the mood started to change... Thus, was the way paved for the creation of the HSS, with its first president being Panagiotis Smyrnis 2006 and the first successful meeting organised by the new president George Sapkas in 2007.

The first formal invitation to neurosurgeons was extended for the 33rd "N. Giannestras-P. Giannestras-P. Smyrnis" Symposium (organised by C. Zachariou) in Mykonos to the President of the Society for Neurosurgery P. Selviaridis and I cannot remember the second one. [1]2]

The new blood in scoliosis and Spine surgery.

Much later Greek doctors return from abroad having received initial or advanced training in spine surgery, such as P. Korovesis, T. Christodoulou, P. Katonis whom we unfortunately lost him very early, D. Dimitriades, P. Zoumpoulis, E. Papadopoulos, J. Gelalis, T. Apostolou, K. Soultanis, etc.

Here I will mention the doctors that were trained not only for one semester but for many at the Department of Scoliosis and Spine of KAT, who today also work with spine surgery, such as M. Tsafantakis and A. Bountis that were also heads of the Scolio-

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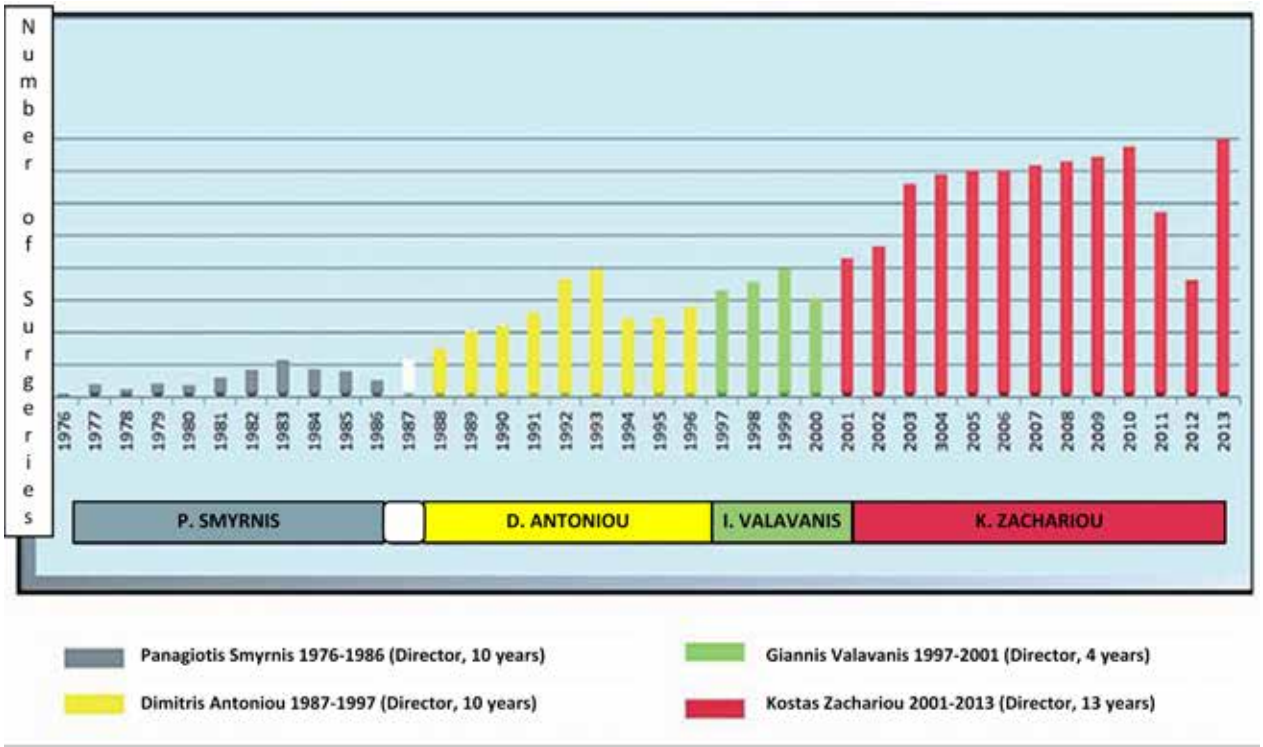

Table 1. *The Volume of operations from 1976 until 2013*
The reduction in surgeries in 2011 and 2012 coincides with the actions of the Director of Medical Services to usurp and seize surgical time, in Dep. of Scoliosis& Spine. [1][2]

sis and Spine Department, G. Georgiou, I. Hager, S. Papastefanou, L. Kolintzas, P. Aggourakis, I. Papadas, A. Tsagkalis, N. Benardos, A. Kalampokis, I. Chatzikomninos, A. Morakis, S. Moschos, etc.

Among the neurosurgeons that today we are in the same team of spine surgeons, I will mention those that I have worked with, such as D. Bouramas, I. Magras, P. Selviaridis, D.I. Polythodorakis, K. Vlachos, K. Markogiannakis, C. Antoniadis, etc.

Surely, I may have forgotten enough from both specialties, but I did not do it on purpose.

At this point, I would like to note the great effort made by George Sapkas who organised for years the Spine Biomechanics Symposia. All these talks were published by G. Sapkas in five books that until this day have been a source of study.

With the implementation of NHS 1987 P. Smyrnis leaves state and the position is taken by Dimitris Antoniou until 1997 when, he too left. J. Valavanis assumed the position of Director for a short period until 2001 and then took over as Coordinating Director of the Scoliosis and Spine Department C. Zachariou, who remained until 2013. (Figure 13)

A special mention should be made for Dimitris Antoniou, who after Panagiotis Smyrnis, was the Director of the Scoliosis and Spine Department. During his service, spine operations increased throughout the spectrum of surgery (an achievement held and surpassed), so much so that I consider him as the "father" of spine surgery of orthopaedic surgeons. (Figure 14)

The Scoliosis and Spine Unit by decision of the Ministry of Health, Government Gazette 9/15-1-87, is weaned from the E' Orthopaedics clinic and was made into an autonomous functional Unit and by decision Government Gazette 2269/5-11-2008 upgraded to an autonomous medical Department with its own nursing beds, surgical time, medical and nursing staff in its own offices. [1][2]

Conclusions

In conclusion I believe that in Greece the surgery

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of Scoliosis, Kyphosis and more generally of the Spine developed rapidly and had great growth alongside Europe and the USA after 1975. The materials and tools were quite timely, and their application was almost immediate.

Let us not forget that the training of doctors was informally undertaken by the medical companies of materials, which sent for training abroad to special surgical centres of scoliosis and Spine, young and older orthopaedics.

Conflict of interest

The authors declare no conflicts of interest.

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Biological approaches in degenerative disc disease. Where are we now?

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ABSTRACT

Intervertebral disc (IVD) disease consists one of the main chronic- age related diseases mostly in patients over 60 years old. IVD degeneration is considered a multifactorial process with interaction of genetic, nutritional and environmental factors. Any nutritional and compositional imbalance leads to disturbance in biochemical and structural integrity.

Unfortunately common therapeutic methods- conservative and surgical- focus mainly on the patients and rather to the pathology of disc degeneration. Biological treatment strategies approach the condition at a molecular level and according with the stage of degeneration are classified into biomolecular therapy, cell therapy and tissue-engineering (TE) therapy.

During the first stage of the disease, where there is damage to biomolecules, biomoleucular therapy is suitable for promoting extracellular matrix (ECM) synthesis. This is achieved through injection of protein solutions (bone morphogenic proteins, osteogenic protein-1, transforming growth factor superfamily), platelet-rich-plasma and gene therapy injection (viral or non-viral vectors). In the midstage of disease, with cell amount reduction, cell therapy through mesenchymal stem cells and chondrocyte transplantation forms the best option for production- differentiation of ECM components and disc repair. Lastly, as degeneration reaches the final stage, implantation of TE disc-like constructs is considered the most optional reconstruction therapy for disc repair.

Biological therapeutic strategies in IVD disease consists a revolutionary method, address not to symptoms but to pathophysiology of the degeneration with purpose to improve population's quality life

KEY WORDS: intervertebral disc disease, biological therapies, tissue engineering

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Introduction

Low back pain is one of the main chronic age-related diseases that burdens global health leading to a significant reduction in patients' quality of life [1]. Approximately, 90% of the general population over the age of 60s is more likely to suffer from low back pain due to degeneration of intervertebral disc disease (IVD) [2].

IVD is situated between two adjacent vertebrae with an outer fibrous annulus fibrosus (AF) enclosing a central gelatinous nucleus pulposus (NP) and the cartilaginous end plates (CEP) connecting discs to adjacent vertebral bodies. Discs are avascular, aneural tissues that exchange nutrients and metabolites through microvessels in the CEP and outer AF [3]. Thus, considering that IVD degeneration is a complex interaction between genetic, nutritional and environmental factors [4], any case of restriction in nutritional supply and compositional changes may lead to the disturbance of the structural integrity and biomechanical properties of the IVD as a respond to loads and injuries [5]

Conservative and surgical therapies are aiming at the symptoms and fail to address the underlying pathology, leading to higher rates of reoperation, adjacent segment disease and pseudarthrosis [6]. In order to surpass these restrictions our great interest is focused on the biological repair strategies as a feasible way to understand and treat pathologic disc segments. Biologic therapies approach the condition at a molecular level, in an attempt to alter the process cascade rather than treat patient's symptoms.

According with the stage of degeneration, biological strategies are classified into three categories: 1) biomolecular therapy, 2) cell therapy and 3) tissue-engineered disc like construction [7]. In early stages in which the disc still contains sufficient amount of cells, biomolecules are used, with the ability to enhance protein expression and facilitate extracellular matrix (ECM) synthesis. In midstage degeneration, where cells are now rapidly reduced and hypoactive, cell therapy is the choice through cell implantation. Lastly, during the terminal stage, with complete structural and functional disruption of the disc the most optimal method is the implantation of tissue-engineered (TE) IVD constructs for attempt of reconstruction of the disc segment [8].

In this review we focus on novel applications as therapeutical strategies for discogenic pathology, according with the stage of degeneration based on clinical and research trials.

Biological treatment strategies

Biomolecular Treatment

During the early stage of degeneration, there is damage to biomolecules (DNA- proteins) due to inflammatory and oxidative stress so the disc undergoes an imbalance of anabolic and catabolic factors leading to degradation of ECM [9]. In that stage recombinant proteins and genes can regenerate expression of the targeted molecules by increasing anabolic or decreasing catabolic factor production and thus promoting ECM synthesis.

Protein solution injection

It has been shown that injection of protein solutions into discs can trigger cell growth, shift cellular metabolism to the anabolic state thus restoring its biochemical properties reversing degeneration process. The mostly used proteins are bone morphogenic proteins (BMPs), osteogenic protein-1 (OP-1), transforming growth factor (TGF)-β superfamily [10]. Gruber et al. proved that the addition of TGF-β triggers the synthesis of proteoglycans (PGs) and stimulates cell proliferation of human AF [11]. BMP family has been found to increase PG synthesis and metabolism of IVD cells and stimulates production and formation of ECM [12]. Wehling P proved that the use of autologous growth factors (IL-1 receptor antagonist, IGF-1) may reduce the rate of apoptosis and the production of IL-1, inflammatory cytokines [13]. In 2015, Liu et al studied that Mineralization Protein-1 (LMP-1) suppresses TNF-a induced IVD degeneration, by maintaining pro-

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duction of NP and ECM [14].

The only limitation here is that a direct injection into IVD requires many repeated doses due to chronicity of the condition and the short biologic half-lives of these factors, thus limited therapeutic effect. Many proposals have been made for development of slow-release carriers or gene-based delivery [8].

Platelet- Rich Plasma (PRP)

As a therapeutic strategy, PRP is consistently being utilized in stimulation and acceleration of bone and soft tissue healing, with many studies proving their increased efficacy in osteoarthritis, cartilage damage and recently in the treatment of DDD [16]. These platelets release a variety of growth factors, such as platelet- derived growth factor (PDGF), TGF-β1, vascular endothelial growth factor (VEGF). PRP seems to be an effective stimulator of cell proliferation and PG and collagen synthesis in porcupine NP and AF cells [17]. Clinical evidence for PRP treatment of discogenic low back pain in humans has been reported since 2011, by Akeda et al, who injected autologous PRP in 6 patients with chronic low back pain [18]. At 6 months follow-up, patients showed a remarkable decrease in mean pain score and adverse effects after the injection were reported. Cho et al. demonstrate that PRP can decrease the expression of proteolytic matrix metalloproteinases and increase synthesis of ECM in a in vitro porcine model [19]. Gelalis et al. proved that intradiscal PRP treatment in DDD provokes the maintenance of the disc's basic morphological characteristics in rabbit IVD [20]. Autologous PRP therapy has the benefit of avoidance disease transmission and immunological reaction in comparison with artificially synthesized GF [16]. Finally, PRP when used in the early stage of degeneration can better enhance disk height and hydration [21].

Gene therapy

Gene therapy has been used for several years, through gene mapping, nucleic acid modification and is widely used in the therapeutic strategies for DDD. The selected genes are delivered through viral (adenovirus, lentivirus) or non-viral vectors which are then injected into the tissue or transferred into cells in vitro and then transplanted into viable tissue [22]. Many in vitro and in vivo studies have shown that viral delivery of BMP-7, TGF-β3 improves IVD extracellular environment with increased synthesis of type II collagen, and glycosaminoglycan [23]. Although, there is an increased rate of immunogenicity, toxicity and insertional mutagenesis through viral vectors, which is why there is a great interest toward non-viral gene delivery systems [24]. However, those delivery systems are limited due to their low transfection efficiency.

Cell therapy

As degeneration progresses, the amount of cells that respond to biomolecular therapy start to reduce, which makes cell therapy the optimal treatment for midstage degeneration.

Mesenchymal Stem cells (MSCs)

Attention has been posed on stem cells as a potential source of cells to regenerate the IVD. There are a large number of potential sources of MSCs [25], including adipose tissue, bone marrow, embryonic and fetal stem cells, which are pluripotent cells with a potential to differentiate into any body tissue. These cells are able to differentiate into any type of tissue thus making the ideal method for disc repair and also due to their ability to produce the required proteoglycan and collagen for disc's ECM [8]. Although is more technically demanding process than PRP, is easy to collect and post-collecting algorithm is simple, leading to its popularity as therapeutic option for DDD. Yoshikawa et al. in 2010 analyzed the regenerative restoration ability of autologous MSCs in degeneration of IVDs in 2 patients with chronic low back pain, leg pain, and numbness [26]. bMSCs were isolated coupled with colla-

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gen sponges and grafted percutaneously to the degenerated IVD. After a 2 year follow-up both patients had significant symptomatic reliefs and MRI results showed high NP hydration without progressive degeneration. Pettine and colleagues in 2015 injected autologous bMSCs in 26 patients with discogenic back pain. It was observed clinical improvement with pain relief, functional and imaging improvement at a two-year follow up [27].

Adipose stem cells (ASCs) have been the focus of recent studies in autologous biologic research due to a number of promising characteristics [16]. In fact, ASCs are easier to harvest, contain a higher frequency of stem cells, are more potent immunomodulator than bMSCs and they are characterized by their ability to differentiate into NP- like phenotype [28]. For all these, aMSCs make an attractive single-step therapeutic method for DDD. In vitro experiments show that ASCs may provide mechanical protection by decreasing degradation enzymes and inflammatory factors and increasing expression of genes and proteins involved in maintenance of ECM integrity [29].

Chondrocytes transplantation

Implantation of chondrocytes can produce the appropriate amount of ECM components (proteoglycans, collagen type I-II) under nutritional stress and hypoxia and meet the increased cellular and metabolic demands of the disc [30]. Ganey et al. through canine model proved that implantation of chondrocyte in NP disc contributes to ECM regeneration and halt further disc degeneration [31]. Unfortunately, no matter how promising this technique is there are some limitations such as, donor site morbidity, immunocompatibility complications and disease transmission.

Tissue-engineering Therapy

TE was defined 25 years ago by Langer and Vacanti in 1993 as an interdisciplinary field of research that applies the effort towards the development of biological substitutes that restore, maintain and improve tissue function [32]. Since the inception of this concept, many attempts have been made for the construction of functional substitutes for damaged disc tissues. As the degeneration process reach the terminal stage implantation of TE disc-like constructs is considered the most optional reconstruction therapy. It is very important to understand the combining role of stems cells, absorbable scaffolds, bioactive molecules like growth factors and mechanical stimuli.

Scaffolds

Injection of scaffold can provide structural support to MSCs injected in to intervertebral space. The content of scaffold must be similar to the natural ECM in composition and physical properties [33]. Examples are natural proteins of alginate, collagen and synthetic polymers. In this hypoxic and nutrient-poor environment of the IVD these method assist cellular survival by enhancing adhesive strength and providing a healthier ECM microenvironment [16].

Tissue-engineered constructs

In recent years, advanced TE enables whole IVD construction, through the combination of constructed tissue engineered AF and NP, in vitro which can be implanted in vivo. In 1976, Mizuno et al. were the first to construct whole IVDs consisting of sheep AF and NP cells seeded on polyglycolic acid and calcium alginate matrices [34]. The disc implants were implanted in the subcutaneous space of the dorsum of athymic mice. Gross morphology and histology of the constructs strongly resembled those of the native IVDs. TE AF was rich in type I collagen but NP contained type II collagen similar to the native. Moriguchi et al constructed TE-IVD components using adult canine AF and NP cells seeded into collagen and alginate hydogels. After cervical spine discectomy implantation of TE-IVD was performed. Implanted TE-IVDs maintained their

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position, structure and hydration as well as disc height over 16 weeks in vivo [35].

The construction of whole disc implants through tissue engineering consists of a revolutionary progress in the treatment of DDD with extensive biological and functional challenges in vivo.

Conclusion and Perspectives

Over the past two decades there has been a significant development in the conservative and surgical treatment of spinal disorders. Unfortunately, all these methods affect the symptom rather the underlying pathology, as there is still limited understanding of the biology of the IVD thus limited understanding of DDD pathogenesis and progression. Therefore, scientists focused on the value of biological treatments for DDD.

It is crucial to select the proper therapeutic protocol according with the patient's profile and the stage of degeneration. Injection of biomolecules, genes and cellular therapy can attenuate the degenerative process at the early to mid-stages of the disease progression. Until now, some first clinical trials with recombinant proteins are underway. Cellular therapy seems to be effective, according with animal and human studies, in treating pain in patients in middle stage of degeneration. TE-IVD is useful in the terminal stage of degeneration, where there is complete structural and functional disruption of the IVD, through regeneration disc morphology and functionality postimplantation. Until now, only two studies have demonstrated the in-vivo transplantation of TE-IVDs.

We anticipated future research in the field of biological therapy for identify the ideal solution for each special pathogenesis and for each individual.

Conflict of interest

The authors declare no conflicts of interest.

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Cell-based therapies for the regeneration of the intervertebral disc: promises and challenges

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ABSTRACT

Intervertebral disc (IVD) degeneration (IDD) has been yet inextricably associated to the manifestation of low back pain, a major cause of disability with a vast socioeconomic impact worldwide. IDD treatment has been challenging given that IDD is characterized by a constellation of changes, major among them being the reduction in cell number and the modification of the cellular phenotype and function, ultimately contributing to tissue structural breakdown. As alternative options to the conservative and surgical approaches that only target IDD symptoms, injection of bioactive substances, gene therapy or cell transplantation have been attempted with some encouraging results even though no complete restoration of the injured tissue has been achieved thus far. In this short review we discuss the effect of the particular IVD environment (a combination of nutrients' and oxygen deprivation, mechanical and oxidative stress, high osmolality and acidic pH) on several parameters of the physiology of the resident or implanted cells that should be taken under consideration for a successful regenerative intervention. The role of cells' senescence in IVD physiology is also discussed as a putative novel therapeutic target for IDD. Deep understanding of the molecular alterations underlying IVD cells' responses could lead to more effective IDD treatment modalities.

KEY WORDS: intervertebral disc, low back pain, cell-based therapy, gene therapy, senescence

1. Therapeutic strategies for the treatment of intervertebral disc degeneration

Intervertebral disc (IVD) degeneration (IDD) with a yet established incrimination in the aetiology of chronic low back pain (LBP) [1, 2] represents the leading cause of disability, activity limitation and loss of productivity in the adult population in Greece [3] and worldwide [4, 5].

IVDs, charged to play the role of suspension for the spine, intervene between vertebrae, with direct adjacency to the superior and inferior cartilage endplates. They consist of an outer layer of concen-

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trically arranged fibrous lamellae (containing cells similar to fibroblasts) and a gelatinous core (with chondrocyte-like cells), namely annulus fibrosus (AF) and nucleus pulposus (NP), respectively [2]. In addition, native IVD stem/progenitor cells, expressing a set of mesenchymal stem cells' surface markers, have been isolated from human degenerated discs [6]. The IVD is mostly extracellular matrix (ECM) characterized by a rigid AF collagenous network that encapsulates a well-hydrated NP proteoglycan (mainly aggrecan) matrix [2]. The negatively-charged IVD ECM and the diurnal compressive load-driven water loss due to posture and other activities constantly expose IVD cells to extreme variations in extracellular osmolality [7, 8]. In addition, the avascular nature of the tissue leads to oxygen deprivation, nutrients' deficiency, acidic pH and accumulation of IVD cells' metabolic byproducts and oxidative stress [7, 9]. As a consequence of this harsh microenvironment, a very low number of cells are embedded in the IVD ECM [2, 7, 10], with a pivotal role though in maintaining disc homeostasis, since they are the producers of ECM molecules, as well as of the ECM-degrading enzymes [e.g., matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs)].

IVD degenerative changes concern the number, phenotype and secretome of IVD cells, the accumulation of inflammatory mediators and the disorganization of the ECM [11, 12], characterized by depletion, cross-linking and oxidation of collagen and lower aggrecan content, which all lead to greater stiffness and progressive dehydration [12-14]. Furthermore, cell number is reducing due to apoptosis at the same time that cell clusters are appearing possibly due to the degradation of the surrounding restrictive ECM. IVD ECM structural breakdown ultimately allows disc herniation and nerve intrusion that lead to LBP. Current IDD treatments such as administration of analgesics, non-steroidal anti-inflammatory drugs and opioids, exercise, physiotherapy and spinal manipulation for rehabilitation mostly target symptoms' alleviation without addressing the causes of the disease [12, 15]. On the other hand, invasive disc and spinal surgical procedures (discectomy, spinal fusion or arthroplasty) stand as the last recourse as they are high-cost and in many instances non-effective or even risky for post-operative complications [12, 16, 17].

In an attempt to override the limitations of the hitherto employed therapeutic strategies against IDD, injection of bioactive substances, genetic interventions or cell transplantation could serve as promising alternative options [12, 15]. One of the first approaches was based on the injection of growth factors in the degenerated disc, since these molecules induce not only disc cell proliferation and survival, but also the local production of ECM constituents by the cells [18, 19]. Indeed, disc cells secrete growth factors to which they respond with the activation of pivotal signalling pathways leading to cell proliferation [20-22]. Some of the growth factors that have been investigated in animal models against experimentally induced IDD include TGF-β, IGF-I, basic fibroblast growth factor (bFGF) and various bone morphogenetic proteins (BMPs), with BMP-14 or growth and differentiation factor-5 (GDF-5) [23, 24], while natural mixtures of multiple growth factors, such as platelet-rich plasma (PRP) have been also proposed for such use [25, 26]. Among the disadvantages of this approach are its high cost, the *in vivo* proteolysis of growth factors and the possible adverse effects due to enhanced angiogenesis in the IVD. Still their use *in vivo* could be possible in conjunction with appropriate biomaterials offering the capability of controlled release [17]. Unfortunately, the injection of growth factors (e.g., GDF-5 and BMP-7) and other bioactive substances (e.g., the IL-6 receptor antibody tocilizumab and the TNFα selective inhibitor Etanercept) had no conclusive results in most cases so far [15, 17].

Gene therapy - that is the *in vivo* or *ex vivo* genetic manipulation of cells aiming at the modification of the deduced encoded products at the RNA and protein level - can be carried out using viral or non-viral vectors. Furthermore, genetic engineering techniques employed for gene therapy could be RNA interference or the recently discovered state-of the-art clustered regularly interspaced short palindromic repeats (CRISPR) [27]. TGF-β1, TGF-β3, connective tissue growth factor (CTGF), BMP-2, BMP-7, IGF-I,

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latent membrane protein (LMP)-1, SRY-box transcription factor (SOX)-9 and tissue inhibitor of metalloproteinases (TIMP)-1 delivery resulted in significant anabolic effects and increased ECM deposition [27, 28]. Despite these auspicious findings, skepticism remains regarding the usage of viral vectors in clinical applications in humans due to the existing risk of insertional mutagenesis and immunogenicity [29-31]. On the other hand, miR-29a, miR193a-3p, miR93, miR146, mR146a have shown ECM-promoting or anti-inflammatory properties [17, 27]. Small interfering RNA (siRNA)-mediated knockdown has been used to target Fas ligand, ADAMTS-5, caspase-3 and mTOR *in vitro* and/or *in vivo* [27, 28]. CRISPR genome and epigenome editing have been also endeavored with some positive results [32, 33]. Non-viral gene therapy methods seem to be safer, but still have the disadvantage of lower transfection efficacies compared to viral vector methods [34].

2. Challenges for a successful IDD cell-based therapy

As mentioned earlier, one of the initiating events of IVD degeneration seems to be the decline in the resident IVD, and especially NP, cell number, which disrupts the balance between anabolic and catabolic processes in ECM synthesis. Taking this into account, punctual NP supplementation by direct transannular or transpedicular intradiscal injection with functional cells - owning themselves or stimulating in the resident cells a desired ECM-restoring and/or anti-inflammatory phenotype - can offer a potential solution for preventing or delaying IDD. Available cell sources for IVD cell-based therapies are autologous and allogeneic NP cells or articular chondrocytes; mesenchymal stromal cells (MSCs) able to both replenish the number of NP cells and to stimulate NP reconstruction; induced pluripotent stem cells (iPSCs) [17, 35]. Although autologous NP cells would be the ideal foolproof selection, followed by articular chondrocytes, their low availability and proliferative potential or already acquired catabolic phenotype along with their high prevalence for de-differentiation when cultured *in vitro* have rendered them challenging or sometimes unsuitable candidates for cell therapy. For that reason, the requirement for alternative options, such as NP and chondrocytic cells of allogeneic origin or MSCs and iPSCs, has emerged. Adult stem cells may contribute to IVD regeneration either by their differentiation into NP-like cells or by acting as feeders that induce the up-regulation of ECM synthesis by their native NP counterparts [36]. IVD progenitor cells also hold prospects for their potential use in IDD treatment [6, 12]. It is intelligible that in favor of using cells of allogeneic origin is that the patient is only subjected to one-step surgery, but the risk of stimulating an immunogenic effect always exists. Then again, the use of MSCs or iPSCs involves the peril of tumor formation [17]. As already mentioned above for growth factors, the use of biomaterials seems to be necessary for cells' delivery in the disc, as well. These include hydrogels based on proteins (e.g. collagen) or polysaccharides (e.g. alginate) [37, 38], composite systems, such as a collagen hydrogel supplemented with chondroitin sulfate [39], hydrogels cross-linked or in the form of microparticles and natural materials [40]. The first clinical trials based in the use of autologous or allogeneic MSCs resulted in pain relief. Clinical studies using discogenic cells, autologous disc chondrocytes or MSCs combined with biomaterials have been also conducted [14, 17]. Still, there is no until now strong evidence to support the preference of anyone of the cell sources.

An important step for the refinement of IVD cell therapy is the determination of the optimal timing and expedient precise cell number for intradiscal delivery (accounting for the putative cell leakage during injection at the delivery site and/or the cytotoxicity ensuing from the shear forces applied by the needle or from the harsh conditions of the final destination) in order to achieve maximal benefit. It is, for instance, important to apply the treatment when the grade of degeneration is still low, prior to the launching of an advanced and irreversible IDD to expect a possible successful regenerative effect. In addition, given that implanted cells (irrespective of the source) not only need to be able to survive but also to be functional and to produce ECM of the desired quality, it is essential to consider the hostile local IVD microenvironment, which worsens with the progression of degeneration [35].

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IVD cells' responses to inflammatory cytokines

Inflammatory mediators including interleukins (ILs) and TNFα have been shown to be expressed in the human NP and what is more their expression along with the expression of their receptors increases with age and in symptomatic and degenerated discs [41, 42]. ILs and TNFα have been reported to exert a catabolic/anti-anabolic effect in the IVD [43] [41]. We have shown that TNFα up-regulates MMP-3 expression in bovine NP cells, which is attenuated by the presence of glucosamine [44].

IVD cells' responses to mechanical stress

Mechanical loading is indissolubly connected with IVD homeostasis [45]. We have shown that cyclic tensile stress stimulates the expression of the pro-inflammatory genes, cyclooxygenase-2 (COX-2), IL-6, and IL-8 in AF IVD cells, mediated by members of the MAPK superfamily [46]. Moreover, changes in type II collagen expression and altered proteoglycan synthesis have been reported as a response to the application of mechanical loads and hydrostatic pressure [45].

IVD cells' osmo-regulatory response

High osmolality raises a torrent of biochemical events in NP IVD cells, as shown by our whole-genome array analysis, revealing the simultaneous transcriptional change of >200 genes [47]. We have shown that this stress is genotoxic and has an anti-proliferative effect on NP cells [48, 49]. In addition, high osmolality restrained the mitogenic effect of platelet-derived growth factor (PDGF) or IGF-I via ERK and Akt activation [50]. This strict control of hyperosmolality on the proliferation of NP IVD cells is retained even after the administration of glucosamine, shown to result in an increase in the glycosaminoglycan content [51]. Regarding ECM components, it has been reported that aggrecan and collagen type II were up-regulated, while collagen type I expression was inhibited by high osmolality in human IVD cells [45].

IVD cells' responses to oxidative stress

The presence of oxidative stress in the IVD has been established *in vivo* [9, 52-54]. We have shown that oxidative stress activated survival and stress signalling pathways in human NP cells, while it proved to be genotoxic, triggering the activation of the DNA repair response [55]. Oxidative stress-induced NF-κB activation has been also shown in the human NP *in vivo* [42].

Moreover, we have shown that a combination of all IVD conditions (i.e. low glucose, hypoxia, high osmolality and absence of serum) is anti-proliferative for IVD cells [56] and it has been reported that a concurrent exposure to low glucose, acidic pH and hypo-osmolality down-regulates the expression of ECM components and up-regulates the expression of MMPs [45, 57].

3. IVD cells' senescence

A key step for the elucidation of IDD-related modifications in the IVD tissue microenvironment was the discovery of senescent cells in IVDs *in vivo*, first reported by Roberts et al. [10, 58] and later verified by other groups [59, 60]. There are two types of cellular senescence: the "replicative senescence" attributed to telomere attrition arising from the consecutive replications of the cells and the "stress-induced premature senescence" (SIPS) manifested as the result of several genotoxic stresses encountered by the cells [10, 13]. Given the restraining physicochemical conditions of the IVD microenvironment [61], senescence in the IVD is most probably stress-induced rather than replicative [10]. Beyond their enlarged and irregular shape and their inability for proliferation, senescent cells are characterized by a catabolic and pro-inflammatory phenotype namely the "senescence-associated secretory phenotype" (SASP) (consisting of soluble inflammatory mediators, proteolytic enzymes or growth factors and insoluble ECM components) [13, 62, 63] that may contribute to the IDD-associated tissue remodelling. We have shown that senescent human NP cells up-regulated MMPs and ADAMTSs and down-regulated aggrecan, biglycan, decorin and versican [55, 64]. MMP-1 has been also shown to be up-regulated in line with the degree of the deformity in an experimentally induced scoliotic deformity rat model [65]. This senescence-induced catabolic phenotype of the IVD cells has been confirmed using several means of se-

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nescence induction, as well as in a progeria mouse model *in vivo* [13]. Most importantly, we recently demonstrated that the IVD cells' senescent phenotype is maintained when cells are cultured under the actual conditions they face *in vivo* (hyperosmolality, low oxygen and glucose concentration and serum starvation), which supports their possible implication in IDD [56].

The implication of senescent cells in age-related diseases and the improvement of tissue homeostasis by their elimination have been recently experimentally supported by using the p16-3MR transgenic mouse model in which the $p16^{INK4a}$-positive senescent cells can be removed by ganciclovir [66]. Reducing the number of senescent cells in aged mice increased IVD proteoglycan matrix content, thus improving the histological features of the disc [67] and indicating that cellular senescence could be a therapeutic objective for IDD. However, the above-mentioned approach cannot be applied to humans. A recently developed alternative is the use of new class of drugs that can selectively kill senescent cells (senolytics) or reverse the inflammatory phenotype of senescent cells (senomorphics). Senolytics activate the apoptotic machinery in senescent cells. Interestingly, the combination of the first senolytics discovered, i.e. the well-known anticancer drug Dasatinib and the natural flavonoid Quercetin led to an increase of proteoglycans in the NP of prematurely aged transgenic animals [68], while the MDM2 inhibitor RG-7112 and the natural anti-oxidant and anti-inflammatory compound o-Vanillin express senotherapeutic properties in IVD cells and an *ex vivo* model [69, 70]. The above indicate a novel, non-invasive, approach for preventing or treating IDD and LBP.

4. Conclusion

Based on the above, it becomes unambiguous that IVD microenvironment is a parameter that must be taken into account in the design of cell-based therapies. The heretofore carried out pre-clinical and clinical trials using NP cells, chondrocytes or MSCs had already some encouraging results [14, 17]. Better survival in the disc environment and improvement of the clinical success for patients could be achieved by preconditioning of exogenous cells prior to implantation (e.g. under hypoxic and acidic conditions and with culture medium enriched with growth factors), CRISPR-mediated knockout (e.g. of cytokine receptors to reduce inflammatory responses or of cell cycle regulators to delay senescence) and knockin (e.g. of ECM components) or co-administration of senotherapeutics [35, 71]. Thus, more efficacious therapeutic options could be developed in the future, involving the joint application of appropriate cell sources, targeted genetic manipulations, bio-active substances and bio-compatible scaffolds.

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Conflict of interest

The authors declare no conflicts of interest.

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REVIEW ARTICLE VOLUME 72 | ISSUE 1 | JANUARY - MARCH 2021

Cervical sagittal balance after AIS instrumentation

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ABSTRACT

Cervical sagittal balance is one of the trending topics in the literatures. More than 60 articles were published on this hot topic. The harmonious relationship between spinal curves and kyphotic deterioration proximal to instrumentation made the researchers' main intentions. Most authors investigate the changes in cervical sagittal curves after AIS instrumentation and look for any correlation between the sagittal parameter that could hint at potential changes after instrumentation. Some authors look into the upper instrumentation level effect on cervical alignment others searched for coronal plane deformities effect on the sagittal plane. Prospective studies will be more convincing since retrospective studies show the opposite results. A meta-analysis of future prospective studies will clarify the confusion on upper instrumentation level effect on CSB, implant choice of instrumentation, PJK reasons, correlation with global spine balance, and finally, relationship with whole-body alignment. Correction of thoracic hypokyposis, especially proximal thoracic, could stimulate cervical lordotic changes over time. Flattening of the entire spine either by surgery or bracing ends up with cervical kyphosis. In this updated historical review of cervical sagittal balance after AIS instrumentation, we want to report the most current and organized knowledge of this exciting area of the spine studies. To make it more systematic, we subdivide primary theme into six main sections to answer all the potential questions of the readers. While giving essential information about cervical sagittal balance, we also delve into details to clarify this very confusing area.

KEY WORDS: Scoliosis, cervical sagittal balance, spinal instrumentation

Introduction

Cervical sagittal balance is under the scope of spine authors in the last decade after well understanding the sagittal plane on AIS patients' overall quality of life. More than 60 articles were published on this hot topic. The harmonious relationship between spinal curves and kyphotic deterioration proximal to instrumentation made the researchers' main intentions. Most authors investigate the changes in cervical sagittal curves after AIS instrumentation and look for any correlation between the sagittal parameter that could hint at potential changes after instrumentation. Some authors look into the upper instrumentation level effect on cervical alignment others

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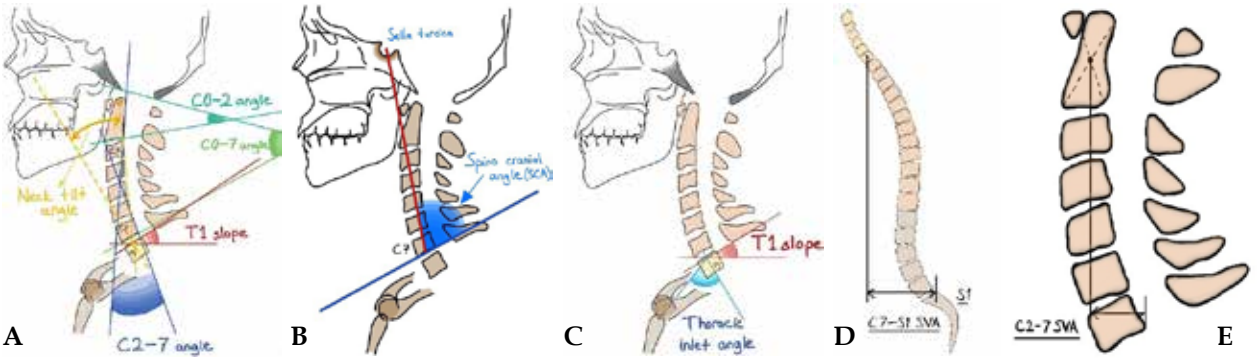

Figure 1 A,B,C,D,E. *Cervical and GLobal Sagittal Parameters*

searched for coronal plane deformities effect on the sagittal plane. This review will delve into the most recent knowledge of Cervical Sagittal Balance(CSB) after AIS instrumentation.

Discussion

1. Defining Cervical Sagittal Balance

Cervical sagittal balance is a term used to define the cervical vertebral segment's actual position over the rest of the spine and its relation with the cranium. It is known that cervical mechanisms have an essential role in the compensation of pelvic and global spinal changes. The cervical spinal segment's role in global spinal balance was underestimated previously due to the sagittal vertical axis (SVA) measurement through the C7 vertebral body. CSB is a collection of measurement parameters for sagittal plane alignment. These consist of C0-C7 sagittal vertical axis (SVA), C2-C7 SVA, T1 Slope, Chin Brow Vertical Angle (CBVA), Thoracic Inlet Angle (TIA), Spino Cranial Angle (SCA) Head Tilt, Neck Tilt and other numerous parameters that published in every separate article(1). SCA is an angle between a line from cella turcica to C7 upper endplate and a line tangential to this endplate. It gives an impression about head offset over cervicothoracic transition(2).

For C2-C7 SVA, the distance from the vertical plumb line drawn from the C2 vertebral body to the C7 vertebra posteroinferior corner is measured, and >4 cm is accepted as abnormal (3). It is shown that abnormal C2-C7 measurement is related to low health-related quality of life scores (4). For the T1 slope, the angle between the T1 vertebra upper-end plate line and the horizontal reference line is measured. (Fig 1) The increase in the T1 slope can be seen after thoracic hyperkyphosis, or it can be secondary to a positive global balance by an increase in the anterior tilt of the body. The increase in the T1 slope is compensated by cervical lordosis enhancement to maintain a horizontal gaze. However, sometimes if decompensation involves the cervicothoracic region, pelvic retroversion can take the role to maintain a horizontal gaze. The preliminary results of an ongoing study from our clinic showed that the T1 vertebra plays a keystone role for the whole spine as it is correlated with LCL, T5-T12K, SVA, and C2-C7SVA. According to a recent systematic review, the most important parameters to study the cervical sagittal balance as stated by the literature for good clinical outcomes are the following: C7 or T1 slope, average value 20°, must not be higher than 40°, SVA must not be less than 40mm (mean value 20 mm), and SCA (spine cranial angle) must stay in a norm (83° ± 9°)(1). A recent meta-analysis showed that the T1 slope has the most potent correlation with cervical lordosis(5). Thoracic kyphosis and cervical lordosis correlation were moderate, but the correlation between CL and lumbar lordosis and other pelvic parameters was weak.

2. Relationship with global spine

To understand the CSB relationship with spinal alignment and its role in global balance, we should first understand the transitions of spinal curvatures and different types of whole spine sagittal alignment. Thanks to Kariman et al., they filled the gap in Lenke Classification by introducing a sagittal plane classification. (6) New classification based on the

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sagittal profile of spine which includes Type 1 with normal sagittal alignment (standard TK, straight thoracolumbar transition and standard LL), Type 2a with thoracic hypokyphosis, Type 2b with thoracic hypokyphosis+thoracolumbar kyphosis, and Type 3 with cervicothoracic kyphosis + thoracolumbar lordosis. They claimed that this classification would guide surgical treatment to create a normal sagittal contour for each curve type, such as in Type2b, the correction of thoracic hypokyphosis, and flattening thoracolumbar transition or in Type 3 to lower the inflexion point from upper levels to its normal corresponding thoracolumbar level. They also did a 3d validation for this new classification system, which showed only the type 3 group has a variation in the TL angle compared to 2dEOS due to increased thoracolumbar lordosis in this group.

Cervical spinal balance (CSB) and global spinal balance (GSB) have a mutual relationship. An increase in PI can increase lumbar lordosis, which causes an increase in thoracic kyphosis secondarily and cervical lordosis tertiary(7). On the other hand, the decrease in lumbar lordosis causes pelvic retroversion and positive SVA, increasing cervical lordosis. If spinal deformity originates from the cervical region as in increased cervical kyphosis, pelvic retroversion is increased to supply enough pelvic tilt to maintain a horizontal gaze. Contrary to common belief, the increase in lumbar lordosis accompanies the pelvic tilt increase in this situation where the deformity originated from the cervical region rather than the lumbar region.

T1 pelvic angle is a valuable parameter of CSB, which is the intersection of two lines; one started from the T1 vertebra to the bifemoral head center, and the other started from the S1 vertebra upper-end plate center to the bifemoral head center. It is valuable due to being cleared from pelvic compensation or positional changes (8).

Moreira et al. showed that proximal thoracic kyphosis is the defining factor for cervical spine sagittal alignment. It is a similar relationship between proximal lumbar lordosis and thoracic kyphosis. (9) Akbar et al.(10) showed that upper cervical and cranial parameters were not statistically different in their study groups, including hypokyphotic and normokyphotic populations, which shows that the upper cervical spine was not recruited for compensation in order to maintain a horizontal gaze. In contribution to this, Pepke et al.(11) showed that after AIS surgery, cervical curvature is influenced by TK, T1 Slope, and SVA and has changes in the lower cervical spine and no effect seen on the upper cervical spine.

In another study concentrated on the sagittal profile of the AIS population, Ito et al. (12) divided the AIS population according to their cervical lordosis >4°, cervical kyphosis < -4°, and sigmoid (one segment kyphotic and one segment lordotic) cervical alignment. They further divide cervical kyphosis groups into CK H where TK apex is above T4, CK m where TK apex is between T4-T9, and CK L where TK apex is below T9 level. They claimed that the CK H group is a compensation cervical kyphosis for the relatively hypokyphotic thoracic region. Hilibrand et al. (13) showed that the AIS population's cervical kyphosis angle is 6±11°. When they further divided this population according to the TK level, they realized postoperatively an increase in cervical kyphosis degree in normokyphotic or hyperkyphotic patients where an improvement into lordosis was seen in the hypokyphotic group. Although postoperative TK was in normal limits in preoperatively normo and hyperkyphotic groups, a tendency to postoperative cervical kyphosis is apparent in the AIS population. We have similar results in our ongoing research. Hypokyphotic thoracic spine has a better response in sagittal plane recreation compared to normo or hyperkyphotic thoracic spine.

It is known that thoracic alignment affects sagittal alignment inevitably. T6-T12 thoracic vertebrae are responsible for %10 of cervical movement(14). It is normal to anticipate that cervical lordosis will improve after the correction of thoracic hypokyphosis. However, Canavese et al.(15) found out that cervical alignment was not affected by thoracic kyphosis, even was not affected by the upper instrumentation level. They attributed these results to the ongoing rigidification of cervical vertebrae with age. These results were different from the rest of the literature.

An article from Shimizu et al. (16) investigates

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whole body sagittal alignment after thoracic instrumentation in the AIS population. They found out previously published data of reciprocal improvement of lordotic curves of the spine in response to thoracic curve correction. Interestingly they did not find any change in lower extremity sagittal alignment after TK instrumentation. However, they noticed a correlation between TK instrumentation change and knee flexion angle change, which indicates that iatrogenic inadequate alignment change in the thoracic curve could prompt knee alignment change as a compensatory mechanism.

The brace treatment also has an impact on cervical alignment. Thoracic pads' pressure to correct coronal plane curvature and rib convexity has a hypokypotic effect on the thoracic spine. It causes a flat spine with decreased sagittal curves of lumbar lordosis, thoracic kyphosis, and cervical lordosis.(17) The authors also showed that the thoracic anteroposterior diameters declined after two-year bracing, which may result from reduced TK and contribute to further pulmonary function impairment.

3. Upper Instrumentation Level

It is the literature that shows that upper instrumentation does not affect cervical alignment, and it has. That is why it should be clarified with future prospective studies and later meta-analysis of these studies. In a study investigating the effect of the upper instrumented vertebra level on cervical sagittal alignment in Lenke 1 adolescent idiopathic scoliosis, the authors reported that T2-T3 instrumentation has a kyphotic effect on cervical lordosis, cause diminishing of T1 slope and T1-T5 kyphosis while t5-T12 kyphosıs was not affected(18). In contrast to this, Zhao et al. showed no relation between cervical kyphosis and upper instrumented vertebra in a study to investigate the effect of instrumentation of T2, T3, and T4 on the cervical spine of Lenke 1 AIS patients. Both groups were Lenke 1 AIS (19)

The only comparative study in instrumentation comparison Legaretta et al(20) also mentioned upper instrumentation level effect on cervical alignment. They showed that in either pedicle screw construct or hybrid techniques, the patients with upper-instrumented vertebra at T4 or below showed a lordotic effect that was more evident in the hybrid constructs (+9.4° ± 11.3 vs. +0.3° ± 11.4). In those with the upper-instrumented vertebra at T3 or higher levels, both techniques had a kyphotic effect that was more severe in the patients of the pedicle screws group (-7.0° ± 12.6 vs. -2.8° ± 10.5).

For Lenke type 3c and 6c curves where extensive fusions are needed to the proximal thorax, UIV level of T2, T3, T4 options did not significantly affect the absolute outcome of cervical kyphosis. It is essential to see that T5-T12 kyphosis has the primary responsibility in decreasing cervical lordosis; neither T1-T5 kyphosis nor upper instrumented vertebra could affect cervical kyphosis in this group(21). It makes it logical to choose UIV regarding to shoulder imbalance without an increased risk of cervical kyphosis. This is different from lenke 1 curves at where T2-T3 instrumentation has a significant kyphotic effect where T4 is spared(18). We also see in our cohort that T2 instrumentation has a kyphotic effect in lower cervical alignment, and most of the patients are in Lenke 1 group.

4. Proximal Junctional Kyphosis

Proximal Junctional Kyphosis is described as an increase of more than 10° of the sagittal Cobb angle between the inferior endplate of the upper instrumented vertebra and the superior endplate of two vertebras above between pre and postoperative measurements. PJK is not a complication only specific to the adult degenerative spine. (Fig 2) The etiology is multifactorial, and many risk factors have been described. One of them is the disruption of musculo-ligamentous and bony tissues above the UIV during surgery. If the elaboration of structural curves, especially on the sagittal plane done negligently, the fixation level could end up with C2 instrumentation(22). So it is crucial in an adolescent deformity that adequate preoperative planning, including clinical and radiological study, must be carried out, paying particular attention to the sagittal plane to identify major and minor structural curves.

Sun et al. (23) showed in thoracolumbar/lumbar AIS population that the location of the lower instrumented vertebra (LIV) above or equal to L3, a higher postoperative lumbar lordosis (LL), and a backward

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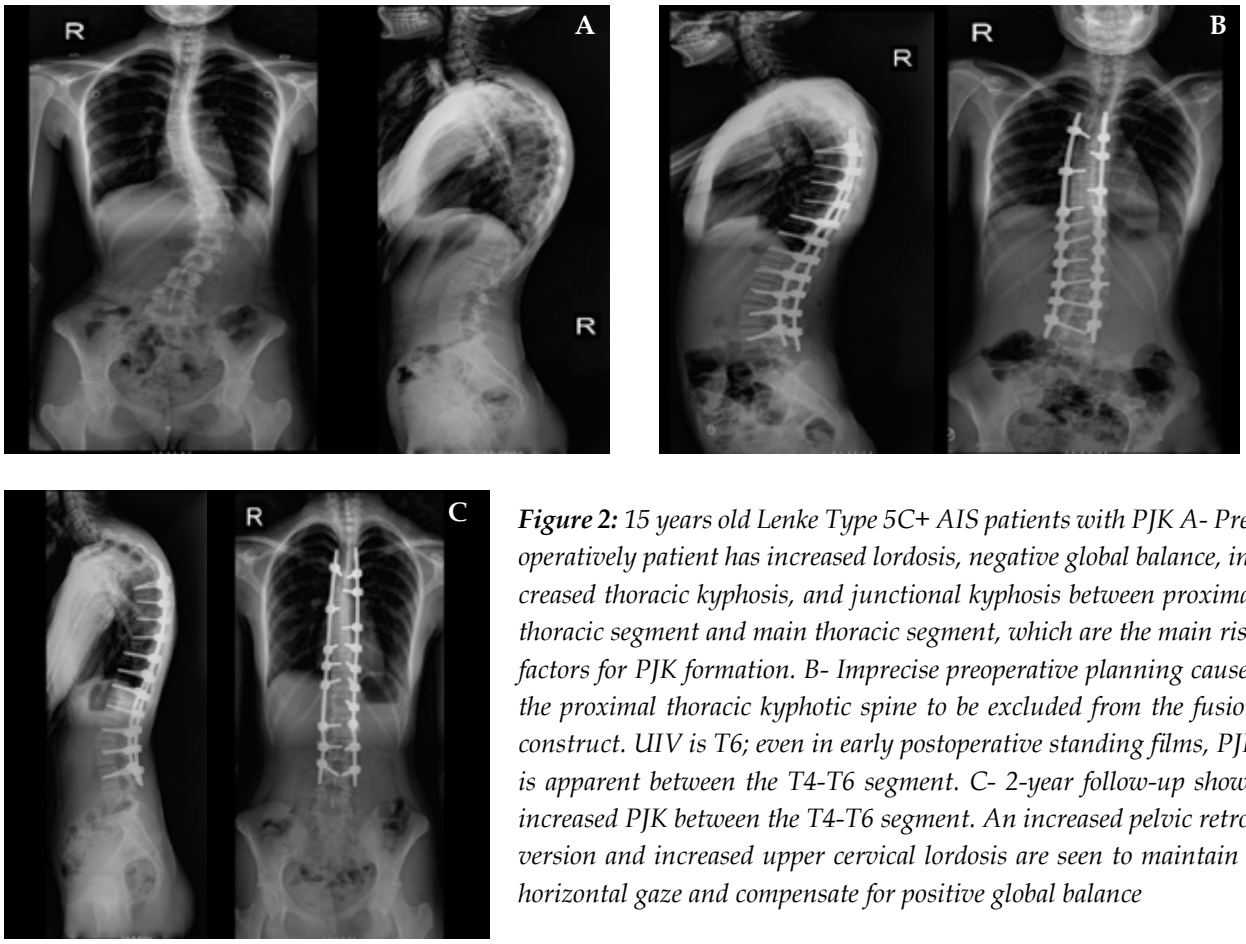

Figure 2: *15 years old Lenke Type 5C+ AIS patients with PJK A- Preoperatively patient has increased lordosis, negative global balance, increased thoracic kyphosis, and junctional kyphosis between proximal thoracic segment and main thoracic segment, which are the main risk factors for PJK formation. B- Imprecise preoperative planning causes the proximal thoracic kyphotic spine to be excluded from the fusion construct. UIV is T6; even in early postoperative standing films, PJK is apparent between the T4-T6 segment. C- 2-year follow-up shows increased PJK between the T4-T6 segment. An increased pelvic retroversion and increased upper cervical lordosis are seen to maintain a horizontal gaze and compensate for positive global balance*

change of SVA postoperatively were potential risk factors for the occurrence of PJK. Although we have not seen PJK in our cases if LIV is chosen as L2 or above it, we saw an increase in upper cervical lordosis to maintain horizontal gaze. We interpreted this as a compensation positive sagittal balance.

The position of UIV seems to be predictive in future sagittal alignment, basically through a proximal junctional angle (PJA). A larger anterior shift of the UIV in first erect X-ray relative to preop is highly related to PJK, affecting cervical sagittal alignment(24).

Ferrero et al.(25) investigate the risk factor for postoperative cervical decompensation in AIS. Fifty-seven patients have proximal junctional kyphosis (PJK) in 365 Lenke type 1 and type 2 groups. In patients with PJK preoperative Pİ, LL and C7 slope were significantly higher than the others. Postoperatively in this group, thoracic kyphosis did not change, the C7 slope decreased, and LL increased. The inflection point that resembles lumbar lordosis's transition to thoracic kyphosis is also located in more upper segments postoperatively. In patients without PJK, postoperative TK increased, LL did not change. In conclusion, the authors declared that increased lumbar lordosis (that causes posteriorly located negative spinal balance), insufficient compensation of thoracic segments to increased lordosis, and superior location of inflexion point make three risk factors for postoperative PJK in the AIS population.

Ghailane et al.(26) reported on the effect of hybrid construct on PJK, and they showed that no increase in PJK ratios with disruption of soft tissue above UIV, especially ligamentum flavum and posterior interspinous ligament, to put proximal anchors for curve correction. Interestingly in this fifty AIS population, they found out that the PJK angle was not statistically correlated to thoracic kyphosis changes, SVA changes, or LL changes.

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5. Instrumentation relation

After the introduction of thoracic pedicle screw instrumentation, an increasing number of literature query its hypokyphotic effect on already decreased thoracic kyphosis. In concordance with this, cervical sagittal alignment also comes into the attention of authors after the results of flat spine cases published(27). Legaretta et al.(27) showed that although the cervical spine tends to decompensate and acquire a kyphotic sagittal profile regardless of the surgical technique used, the hybrid system is better in terms of cervical kyphosis correction when compared to all pedicle screw construct due to their thoracic kyphosis recreation effect. They also noticed for further surgeries that instrumentation above the T4 level has a cervical kyphotic effect and suggests it should be avoided if it is possible. Similarly, in another study, cervical lordosis after thoracic instrumentation was best accomplished with hybrid instrumentation compared to all pedicle screw constructs(28). The authors also showed a gradual increase in cervical lordosis postoperatively in 2 years.

Another study investigated the hypokyphotic effect of the pedicle screw construct and showed that the low-density strategic pedicle screw construct system is favorable in terms of avoiding hypokyhosis. They also reported favorable sagittal pelvic parameters regarding increased sacral slope and correction of pelvic retroversion(29). To summarize, they showed low-density constructs favorable in avoiding flat back with sufficient coronal plane correction. Charles et al.(30) howed improved cervical lordosis with instrumentation of hybrid construct and in situ bending in 52 idiopathic scoliosis cases. They also subdivided the population into five distinctive cervical alignment profiles; lordotic,hypolordotic, kyphotic, sigmoid with cranial lordosis, sigmoid with caudal lordosis.

In contrast to previous studies, Berger et al.(31) showed improved cervical lordosis after pedicle screw instrumentation in Lenke 1 curves. However, they did not stratify the population into who have Ponte like osteotomies, which is done with the intention to improve thoracic kyphosis.

Simultaneous double rod rotation technique (SDRRT) has improved to restore normal thoracic kyphotic alignment in the AIS population. It is published in the literature that SDRRT increased both hypokyphotic and normokyphotic spine into a more harmonious sagittal plane by an increase in lower cervical lordosis and a decrease in compensation of upper cervical lordosis.(32)

6. Miscellaneous Topic

Cervical sagittal configuration changes after AIS surgery seem to be related to the instrumentation of the thoracic curve, but this is not always necessary. A recent article from Tauchi et al. (33) howed that cervical alignment correction could be achieved with selective instrumentation of Lenke 5c curves. Also, the sagittal modifier negative group has achieved better results in the correction of normal spinal curvatures. Another study of Yan et al. (34) showed that lumbar AIS patients maintain larger cervical lordosis degrees than thoracic AIS patients at 2-year follow-up. Even though both groups have improved cervical lordosis, this is due to preoperative better cervical lordosis in lumbar AIS patients.

It is not only sagittal plane changes that affect cervical sagittal alignment. Coronal plane deformities also have an impact on cervical sagittal alignment. Tang et al.(35) showed in a descriptive study of AIS and normal population comparison, coronal plane changes such as apical vertebral translation, T1 coronal tilt, and lumbopelvic relationship are different in the cervical kyphosis group compared to the cervical lordosis group. In another study, there is a significant correlation between the high coronal thoracic curve and CK prevalence, not with positive cervical sagittal balance (36) Preoperative greater proximal thoracic curve magnitude and C2-C7 lordosis are the risk factors for aggravation of cervical sagittal alignment (CSA)(37). Although improvement was seen in CSA, %54,4 of patients still have cervical kyphosis after AIS surgery, and SRS-22 scores showed no difference based on the CSA in this study cohort.

Conclusion

It seems like cervical sagittal balance still will be one of the main topics of spine authors in future studies. Prospective studies will be more convincing since retrospective studies show the opposite results. A meta-analysis of future prospective studies will clarify

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the confusion on upper instrumentation level effect on CSB, implant choice of instrumentation, PJK reasons, correlation with global spine balance, and finally, relationship with whole-body alignment. Correction of thoracic hypokyposis, especially proximal thoracic, could stimulate cervical lordotic changes over time. Flattening of the entire spine either by surgery or bracing ends up with cervical kyphosis.

Conflict of interest

The authors declare no conflicts of interest.

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Current Concepts in Pathogenesis and Biomechanics of Adolescent Idiopathic Scoliosis

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ABSTRACT

Considerable progress has been made in the past two decades in understanding the pathogenesis and biomechanics of adolescent idiopathic scoliosis (AIS). Biplanar asymmetry has long been considered as the essential of idiopathic scoliosis. Median plane asymmetry is crucial for progression of idiopathic scoliosis.The presence of thoracic lordosis or hypokyphosis has been emphasized in the development of AIS. The changes in the cartilaginous endplate and the intervertebral disc are key factors in the progression of scoliosis and the way the curve responds to different therapeutic regimens. This article aims to analyze the current concepts in pathogenesis and biomechanics of AIS as well as to describe conservative and surgical treatment biomechanics. Biomechanical differences between AIS and degenerative scoliosis are also analyzed.

KEY WORDS: biomechanics, adolescent idiopathic scoliosis, classification, rotational imbalance

Introduction

Idiopathic scoliosis is classified into three types according to the age of onset: infantile (0-3 years old), juvenile (4-9 years old), and adolescent (10 years old to skeletal maturity) [1-3] with adolescent idiopathic scoliosis (AIS) being the most frequent type. With the general belief that AIS is a multifactorial disorder, it is likely that its pathogenesis involves different degrees of interaction between different factors in linear and summation causality [4].

Classification systems of AIS include Ponseti, King, Lenke, Peking Union Medical College, and Three-dimensional classification. Nowadays, Lenke's classification [5] is the most commonly. The six curve types of Lenke's classification are summarized in Table 1.

This article aims to analyze the current concepts in pathogenesis and biomechanics of AIS as well as to describe conservative and surgical treatment biomechanics. Biomechanical differences between AIS and degenerative scoliosis are also analyzed.

Biomechanics of AIS

Biplanar asymmetry has long been considered as the essential of idiopathic scoliosis [6]. Median plane asymmetry is crucial for progression of idiopathic scoliosis.

The presence of thoracic lordosis or hypokyphosis has been emphasized in the development of AIS [6]. Lordosis can be defined as the deviation of the scoliotic spine that occurs with axial rotation of the vertebral bodies towards the convexity of the lateral curve,

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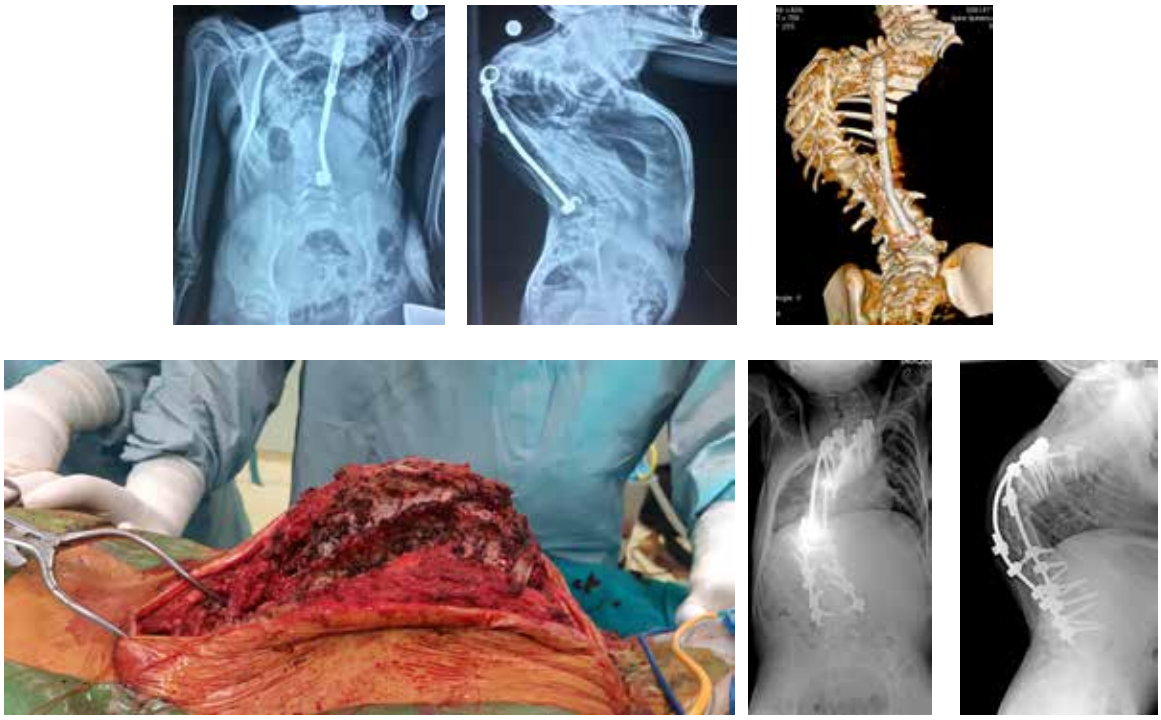

Figure 1. *A simple mathematical model for the investigation of the efficiency of different loads to correct a scoliotic curve. Taken from: White AA, Panjabi MM. Clinical biomechanics of the spine. JB Lippincot Co. Philadelphia, Toronto, 1990.*

producing a three-dimensional deformity in which the vertebral bodies form a greater arc than the posterior structures.

Median plane asymmetry is characterized by increased anterior vertebral height at the apex of the curve and posterior end-plate irregularity [7]. The vertebral bodies have a faster growing rate than the posterior elements [8]. This discrepancy in growth between the anterior and posterior elements is of unknown etiology and results primarily in lordosis. The slower growth of the posterior elements impedes the vertebral bodies from increasing in height, forcing them to become distorted in order to create space for themselves. This, in turns, results in rotational lordosis [7].

Regarding the pathomechanism of AIS, the concept of a primary skeletal change which affects the sagittal plane of the spine with anterior increments and posterior decrements of vertebral growth has been adopted. In a study of 2003 [8], after applying whole spine MRI in female patients with AIS, the investigators concluded that the scoliotic spines have longer vertebral bodies, shorter pedicles, and larger interpedicular distance than the normal spine. It was also noticed that the ratio of anteroposterior vertebral body components correlated significantly with the severity of scoliosis. The authors, after comparing age-matched females with scoliotic or normal spines, suggested that the longitudinal growth of the vertebral bodies is faster and disproportionate in scoliotic spines and mainly occurs by endochondral ossification. On the other hand, the circumferential growth by membranous ossification is slower in females with AIS when compared with normal controls in both vertebral bodies and pedicles.

According to a study of 2011 [9], the direction of the spinal curve in idiopathic scoliosis is determined by the rotational pattern that the spine exhibits at the time of onset. The predominance of right sidedthoracic curves in adolescent idiopathic scoliosis and left-sided curves in infantile idiopathic scoliosis can be explained by the observed patterns of vertebral rotation that preexist at the corresponding age. The rotational pattern in nonscoliotic adult spines that corresponds to the most common curve types of AIS, i.e. the right sidedthoracic curve, is predominantly seen in females [10].

The vertical position of the spine results in reduced anterior shear forces as compared to the horizontally positioned (quadruped) spine. In case of a backwardly declined vertebra, e.g. during growth, anterior shear

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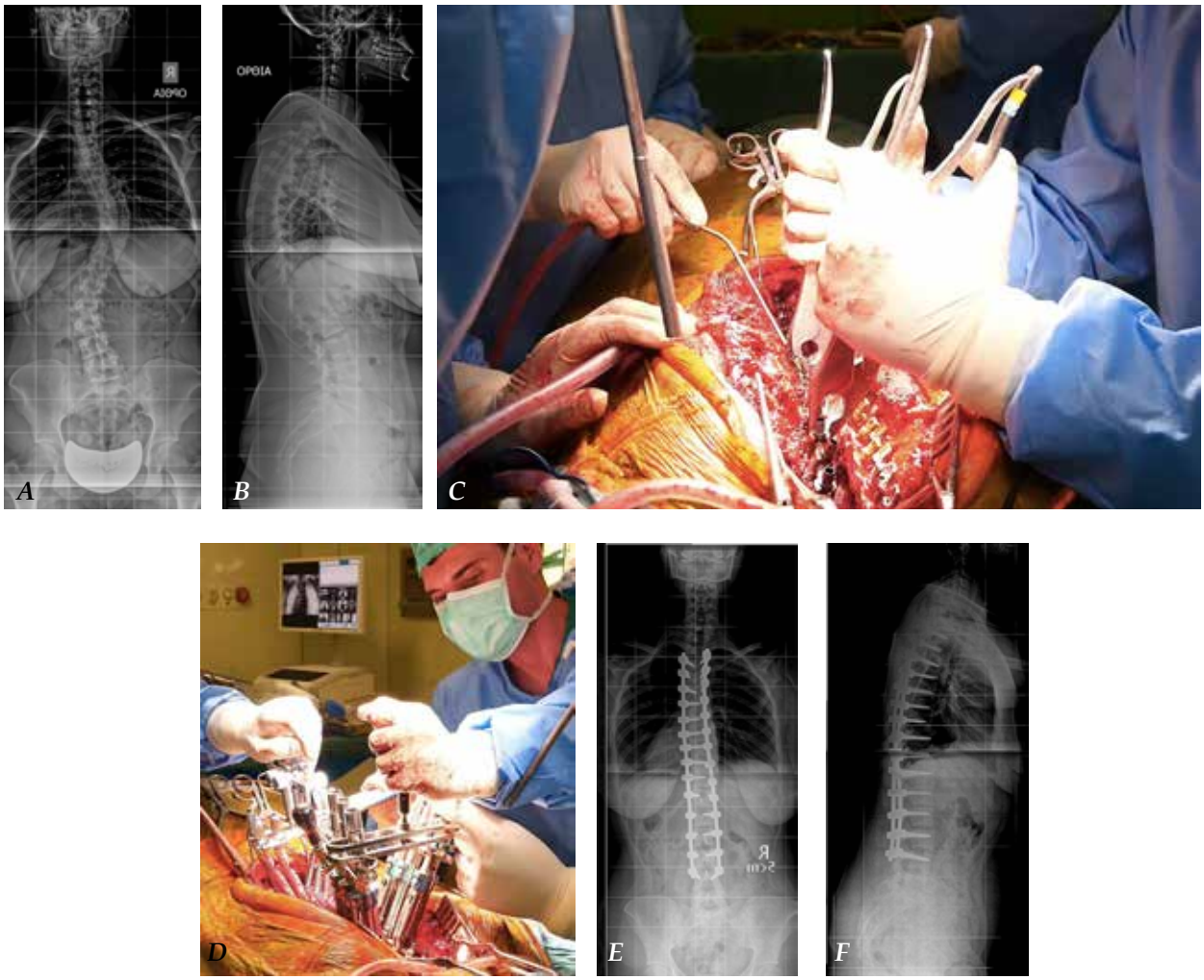

Figure 2. *Anteroposterior (A) and lateral (B) x-rays of a 16 year-old girl with AIS. Her right thoracic curve measured 58° and her left lumbar curve 50°. Intraoperative pictures showing three dimensional deformity correction with rod derotation maneuver (C) and apical vertebra derotation (D) using the VCM system (Medtronic, Memphis, USA). One year after posterior spinal fusion from T4 to L3, anteroposterior (E) and lateral (F) x-rays revealed a right thoracic curve of 6° and a left lumbar curve of 0°.*

forces are reduced further and may turn into dorsal loads [11]. In this case, a slight preexisting vertebral rotation may be enhanced resulting in a progressive deformation of the backward inclined growing spine because of the Hueter-Volkmann principle. Facet joints contribute significantly to rotational stability of the spine. In the upright position, anterior shear forces diminish and may even turn into dorsally directed forces. When the anterior shear forces become negative, the stabilizing mechanism of facet joints is diminished androtational imbalance must be counteracted by internal forces (strains). Inevitably, this will result to asymmetric loading in the transverse plane of the vertebrae, intervertebral discs, and attached ligaments, enhancing slight pre-existing asymmetries [11].

The intervertebral disc is also involved in biomechanics of idiopathic scoliosis. The intervertebral disc becomes significantly and irreversibly wedged in patients with progressive scoliosis [12]. However, intervertebral disc wedging is not considered a primary factor but a contributing variable to the deformity [13]. It is very likely that the changes in the cartilaginous endplate and the intervertebral disc are key factors in the progression of scoliosis and the way the curve responds to different therapeutic regimens [14]. An increased torsional rigidity of the intervertebral disc

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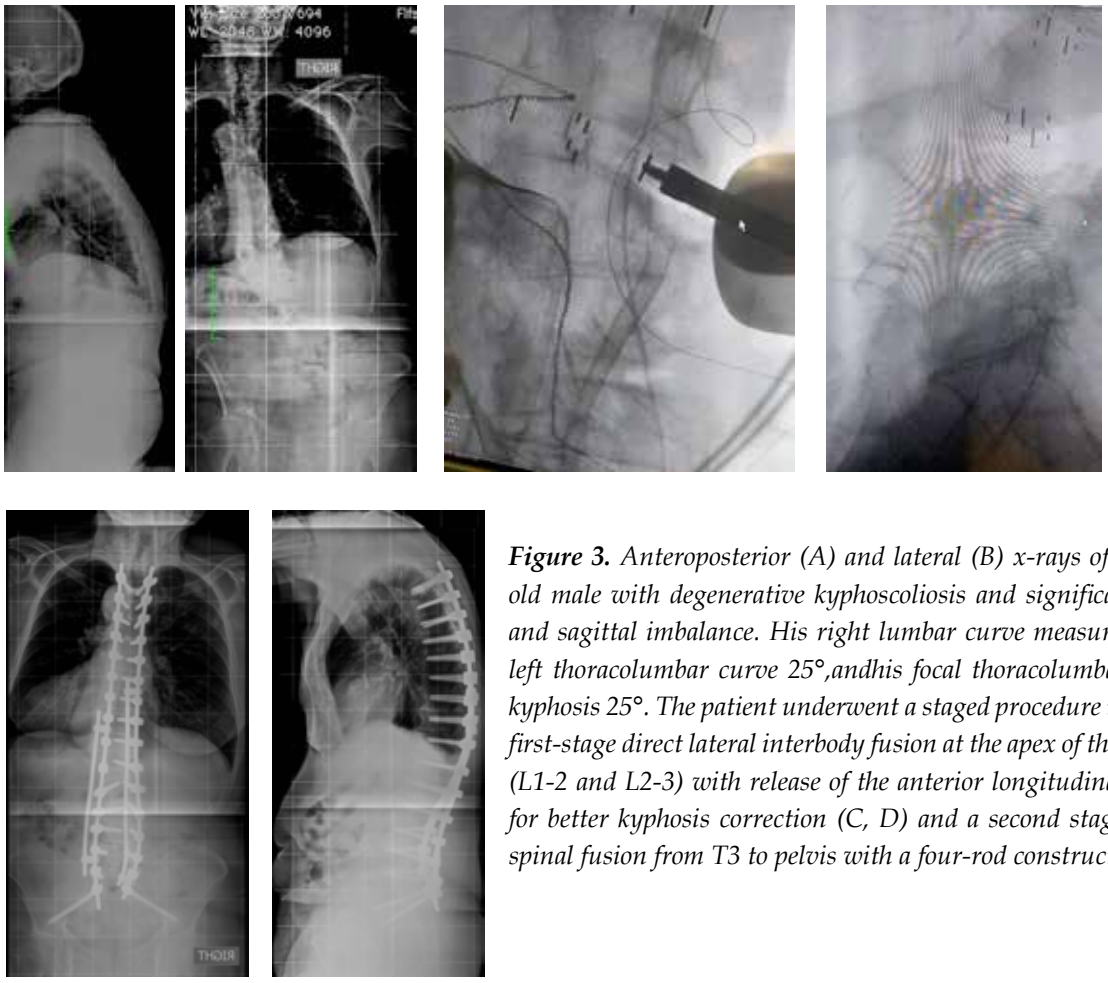

Figure 3. *Anteroposterior (A) and lateral (B) x-rays of a 72 year-old male with degenerative kyphoscoliosis and significant coronal and sagittal imbalance. His right lumbar curve measured 30°, his left thoracolumbar curve 25°,andhis focal thoracolumbar junction kyphosis 25°. The patient underwent a staged procedure including a first-stage direct lateral interbody fusion at the apex of the deformity (L1-2 and L2-3) with release of the anterior longitudinal ligament for better kyphosis correction (C, D) and a second stage posterior spinal fusion from T3 to pelvis with a four-rod construct (E, F)*

throughout growth that favors the progression of early scoliotic curves has been reported [15].

In 2006 [16], 70 children with a scoliotic curve were reviewed in order to investigate whether the deformation of the intervertebral disc contributes to the progression of idiopathic scoliosis. The authors concluded that the adjacent to the apical vertebra intervertebral disc wedging is a more important parameter in the progression of idiopathic scoliosis than the apical vertebral wedging, which appears later when the Cobb angle has already increased. Idiopathic scoliosis is associated with distinctive intravertebral deformity, with smaller pedicles on the concave side and a shift of the dural sac toward the concavity [17]. These findings highlight the importance of the intervertebral disc in idiopathic scoliosis pathogenesis and biomechanics.

Biomechanics of treatment

The main goal of treatment is to return the spine to a normal configuration. Several techniques with correcting loads have been proposed in order to correct the deformities in idiopathic scoliosis with either surgical or non-surgical measures.

Conservative treatment of idiopathic scoliosis involves stabilization of the unstable spine and transmission of forces that could restore the natural geometric configuration.

Bracing

A simple mathematical model proposed for the investigation of the efficiency of different loads to correct a scoliotic curve is composed by 2 rigid links (AC and AB) connected at C by way of a torsional spring in the coronal plane (Fig. 1). When the spine is subjected to a transverse force (F) at point C, reactive forces equal half of the force applied (F/2) are taken up at points A and B (Fig. 1C). The corrective bending moments created at the disc spaces allow angular correction of the

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TABLE 1.

Curve types according to Lenke's classification

Curve Type	Curve Name	Proximal Thoracic (PT)	Main Thoracic (MT)	Thoracolumbar/ Lumbar (TL/L)
Type 1	MT	-	Structural	-
Type 2	Double Thoracic	Structural	Structural	-
Type 3	Double Major	-	Structural	Structural
Type 4	Triple Major	Structural	Structural	Structural
Type 5	TL/L	-	-	Structural
Type 6	TL/L-MT	-	Structural	Structural

curve in the frontal plane. The corrective bending moment at the apex can be calculated by multiplying the half of the transverse force (F) applied by the perpendicular distance to the apex of the curve (D). The corrective bending moment decreases as the perpendicular distance to the apex, and thus, the deformity increases. This type of loading is utilized in conservative management of scoliosis with bracing. Scoliotic spine response to brace treatment is determined by two factors: 1) the vertebrae remodeling capability in accordance with the Hueter-Volkmann principle and 2) the capability of the viscoelastic structures to react to the imposed actions appropriately. No mechanical action can produce the remodeling process without an adequate response from the viscoelastic structures involved. These structures, and in particular the intervertebral disks, can modify the areas subject to tension concentration by absorbing and by redistributing the actions of the brace on a singular vertebra [18].

Similar to transverse loading, when axial loading is applied at the cephalad and caudal end vertebrae (points A and B in Fig. 1B), corrective bending moments are created at the various disc spaces correcting the spine deformity. The corrective bending moment created at the apex of the curve equals the axial force (F) multiplied by the perpendicular distance to the apex of the curve (D).

Surgical

Segmental fixation with hooks has been gradually replaced by pedicle screw fixation which, theoretically, provides stronger biomechanical fixation and allows improved three-dimensional correction and maintenance of the spinal deformity [19-21]. In a comparative study [22] of different implant densities, the difference in the density of screws did not lead to significant difference as far as it concerns the main thoracic Cobb angle and the main thoracic apical axial vertebral rotation. There were also on average 13% more pedicle screws and 30% more bilaterally placed pedicle screws in the higher versus lower density group. The authors concluded that with the same fusion levels, lower density screws allowed achieving similar deformity correction and it was more likely to have lower screw-vertebra loads. During the last years, the three dimensional deformity correction with segmental pedicle screw fixation has gained supporters, since the rod derotation maneuver enables a powerful coronal and sagittal plane correction as well as rotational correction in the axial plane,replacing distraction or supplementing it as current method of correction (Fig. 2).

The basic biomechanics of a pedicle screw are based on the following parameters:

- The outer diameter of the screw determines the pullout strength, while the inner diameter the fatigue strength
- When inserting a pedicle screw, the dorsal cortex of the spine should not be violated and the screws on each side should converge and be of adequate length

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- Rotational stability can be improved by adding transverse connectors [23]

Pedicle screw is considered biomechanically advantageous compared to the hybrid hook-screw system, since the pedicle is the hardest part of the vertebra [24]. In a retrospective comparative study of 58 patients with AIS treated with either pedicle screw or hybrid instrumentation, Kim et al. [25] found that immediately after surgery average major curve correction was 70% for the pedicle screw group and 56% for the hybrid group. Significant difference between the 2 groups was also noted at 2-year follow-up, with the all-pedicle screw construct achieving 65% of correction and hybrid instrumentation 46%. In another comparative study of patients with AIS treated with pedicle screw or hybrid instrumentation with a mean follow-up of 41 months [24], the authors demonstrated the ability of the all pedicle screw construct to fulfill the long-term traditional goal of scoliosis surgery: maximum coronal plane correction and prevention of deformity progression while maintaining balance. In the sagittal plane, although both systems achieved similar correction of lumbar lordosis, the hybrid construct was found to have less kyphogenic potential to the thoracic spine than the pedicle screw system.

Biomechanical differences between AIS and degenerative scoliosis

In contrast to AIS, in which the main deformity component is rotational lordosis, degenerative scoliosis has a rotational and a kyphotic component. The rotational deformations are manifestations of an asymmetrical load or a rotatory load applied to a spinal segment. The application of a rotatory or torsional load to the spine can cause the spinal segments above the unstable segment to rotate in an opposite direction to those below the unstable segment. At the thoracolumbar spine, the disc degenerative changes are directly related to the development and progression of scoliotic curves (Fig. 3).

In contrast to AIS, in which the intervertebral disc is not a primary factor but consists a contributing variable to the deformity, in the degenerative form of scoliosis the changes of the intervertebral disc play an important role in the development of spinal deformity. In 1995 [26] it was suggested that flexion-extension, lateral bending and axial rotation decrease on an average of 23%, 31% and 25%, respectively for patients more than 50 years of age compared with patients 20-29 years of age. By aging, the intervertebral disc progressively loses its viscoelastic properties which results in decreased shock absorption and uneven stress distribution [27]. The dehydration of the nucleus pulposus results in reduced intradiscal pressure which along with the thinning of the cortical bone may cause anterior wedging of the vertebral body and kyphotic deformity.

Conclusion

Considerable progress has been made in the past two decades in understanding the pathogenesis and biomechanics of AIS. Biplanar asymmetry has long been considered as the essential of idiopathic scoliosis. Median plane asymmetry is crucial for progression of idiopathic scoliosis. The changes in the cartilaginous endplate and the intervertebral disc are key factors in the progression of scoliosis and the way the curve responds to different therapeutic regimens.

Conflict of interest

The authors declare no conflicts of interest.

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REVIEW ARTICLE

Degenerative Lumbar Spinal Stenosis. When and How Should We Operate On

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ABSTRACT

Lumbar Spinal Stenosis is a degenerative spinal condition affecting 50% of patients usually over 50 years. Is considering the end result of the degenerative cascade with compression of neural tissues by disc displacement anteriorly and by hypertrophy of facet joints and ligamentum flavun posteriorly. The main symptom except Low Back Pain and sciatica is the Intermitted Claudication. There is no always correlation between clinical symptoms and the degree of stenosis in imaging studies. The natural history of LSS is unpredictable but some patient can be benefitted by the conservative treatment. We have to be aware from Cauda Equina Syndrome which is more insidious in LSS. Treatment options range from conservative to surgical according the degree of stenosis and the severity of clinical symptoms. In this article are described the surgical techniques for decompression and the indications for concomitant arthrodesis in cases of instability and deformity.

KEY WORDS: Low Back Pain, Stenosis, Intermitted Claudication, Arthrodesis

Introduction

Lumbar Spinal Stenosis (LSS) is a common disease, that affects usually people over 50 years old. It is a degenerative disease causing changes, in the disc, ligamentum flavum and facet joints with aging, leading to narrowing of the Spinal Canal. First described by H.Verbiest, (1954) as a developmental narrowing of the Lumbar vertebral canal.

The narrowing of the Central canal, lateral recess and foramina, produces symptoms of pain in the legs and back.

The main symptom that forces patient for medical consultation and spine surgery is neurogenic claudication, which is aggravated with prolonged walking and standing relieving by sitting and flexion, due to the central canal stenosis.

When the lateral recess and neural foramina are narrowed,gives rise to symptoms of lumbar radiculopathy.

So the spinal stenosis is distinguished in central and lateral. (1) One of the causes of LSS is the loss of Lumbar Lordosis due to degenerative Disc disease. This leads to hyperextension to compensate with a final result an unbalanced spine. (Fig. 1)

Spinal stenosis is considered as a significant cause of disability in the elderly and the most usual in-

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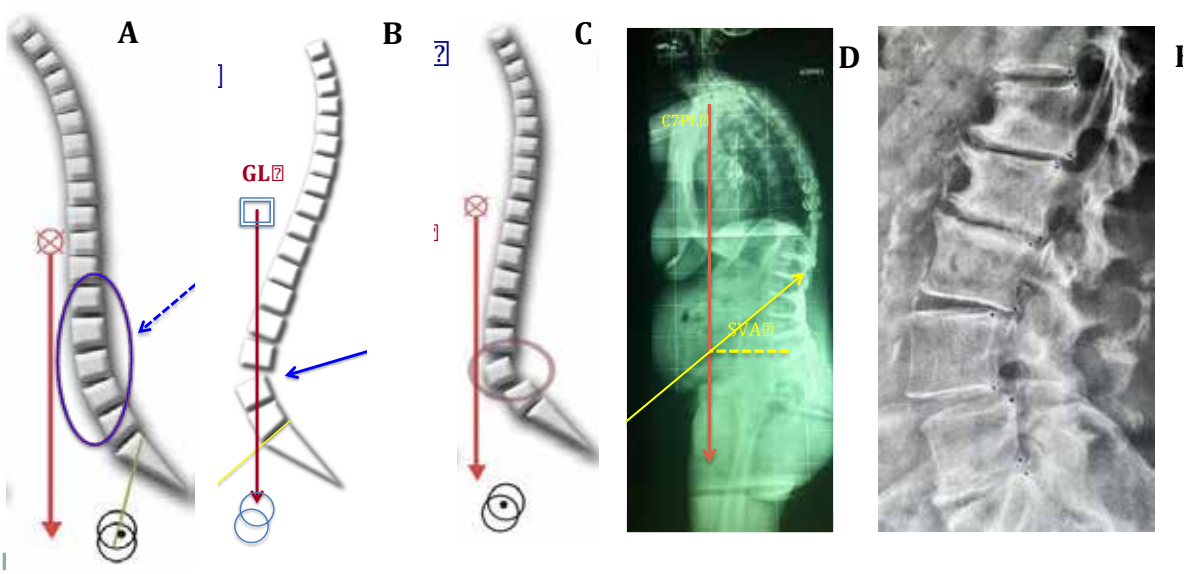

***Fig 1. A** Loss of Lordosis.**B.** Reaction by hyperextension. **C.** Compensation. **D.** Unbalanced spine. **E.** Retrolisthesis,Spondylolisthesis Unbalanced Spine*

dication of spinal surgery in patients over 65 years old.

Clinicians should be very careful, first to diagnose and second to treat LSS effectively.

Etiology:

With aging there is significant degeneration of the intervertebral disc that protrudes posteriorly affecting the mechanical balance of the spinal unit, leading to increased loading of the posterior elements of vertebra (Facet Joints).

These changes lead to osteophyte formation, facet joint hypertrophy, synovial cysts and ligamentum flavum hypertrophy and buckling, which in turn cause spinal stenosis.

Epedemiology

The prevalence of LSS is estimated to be 9% in the general population and up to 47% in people older than 60 years.

Has described by Verbiest as an anatomical concept to a poorly defined Clinical Syndrome.

There is a lack of universally accepted definition of LSS and is difficult to determine the exact epidemiology. In a study (ancillary Framingham Study) (1) where subjects underwent a CT-Scan to determine the central AP diameter of the spinal canal, absolute LSS was defined as diameter <10mm. The prevalence of acquired Lumbar Stenosis was 19.4% for population between 60-69 years and increases with ageing

Developmental Stenosis

Lumbar Spinal Stenosis can be related to congenital malformations of the posterior structures of the Spine which are manifested as Short pedicles and laminae. (2)

In Developmental Spinal Stenosis pre-exists a narrowed spinal canal that makes the neural elements prone to compression and hence stenosis symptoms. The imaging and clinical presentation is similar to degenerative type. Patients may experience claudication and radicular symptoms at multiple levels similar with patients suffering from achondroplasia. Due to multiple levels of narrowing , this group of patients are more susceptible to restenosis after surgical treatment. It is known that the pedicle as a unique structure has increasing widths progressing from cranially to caudally. This explains why the stenotic manifestations are in the Lower Lumbar Spine and especially at L4-L5, in comparison with L5-S1 segment which is more stable due to stabili-

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zation effects on L5 vertebra by the iliolumbar ligaments. Many papers suggest that developmental stenosis play an important role in lumbar spinal stenosis. Critical stenosis has been defined as <14mm at L4,<14mm at L5 and <12mm at S1 (3)

Diagnostic Criteria

There is an heterogeneity of the condition and standard criteria for diagnosis.

Lumbar Spinal Stenosis (LSS) is currently recognized by North American Spine Society as a clinical syndrome of buttock or lower extremity pain which can occur without back pain, associated with diminished space available for the neural and vascular elements in the lumbar spine.ISSL 2019,(4) Deyo et all 2010)

Currently diagnosis is based on a complex integration of factors, including history, physical examination and imaging studies.

In order to be able to refine outcomes assessment and to have more cost effective and targeted clinical care, it is imperative to define a core set of Diagnostic criteria.

In the absence of valid objective criteria it has been suggested that experts opinion be considered the criterion standard for diagnosis LSS.

According the ISSLS paper (4) a set of questions was sent to international experts (20 spine surgeons) on which factors obtained from the history, are the most important for clinical diagnosis of LSS.

The results suggest, that within six questions, clinicians were 80% certain of diagnosis.

The most important history item, including leg or buttock pain while walking, flex forward to relieve symptoms, feels relief when using a shopping cart or bicycle, and motor or sensory disturbance while walking, normal and symmetric foot pulses, lower extremity weakness and low back pain.

Evaluation

There is no doubt, that in patients with a history and physical examination findings consisted with LSS, **MRI** suggested as the most appropriate and non invasive test to confirm the presence of anatomic narrowing of the spinal canal or the presence of nerve root entrapment (NASS). While MRI is considered the Gold Standard, the CT-Scan is helpful in recognizing the bony structures and to plan screw insertion in cases of instrumented fusion. (5)

CT-Myelography is an option when MRI is contraindicated.

Many authors use an intraspinal canal area of less 76mm2 and an AP diameter of <10 mm to characterize moderate to severe LSS. Many times we need a truncal or full body X-Ray to assess the sagittal balance (Fig.2)

On the other hand we must to know that LSS is a common radiological finding in people over 60 years old and there is a lack of correlation between the severity of imaging studies versus the symptom severity reported by patients.

In a study by Boden, (1990) MRI findings of asymptomatic subjects older than 60 years were found to be abnormal on 57% of scans and up to 21% had radiological spinal stenosis. EMG and nerve conduction studies are also used to aid the diagnosis, but mainly to distinguish, polyneuropathy, radiculopathy or other peripheral nerve disorders. EMG exams are often normal in patients with LSS and the decision to proceed or not to decompressive surgery it is not possible to rely on it.

Treatment Options

Conservative vs Surgical treatment

The aim of management of LSS is to reduce symptoms and improve the functional outcome.

Conservative treatment is considering as the first line treatment for this condition.

The usual conservative treatment options consisted of various approaches, including non-steroid anti-inflammatory drugs, epidural injections, physiotherapy, lifestyle modifications and multidisciplinary rehabilitations programs.

The problem with conservative treatment arises, when comparing the results with the surgical treatment, because there is no a description of the specifics of non operative treatment or what kind of physiotherapy was applied.

There is no a real protocol of the different modalities applied in various ways and case by case.

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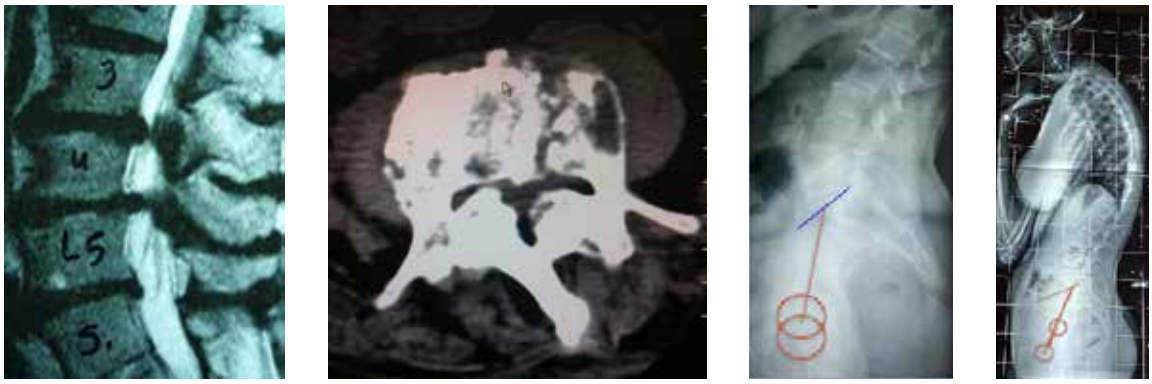

Fig .2 *MRI and CT-Scan of LSS. Plain X-Rays are essential especially whole body in upright position to study sagittal balance*

On the other side, it is understandable that conservative treatment approaches are multimodal involving different manipulations

Whereas for the surgical procedures there is available a very precise description in all the included studies, the prescription of conservative treatment is poor or absent in all studies.

In a paper by Kovacs et all (6) Spine 2011, in a systematic review of randomized trials comprised five high quality RCTs, including 918 patients, comparing surgery (Interspinous devices or decompressive surgery with or without fusion) versus miscellaneous conservative treatment that had failed for 3-6 months, the conclusion was that decompressive surgery with or w/o fusion and an interspinous device are more effective than continued conservative treatment for radicular pain due to spinal stenosis.

In an other study by Gen Innoue et all (5) 2016 comparing surgical and non surgical treatment for LSS (Review of numerous studies including RCTs) the decompressive surgery has the strongest evidence base for patients with LSS who do not improve after conservative treatment.

In a systematic review by Fabio Zaina et al (7) Spine 2016, from 12.966 citations they included five RCTs with 643 participants (322 surgical 321 non operative)

In this review there is a disagreement with other studies, where they found more evidence in favor of surgical approach.

-Their conclusion was: Current evidence by comparing surgical vs non surgical treatment care for LSS is of low quality and it cannot conclude whether surgical or conservative approach is better for LSS nor can we provide new recommendation to guide clinical practice.Given the high rates of side effects (10-24%) associated with surgery, clinicians should be cautious when proposing surgery and patients properly informed about the risks.

-On the other hand, we know that there is severe and mild lumbar stenosis with mild or severe symptoms.

There is no a standard morphologic description in the RCT studies for the group which underwent the standard decompressive surgery. So when speaking for RCTs studies it should be a randomization of the patients irrespective of the spinal stenosis severity. But this is an unethical randomization, by knowing in advance that severe stenosis is not going to lead in a improved outcome.

Indications for Surgical Treatment

It depends on clinical symptoms. As was already mentioned, the classical symptom in LSS is the neurogenic claudication. We have to clarify if there is any sciatica. LBP or other symptoms. Before decided to proceed with surgery, a period of at least 6 months of conservative treatment of any kind, is preceded.

The patient is submitted in a full range of imaging examination, despite the MRI is suggested as the most appropriate and non invasive test, to confirm the narrowing of the spinal canal and foramina.

Plain X-Rays dynamic or not and CT-Scan are

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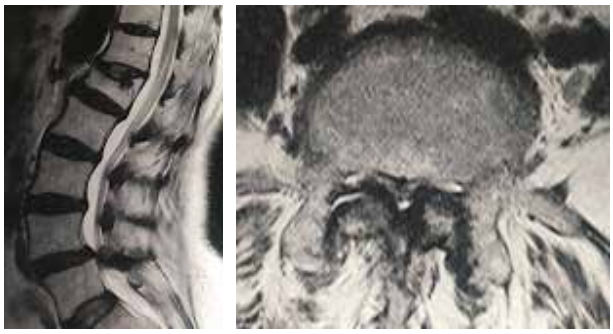

Fig. *3 Deg. Spondylolisthesis*

very helpful to recognize a deformity (Scoliosis degenerative or existed) and any kind of instability, like Degenerative or Lytic spondylolisthesis.

The clinical symptoms must correlate with imaging pictures.

But is it the rule? The answer according the literature is no. This is because the AP diameter and cross sectional area fail to take into account the degree of nerve root entrapment.

-In a paper by Clemens Weber et al (8) (Spine 2016) they concluded that there is no association between severity of Spinal Stenosis on pre-op MRI and pre-op Disability, pain or surgical outcomes. There is no clear correlation and should not be overemphasized, and clinical factors are more important than imaging findings for deciding surgical treatment or predicting outcomes.

In the MRI picture (Fig 3) is depicting a Lady 85 years old today with LSS due to degenerative Spondylolisthesis L4-L5, diagnosed 10 years ago, without aggravation in clinical and imaging picture. (Schizas Classification D)

-In order to decide a Decompressive surgery, we have to rely in objective criteria except the clinical ones. As already mentioned the AP diameter and cross sectional area it is not possible to guide us, because fails to take into account the degree of root entrapment.

So a decade ago has been proposed a morphological classification that grades the CSF content of the spinal canal. This helps for clinical decision making and is linked with the risk of failure of conservative treatment (Fig.4)

They defined (K.Schizas et all Spine 2010) (9) grade A as no or minor stenosis. Grade B as moderate stenosis, C as severe stenosis and D as extreme stenosis. According the classification Grade C and D is an indication for surgery.

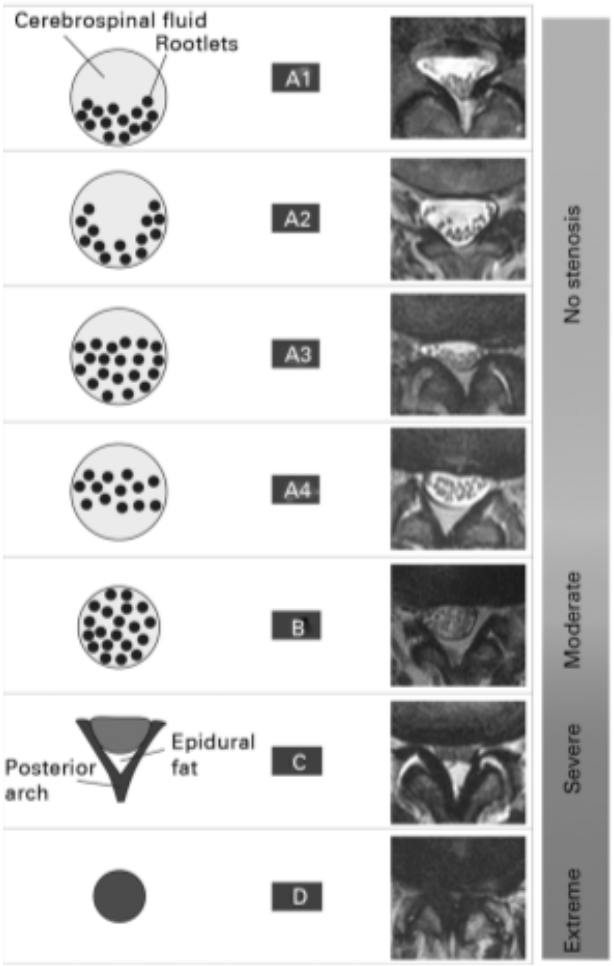

Fig 4. *K.Schizas's Classification of LSS. Courtesy by prof K. Schizas*

Surgical Treatment Options

The decision is based on symptoms severity. Which is the main symptom? Low Back or Buttock Pain, Neurogenic Claudication, Radiculopathy or all of them. How we can address it?

The second question or dilemma, if there is any concomitant deformity, as Degenerative Scoliosis or Sagittal Imbalance, or Lumbar instability (Degenerative or Lytic Spondylolisthesis). Decompression is considered the natural treatment or the gold standard, but simultaneous arthrodesis has been advocated by those who believe that pain is related to osteoarthritic changes at the facet joints. Fig.5

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The rational for sole decompression

The stability of the decompressed spine can be maintained with meticulous operative technique. This is based on, to pay attention and respect on removing <50% of the facets joints. Kanamori et al (10) proposed the Trumpet Technique with preservation at least 50% of the facet joins. (Fig 6)

Kleeman et al 2000 (11) proposed the "Port-Hole" Technique with laminectomies in both sides, preserving the facet joints (Fig.6)

In addition in the elderly patients, the degenerative changes, (Decreased Disk Height, osteophytes, calcified ligaments) increase the stability of the Spin

The Rational for Concomitant Arthrodesis

Arises from the necessity to treat the LBP or Instability caused by degenerative or Isthmic Spondylolisthesis, degenerative scoliosis and Sagittal Imbalance. Especially for Degeneratve Spondylolisthesis one of the main causes of central and lateral spinal LSS, there is abundant literature, proposing concomitant arthrodesis. On the other hand there is an international debate, to fuse or not to fuse after decompression, because sole decompression can lead to further destabilization.

There is a rule, supported by many authors, by making dynamic X-Rays in flexion-extension and if there is a translation >3 mm and >10* angular deformity, then the indication is to fuse. There is and an other opinion supported Fusion, and proposed by Postacchini et al Spine 1991,that continuous motion at the stenotic segment may produce osteophytes and bone regrowth or progressive translation and compression of the nerve roots.

Conventional Laminectomy

There is concern how much Laminectomy can cause damage to the posterior structures , that provide stability. (Facet joints, Ligaments and paraspinal muscles)

Geio et al Spine 1999 had proved that traction of paraspinal muscles >80 minutes can provoke reduction of muscle strength by 50% at six months, leading to LBP.

To avoid this unwanted evolution, other approaches have been invented.

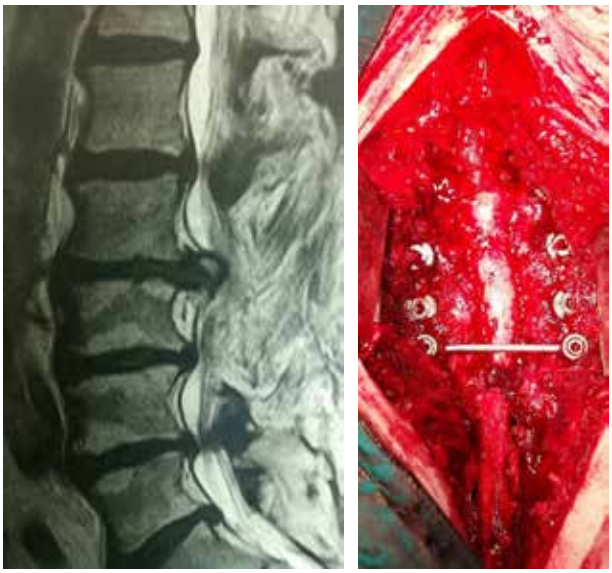

Fig.5 *Lumbar Decompression plus Fusion*

Spetzger et al 1997 (12) described the bilateral decompression via unilateral laminotomy (Fig.7) without any damage to the supraspinous and interspinous ligaments and paraspinal muscles avoiding with this approach LBP.

It is called cross over or over the top technique. It is essential the surgical microscope and the main indication is bilateral central stenosis w/o foraminal.

Conventional Laminectomy vs Unilateral Laminotomy

In a recent RCT study by Sanbong et al 2019 (13) they randomly divided 50 patients who met the inclusion criteria, central canal stenosis.in two groups.

Group C conventional Laminectomy and Group U unilateral laminotomy. They followed and evaluated them at 2 years , by using VAS, ODI, Rolland Morris Disability Questionnaire and SF-36 form. Their conclusion was, except the shorter operative time, for Group U, there were not significant differences in terms of LBP, Buttock pain, radiating leg pain or functional outcome. Fig.8

Sole Decompression vs Decompression plus fusion

This is one of the biggest debates in the international literature and one of dilemmas in decision making for all spine surgeons.

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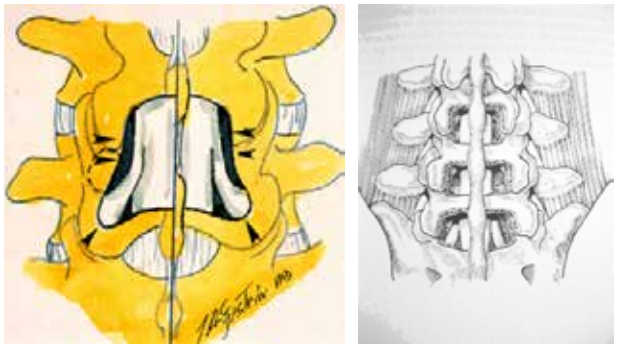

Fig 6.*Trumpet and Port Hole Technique. By Kanamori et al Ref 10 and Kleeman et al Ref 11*

Have been explained the cons and prons for adding fusion in a simple stenosis.

Many years ago Wiltse 1976 wrote: Iatrogenic Spondylolisthesis never occurs in degenerative stenosis where, there is no degenerative spondylolisthesis before operation.

However, this could happen in laminectomies with medial facetectomies between 8-31% 40 mo to 5,8years F.U (Fu et al Spine 2008, (14) and Fox et al J.S Spinal Disorders 1996)

Do we need to fuse all radical laminectomies and can we decompress the lumbar spine without destabilizing it ? (Fig 9)

According a Swiss paper (N.Ulrich 2017) (15) with 135 patients followed for 3 years, 85 underwent decompression alone and 46 decompression plus fusion.

Both groups benefitted from surgical treatment. Fusion surgery was not associated with a more favorable outcome.

This is in agreement with a study by P.Forsth (16) where in a retrospective study with over 5000 patients there was not any significant difference between the groups. In an other study by Eric Tye 2017 (The Spine Journal) (17) the addition of fusion had a negative impact in worker compensation patients.

The Danish Health Authority gave some recommendations for Lumbar Stenosis. (Rikke Ronsing et al Eur Spine Journal 2019) (18)

1.Symptomatic LSS should include decompression

2.Decompression combined with instrumented fusion is not indicated, as there is no evidence of any beneficial effect in the stable spine.

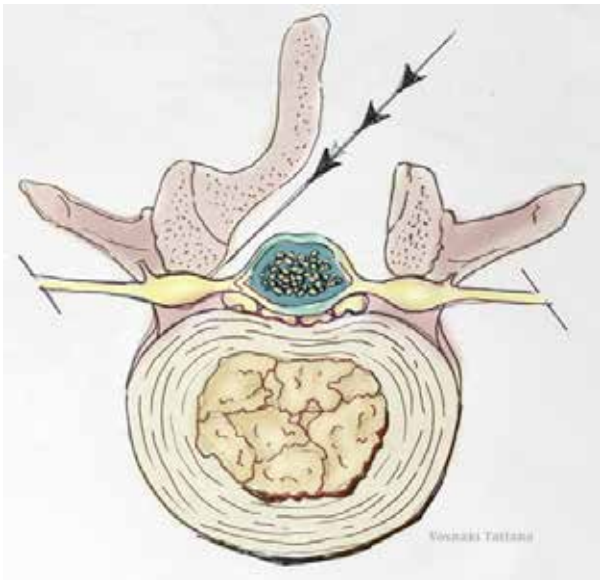

Fig.7. *Over the Top technique*

The conclusion was, Arthrodesis was not associated with better treatment effectiveness.

In a recent paper by G. Lone et all (The Spine Journal 2019) (19) comparing the surgical practice variation and clinical outcomes in 3 National registries, they found that the rate of additional fusion in LSS patients with and w/o spondylolisthesis was in Norway 11%, Sweden 21% and Denmark 28%.The mean improvement for ODI at 1 year FU was at Norway 18, Sweden 17 and Denmark 18. The conclusion was, while the indications for decompression were similar, there were significant differences for concomitant arthrodesis.

But the additional arthrodesis was not associated with better results.

-In support of the same conclusion a multicenter study by Rachid Bech-Azeddine et al 2019 (20) with 2737 patients, underwent sole decompression and followed for 12 months, they had a significant reduction on Low Back and Leg pain (Baseline for LBP 72,1 to 42.1 and Leg pain 71,2 to 41,3. (VAS, ODI, EuroQoL-5D)

In a near opposite opinion, a recent study C.Wang(2020) (21) supporting fusion in severe Lumbar Stenosis (Central and Lateral) where to achieve a satisfactory decompression a wide laminectomy and facetectomy >75% was needed. In order to prevent a post-op instability, fusion was added in 153 pa-

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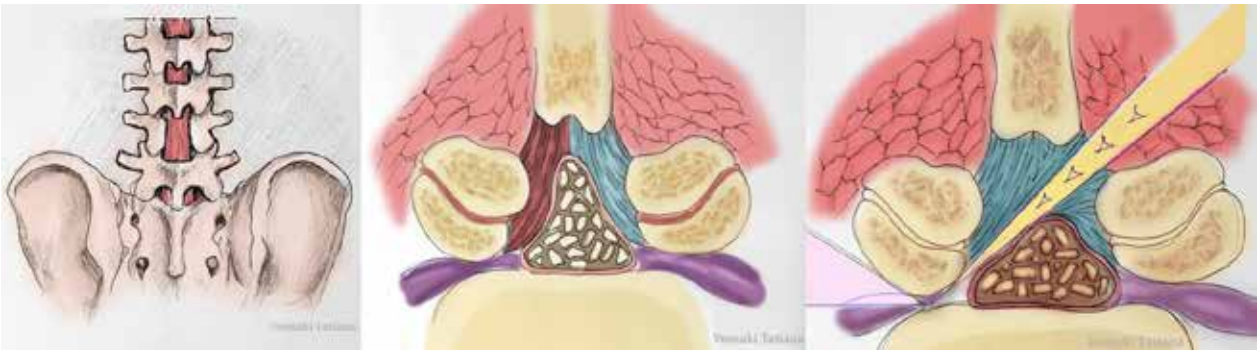

Fig. 8. *Conventional Laminectomy vs Unilateral Laminotomy Over the Top*

tients. Postero-lateral in 77 (PLF) or PLF+Interbody in 76. Both groups achieved significant improvement (JOA,VAS ODI) and high fusion rates in both, making interbody fusion not necessary.

In an attempt to identify, why almost a quarter of patients are not satisfied after a decompressive surgery for LSS, a recent study Yoji Ogura 2020 (22) found that smoking status and scoliosis with mild curve, were associated with dissatisfaction. This conclusion may help surgeons in decision making, by adding fusion even with mild scoliosis.

There is a question that comes out. Is it is possible to have any beneficial effect in LBP by decompression alone for spinal stenosis w/o instability. To this question tried to give an answer a study from Canada 2019 (23) where participated 50 Neuro and Ortho Hospitals (Academic and no Academic) with 1221 patients (1133 had data on LBP) 85% followed at 3 months and 73% at 24 months. All operated for stable Spinal Stenosis (w/o Degenerative Scoliosis or Spondylolisthesis). 72% underwent Decompression alone and Decompression plus Fusion 26%. At 3 months the improvement was 74% and 68% at 2 years. At 12 months the improvement was greater in decompression alone. The addition of fusion did not impact the improvement in LBP.

Interspinous Spacers

A lot has been written about interspinous Spacers, concerning, Indications ,Effectiveness and presumable complications. Main indication, the moderate Spinal Stenosis.

As far as effectiveness in midterm treatment at least comparable with open decompression. Many Authors support, that leg pain, the primary complain decreased by 70% during 2 years FU, whereas after laminectomy by 43-69% Jacola 2010 Stromqwist 2013 (24)….

In a recent RCT study by Vicas Patel et al Spine 2015, (25) 391 patients randomly divided in two groups: Superior 190 and X-Stop 201. Spinous process fracture was the main complication (non healed at two years) largely asymptomatic with no influence on clinical effectiveness of either device.

In an other multicenter RCT study by Meyer and JC.Le Huec 2016 (26) with 163 patients from 19 hospitals sites and 10 countries comparing Interspinous spacers and standard decompression. The results for leg pain (VAS) improved 59% with spacers and 66% for Standard Decompression Surgery (SDS) at 12 months FU.

As far as SF-36, it was equal in both groups.

By equally achieved satisfactory results, opens a window for patients with neurogenic claudication and other comorbidities.

Multisegmental Spinal Stenosis.

The challenge of multisegmental spinal stenosis (MSSS) is whether we can proceed with selective or multisegmental Decompression plus Fusion. (Fig.10)

The choice is based mainly on clinical symptoms and how many Levels should be decompressed and if there is a concomitant Scoliosis or Spondylolisthesis.

Otherwise we can choose the more stenotic level for decompression

In a paper by We Sun at al 2019 (27) they operated

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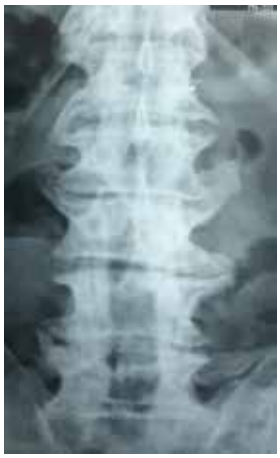
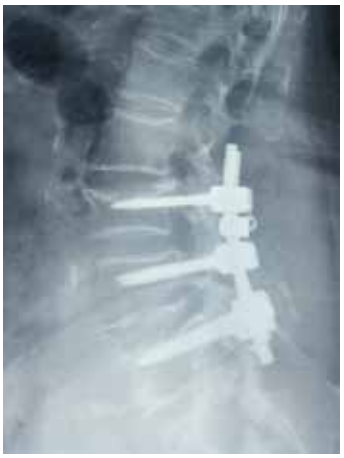
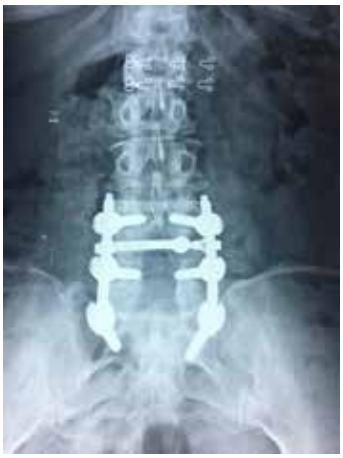

Fig.9 *Sole decompression vs Decompression plus Fusion*

Fig.10 *Multisegmental stenosis*

on 42 patients with MSSS .

In 22 they did selective decompression plus fusion (mainly Deg.Spondylolisthesis) and in 20 multisegmental decompression plus fusion. Their conclusion was that Selective decompression and fusion is safe and effective for the treatment of MSSS, with advantages of shorter operative time, less blood loss and preservation of spinal motion segments.

In multisegmental fusion you have to think of presumable complications as adjacent segment disease, implant failures (rod and screw fractures or screw displacement) and where to stop in the upper levels (Fig .11)

Spinal Stenosis and Degenerative Scoliosis

Many elderly patients have spinal stenosis with concomitant Degenerative Scoliosis mild to severe. The Spine Surgeon faces with the dilemma to proceed to simple Decompression according to symptoms or to Decompression plus Fusion.

Given the elderly patients with LSS and Degenerative Scoliosis often have comorbidities, the question that arises, is Surgery safe and effective? Can Decompression alone alleviate LBP? If we choose to add fusion this should be Short or Long? Can we identify predictors of post-op LBP?

As far as Fusion, Short or Long, the decision making should be based in some parameters. The degree of Scoliosis, the location of apical vertebra and sagittal parameters. In a recent paper by Li Y.2020 (28,29) comparing the effectiveness of Short versus Long fusion for DS with a Cobb Angle 20-40* operated on 50 patients. Long Fusion Group (>3 segments) 23 patients and Short Fusion Group (<3 segments) 27 patients. Their conclusion was that long fusion has more advantages in enhancing spinopelvic parameters (Cobb angle, SVA,LL,PT,SS) and relieving LBP by choosing appropriate fixation levels. (Fig 12) On the other hand Short fusion had less surgical trauma and fewer complications. Yuanqiang Li et al 2020) (29)

Spinal Stenosis and Degenerative Spondylolisthesis

Many patients with LSS have have concomitant degenerative spondylolisthesis. The symptoms of DS are more severe in comparison to simple spinal stenosis mainly due to the local spinal instability, the root entrapment and the accompanied sagittal imbalance.

Howard An and col 2020 (30), they did Dynamic X-Rays, Flexion-extension, registering translational and angular motion, spondylotic changes and lumbar lordosis.

MRI Scan was useful to determine the degree of disc degeneration.(Disc height, degree of slip and translation as well)

They found that in DS patients, the preserved Disc height was significantly related to dynamic instability. In contrast disc degeneration on MRI and spondylotic changes were inversely related to dynamic instability, representing a restabilization mechanism as described by Kirkaldy-Willis many years ago, decreasing the chance of future slip.

Surgical options include, decompression alone or

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Fig.11. *Selective and multi-segmental Decompression plus fusion*

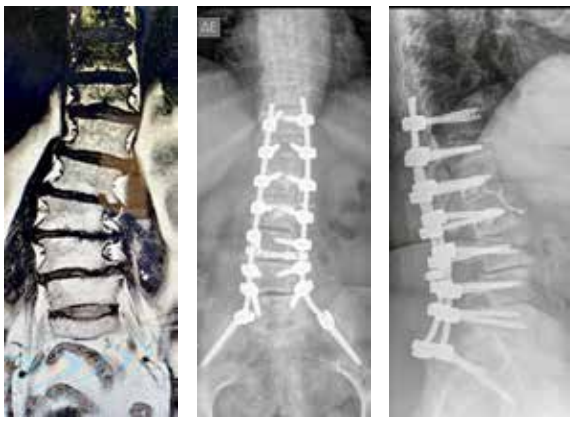

Fig. 12 *Spinal Stenosis and Deg. Scoliosis*

Fig. 13 *DS.Decompression +PLF+TLIF*

decompression plus fusion. Fusion is posterolateral (PLF) or PLF accompanied by Transforaminal Interbody (TLIF) or Posterior Interbody (PLIF) ALIF OR XLIF .

In conclusion the selection of surgical treatment method for Degenerative Spondylolisthesis relies in preoperative factors already mentioned, surgeons experience and discretion, and his familiarity with microsurgical and endoscopic methods. Fig.13

Lumbar Stenosis and Cauda Equina Syndrome

Cauda Equina Syndrome in Adults with Spinal Stenosis is a challenge to diagnose.

The Clinician has to be very suspicious and through directional questions to rule out symptoms related to Cauda Equina Syndrome (CES) This is because the symptoms are not so acute as in situations of CES by a massive Disc Herniation. (Acute onset, Increased Low Back and radicular pain involving both limbs, saddle area paresthesia, gait dysfunction or paralysis and sphincter incontinence)

In spinal stenosis the symptoms are more insidious and the diagnosis more challenging. (High prevalence of retention, Irritation and obstructive symptoms)

Usually patients with LSS and Cauda Equina Syndrome have symptoms only from Urinary tract. The symptoms from the bladder are accompanied by radiculopathy or LBP (more noisy and painful) and are perceived by patients without clinical importance. (Geriatric incontinence)

A Clinician should be very suspicious and persisted to rule out, a neuropathic bladder, with urodynamic studies.

This is a growing clinical issue because of the escalating prevalence of LSS in ageing population.

The clinical presentation may be unclear and be-

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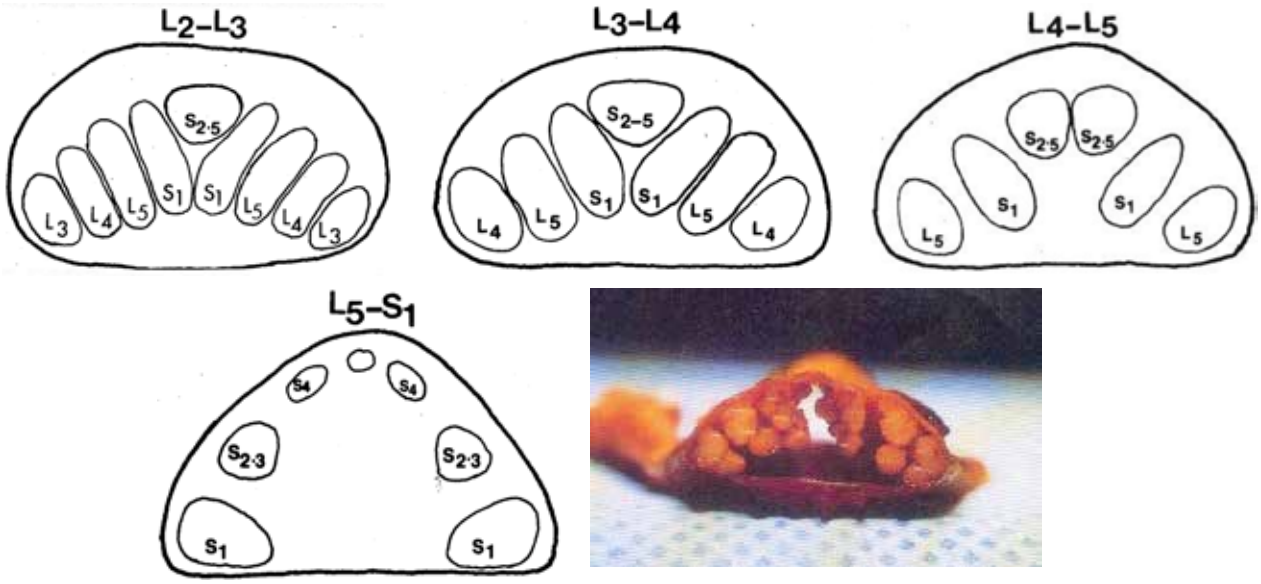

Fig14. *Position of S2-S4 nerve roots in the Dural Sac in Spine Levels L2 to S2. Courtesy by Bjorn Rydevik ref 33*

cause of the slow onset of the grumbling cauda equina symptoms may be overlooked or dismissed (Jacob Oh Asian Spine 2020 (31)

The patho-anatomical changes in lumbar Spinal Canal, especially those leading to the reduction of the AP diameter, are responsible for the onset of symptoms.

The thin sympathetic and parasympathetic nerve fibers to the bladder are highly vulnerable, both to the mechanical and Chemical affection. In a prospective study by Anders Perner et al Spine 1997, 55% of the patients had Lower Urinary Tract Symptoms. (32)

None of them had the typical Cauda Equina Syndrome. (Decreased perianal sensitivity and reflexes and anal sphincter tone)

In 1999 Biorg Rydevic (33) described the Cauda Equina Anatomy. In four levels, L2-L3, L3-L4, L4-L5 and L5-S1 the roots going to the bladder, occupy the middle of equina explaining, why they are more sensitive to the AP diameter reduction instead of the cross sectional area.

In a study by Yoshiro Inoui Spine 2004 (34) is described the relationship between dural sac antero-posterior diameter (AP) and the incidence of neuropathic bladder. They noted that the mean dural sac AP diameter in Normal was 8,26+- 2,3 mm and in patients with Neuropathic Bladder (NB) 6,56+- 2,52 mm

Evaluating the critical size of AP diameter of dural Sac, noted that when the AP diameter was < 8mm, 82,4% of patients presented with Neuropathic bladder while with >8 mm AP, patients with NB were 35,3%. This implies the importance of AP diameter of dural sac more than the cross sectional area. Fig.14

Conclusions

The question was How and When should operate on in spinal stenosis patients

There are not clear answers.

- The operative treatment must be tailored to each patient.
- An old patient w/o signs of instability or severe deformity (typical Spinal Stenosis) can be benefited with sole decompression w/o instrumented fusion
- Patients age it is not a contraindication of Decompressive surgery
- Newer Surgical Techniques are a promising of less invasive surgery with optimal results

Conflict of interest

The authors declare no conflicts of interest.

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REVIEW ARTICLE VOLUME 72 | ISSUE 1 | JANUARY - MARCH 2021

Spinal Surgery in Patients with Parkinson's Disease

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ABSTRACT

Parkinson's Disease (PD) is a degenerative disorder of the central nervous system. Recent advances in the treatment of PD have improved the life expectancy and quality of life of patients. Spinal surgery improves deformities of the spine in these patients. Moreover, a lot of studies have shown that operative treatment of various diseases of the spine in PD patients is associated with a large percentage of post-operative complications, that make a surgery revision necessary.
The purpose of the present review article is to assess the number and type of complications of spine surgery in PD patients and determine whether the presence of PD predisposes patients to a higher rate of such complications.

Key Words: Parkinson Disease; Spinal Surgery; Complications in Parkinson Disease
Short/running Title: Post-operate Spinal Complications

Introduction

Parkinson's disease (PD) is a progressive degenerative disorder of the central nervous system, affecting the substantia nigra in the midbrain and the dopaminergic cells of the substantial nigra. Parkinson's disease follows Alzheimer's disease and represents the second most common neuro-degenerative disease. Its prevalence increases exponentially with age, being estimated at 1,5% of the population over 60 years in Europe (1). Recent advances in the treatment of Parkinson's disease have improved the life expectancy and quality of life of patients. It nonetheless remains a debilitating disease, with those affected becoming increasingly incapable to perform their daily activities. Patients with PD have a wide spectrum of symptoms: Bradykinesia, tremor, rigidity, flexion of the trunk, hip and knees. This disorder leads to abnormal loads of the spine (1,2). Spinal surgery improves deformity of the spine in these patients. Moreover, a lot of studies have shown that surgical treatment of various diseases of the spine in PD patients is associated with a large percentage of post-operative complications that make a revision surgery necessary (3,4,5). PD patients are also affect-

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ed by spinal disorders and as the population ages, are expected to represent an increasingly substantial proportion of patients requiring spinal surgery. The typical parkinsonian posture is flexion of the trunk, hip and knees, thus shifting the center of gravity and subjecting the patient's spine to abnormal loads. In fact, the stooped posture that is so characteristic of the disease as to have been described by James Parkinson himself in 1817, probably predisposes to an increased rate of spinal degeneration, although this remains to be confirmed. Nonetheless, degenerative conditions and particularly degenerative scoliosis have been found to be more frequent in PD patients than their age-matched counterparts (2,6). Furthermore, PD is also associated with an array of postural deformities besides the typical abnormal posture such as camptocormia (marked forward flexion of the thoracolumbar spine), (Figure 1a,b), Pisa syndrome (lateral flexion and axial rotation of the trunk), anterocollis (dropped head syndrome) and degenerative scoliosis (2,4). In addition patients with PD are fragile, having a high rate of falls and osteoporosis (6,7,8). The purpose of this review study is to assess the number and type of complications of spine surgery in PD patients and determine whether the presence of PD predisposes patients to a higher rate of such complications.

Previous studies on spinal surgery in PD patients are sparse and of retrospective design; they all have in common an exceptionally high rate of complications (Table 1).

Surgical complications can be divided in early and late ones. Early complications related to Parkinson systemic impairment are seen in the immediate post-operative period. In a recently published multicenter study **Babat et al,** (7) retrospectively studied 14 patients with PD who had spinal surgery. They noted a high rate of surgical revision (86%). They suggested as primary causes of this high revision rate, the segmental instability at the level of surgery and kyphosis at the junctional levels. This is in accordance with the findings of **Sapkas et al** (11). In their study the revision rate was 57,1%. **Kaspar et al,** (12) assessed the post-operative complications of all types of spinal surgeries in PD patients and found a revision rate of 4/24. They concluded that the complication rate in PD patients was comparable to that of normal population. Furthermore, the functional damage and symptoms directly related to the spinal disease had be masked my PD, causing diagnostic difficulties, especially for cervical arthritic myelopathy.

In a recently published multicentric study, 42% of 48 patients who underwent a long fusion from the upper thoracic spine to the sacrum or pelvis required a revision surgery. The authors pointed out that the main complication were due to pseudarthrosis and junctional kyphosis (16). In a study by Sapkas et al, (11) it was pointed-out that close follow-up in PD patients with a complication is crucial. Their opinion is that the restoration of sagittal balance is always fundamental. But specially in PD patients it is probable even more important .Koller et al, (14) also recommend adding fusion to any decompression surgery and extending fusions as much as necessary into the thoracic spine or into the pelyis using S2 or Iliac Screws. Long fusion were studied in the paper from Bourghli et al (15), wherein 12 patients with PD underwent posterior fusion from T2 to the sacrum for various disorders (Figure 2a,b,c,d,e,f). Revision surgery was performed in 6 patients, 3 for hardware failure, 2 for proximal junctional kyphosis and one for epidural hematoma .

The most common complication reported is instability at the level above the spondylodesia due to adjacent spinal segment degeneration, screw pull-out, flat back and camptocormia (14,15,16). In a study by Sapkas et al, (11), 20 out of 21 patients had worsening of their stability within three years post-operatively. One of the patients who initially treated with fusion from L2 to S1 six months post-operated, developed post-junctional kyphosis. He refused further surgical treatment and he presented three years later with a flat-back. Only one patient who was treated initially for lumbar stenosis, had no complication 8 years post-operatively. Adjacent segment degeneration with proximal junctional kyphosis (PJK) has been widely described after posterior procedures. The etiology of PJK is probably due to various factors among these patients, including the iatrogenic effect of the fusion, the age-related osteoporosis, disc degeneration and the neuromuscular disease. Scenama et al,

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TABLE 1.

Studies about PD patients and rate of revision spinal surgery

AUTHOR	PATIENTS	REVISION RATE	REMARKS
Bouyer et al	40	42%	Mechanical complications
Schroeder et al	96	20.8%	Early complications relative to infection
Babat et al	14	85.7%	Technical complications
Koller et al	23	33.3%	High rate of infection
Sarkiss et al	95	45%	N/A
Scenema et al	19	0%	Follow-up 2 years only
Bourghli et al	12	50%	Long spinal fusion T2-sacrum
Moon et al	20	N/A	Compared to no PD patients
Wadia et al	2	50%	Two cases of camptocormia
Kaspar et al	24	21%	Mean nineteen months follow-up

(17) noticed that there was no association between C7 plumbline and last follow-up in the ODI (Oswestry Disability Index). Bourghli et al, (15) and Koller et al, (14) insisted on the fact that if spinal surgery is indicated in patients with PD, the restoration of spinopelvic balance with focus on lumbar lordosis and global sagittal alignment is required. Statistical analysis revealed that patients with notable post-operative or follow-up sagittal imbalance (sagittal vertical axis (SVA)>10cm) had a significantly increased rate of revision surgery performed or scheduled. Patients who underwent surgery were more likely to have post-operative or final sagittal imbalance (15,17). In a study by Koller et al, (14), 23 PD patients suffering from various spinal disorders, were surgically treated. Fifty two percent (52%) of the patients presented with a complication and 33% of them had revision surgery. However, a high rate of satisfaction among patients reaching 74% of the patients was satisfied with the clinical results. The authors stated that restoration of the sagittal balance is crucial in order to achieve successful results. This observation can be attributed to the fact that PD patients do not require the same degree of restoration of the sagittal alignment, in order

Figures 1a, 1b: *Anteroposterior[1] and lateral 2 photograph of the 65 years old female patient, who is submitted to operative treatment for the correction of her spinal deformity. It is obvious the camptocormia of her body. In addition she has flexed her hips and knees in an effort to improve the stature of the unbalanced body.*

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to enable a line of sight safe enough to walk and also they have reduced mobility and lower functional daily activities than the general population. In a study by Torsney et al, (18) the authors found that osteoporosis was a risk factor of a ratio of 2,61 in PD patients in comparison with healthy controls. Furthermore, a lower bone mineral density (BMD) and an increased fracture risk is also reported. Vitamin D deficiency and antiparkinsonian drugs can be involved in the reduced BMD (20). Schroeder et al, (20) in light of their findings recommend that when treating a patient with PD, the most critical point of discrimination in the severity of the disease. Patients with a modified Hoehn and Yahr (19) stage of >3, surgery should be performed only in cases with myelopathy due to high complications risk. However, in stage <3, other comorbidities of the patients should be evaluated. If no major risk factors are present, then the patient's spine pathological condition should be evaluated. Overall, the surgical risk for the patient is higher than that for the general population (22). Poor clinical outcome is related to natural progression of the pathology (13,6). However, risk factors should be considered in selected patients who might benefit from the surgical intervention. Sarkiss et al, (22) showed that poor outcome was associated to: older age, thoracolumbar kyphosis, osteoarthritis of the hip and increasing level of camptocormia. Risk factors related to the surgery itself, were post-operative SVA greater than 5 cm, inadequate sacropelvic fixation and poor fusion level selection. Another review by Galbusera et al, (23) concluded that poor outcomes related to high rate of complication and revisions are usual, but majority of patients are satisfied with their new quality of life. In addition to low bone quality, postural instability, motor disorders and autonomous nervous system dysfunction are playing an important role of a fracture risk after a fail. On the other hand, is worth to note that all of the patients are of progressive age and they are presented often with comorbidities (25,26). This fact is highlighted in a study by Baker et al, (26), who reported an increased risk of cardiac, pulmonary, hemorrhagic complications in PD patients, in contrast to non-PD patients who underwent spinal surgery (27). According to Vaserman et al, (3) patients with PD have high osteoporosis rate. In combination with the muscular dysfunction, osteoporosis contributes to fusion failure (27,28). In such cases with osteoporotic bones and loss of function of the spinal extensor muscles, directly related to the disease and the age-associated fatty degeneration (steatosis) long spondylodesia by a posterior approach is indicated. Nakashima et al, (8) report on 3 patients with vertebral body collapse that underwent circumferential fusion. All 3 had a marked progression of kyphosis, however no further operations were performed. Peek et al, (16) published a case report of a patient treated for PD associated camptocormia. Due to recurring hardware failures, he required multiple re-operations, lengthy hospitalizations and prolonged immobilization in orthoses and hip spicas. Upadhyaya et al, (6) mention two PD patients that underwent spinal fusion. One was complicated by deep infection; the other underwent revision surgery due to pseudarthrosis and screw pull-out. Wadia et al, (28) report two cases of camptocormia corrected with spinal fusion. The first patient had to undergo two revisions within a year, of hi-index procedure due to hardware failure. The other also experienced hardware failure but was deferred from revision surgery due to poor general health,in a study from Korea. Moon et al, (9) report their results on 20 patients with PD that underwent lumbar fusion. There was no statistically significant difference between the pre-operative and post-operative visual analogue scale (VAS) scores in their cohort. Likewise, there were 4 instances of pseudarthrosis and one instance of screw pull-out. The authors state that their low rate of complications, in comparison to other studies of the same sort, is probably due to the short segment fusions that were performed in their cohort (14 one-level, 5 two-level and 1 three-level). As the population ages and with improved results in medical and surgical treatments, increasing numbers of PD patients will require spine surgery. However, it is becoming increasingly clear that this subgroup of patients is at an elevated risk of complications and adverse outcomes. Indeed, the collective experience so far is that multiple re-operations have been necessary to achieve a satisfactory outcome in patients who already have to cope with a debilitating disorder. Being older, PD patients are expected to have decreased

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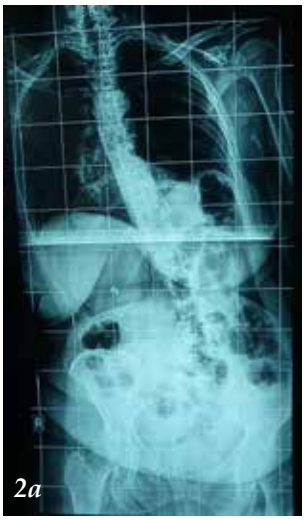
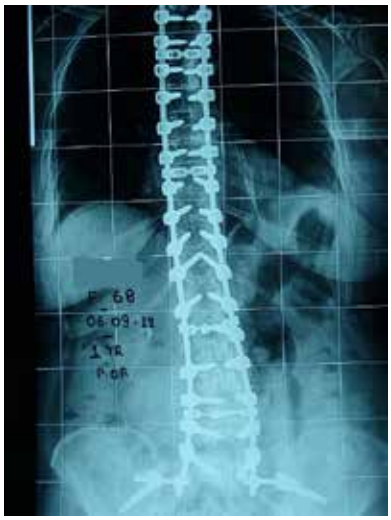
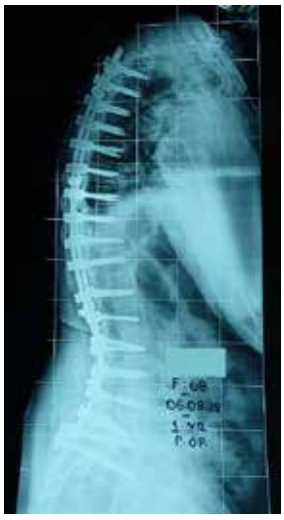
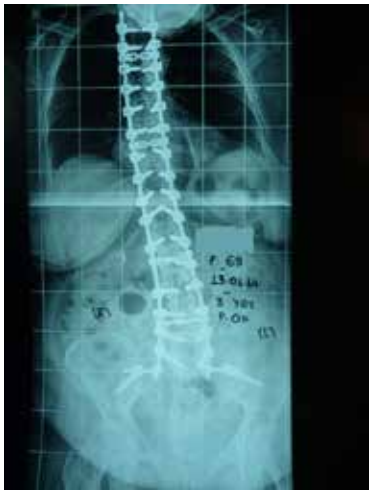


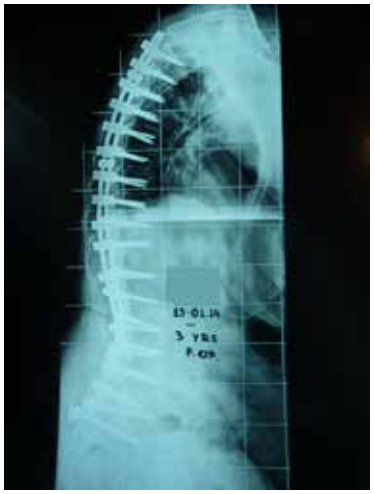
Figures 2a,2b: *Anterior-posterior and Lateral x-Rays of the spine in an standing position. His remarkable ® Lateral Bending of the spine and the subluxation of the 4th over the 5th lumbar vertebra.*





Figures 2c,2d: *First post-operative x-Rays of the patient. The spinal deformity has been corrected and stabilized with Spondylodesia. The spondylodesia is extended from the 3rd thoracic vertebra to the sacrum and iliac bones. Intervertebral cages have been applied to the L4-L5 and L5-S1 intervertebral space.*





Figures 2e,2f: *Three years post-operative x-Rays of the spine. The implants are intact and in their place, without loosening or with-drawing of the screws, apart perhaps loosening of the right iliac screw. It is observed mild swifting of the body to the right and proximal junctional kyphosis. The patient is however very satisfied, because her mobilization and stance have improved a lot, especially following the neurosurgical operation that it was performed in the brain for the Parkinson Disease.*

bone mass. In addition, the very nature of the symptoms of PD forces patients to inactivity. This in turn results in disuse osteoporosis. Indeed, it has been demonstrated that PD patients have decreased bone mass when compared to age matched controls (12,13). Therefore, in addition to muscular dysfunction, poor bone quality further contributes to implant and fusion failure. The muscular dysfunction that results from PD not only makes the posterior tension band weak, but also makes spinal adjustment in areas adjacent to surgical fusions unfeasible. Myopathies of different kinds are quite common in PD patients (14,16) but even in the absence of a frank myopathy, the flexed posture that these patients assume will result in excessive loading of any implant. Reports from orthopaedic and other surgical literature have also shown that PD patients are more likely to develop common complications such as pneumonia, confusion, urinary tract infections and decubitus ulcers (17). Surgical site infections are also quite common, as described in the series of Babat et al (7) and Koller et al (14).

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The Management of spinal conditions, in patients with PD complex because of poor muscular supporting capability, diminished bone mineral density, motor control dysfunction in addition to the increased risk of surgical complications and the presence of comorbidities in this aged population, it is an extremely demanding case. In general, before considering surgery, parkinsonian symptoms should be controlled as much as possible, whereupon a consultation with a neurologist is essential. Bone mineral density should also be evaluated and appropriately corrected. The patient should be monitored closely for the development of post-operative complications and rehabilitation should commence as early as possible(18) For spinal surgery in particular, careful pre-operative planning for proper fusion level selection and restoration of sagittal balance is always fundamental (11,14,15,21), but in PD patients it is probably even more crucial .Sapkas et al (11). Koller et al (14) also recommend adding fusion to any decompression surgery and extending fusions as much as necessary into the thoracic spine and into the pelvis using S2 or iliac screws.

Conclusions

As life expectancy in patients with PD is increased more and patients undergo spinal surgery mainly due to kyphosis or other deformities, these surgeries have a high rate of complications. Therefore, careful pre-operative planning needs to be implemented for the correct selection of patients and the level of the fusion. Furthermore, it is necessary to maintain a close post-operative follow-up despite the fact that the results are disappointing and a revision surgery is often needed. As the evidence amasses, it is becoming increasingly clear that PD patients are a high risk subgroup. Although poor clinical outcomes related to high rate of complications and revisions are frequently reported, most of the patients are satisfied from surgery and report better quality of life compared to pre-operative period. Spinal imbalance in PD patients responds poorly to dop-aminergic treatment and may even be aggravated by it. Neurosurgical treatment by deep brain stimulation of the subthalamic nucleus, that strongly reduces the symptoms it is strongly suggested. However there are very strict inclusion criteria for this treatment and it is reserved for a particular category of patients. For patients with osteoporotic bones facing the loss of function of the spinal extensor muscles directly related to this disease and to age associated fatty degeneration (steatosis), is proposed long Spondylodesia by a posterior approach, extending from T2 to the sacrum. Early preventive physical therapy may be able to delay the onset of postural disorders, but will not prevent their progression.

Abbreviations List

PD= Parkinson Disease
BMD= Bone Mineral Density
PJK= Proximal Junctional Kyphosis
ODI= Oswestry Disability Index
SVA= Sagittal Vertical Axis
ASD= Adjacent Segment Disease
VCF= Vertebral Compression Fracture

Highlights

Spinal disorders in PD patients are often
Spinal Surgeries in PD patients present numerous complications
PD patients have high rate of revision surgeries.

Acknowledgements

Not Applicable

Conflicts of Interest

The authors declare that they have no conflicts of Interest.

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REVIEW ARTICLE VOLUME 72 | ISSUE 1 | JANUARY - MARCH 2021

Sacral fractures in young and elderly patients. One fracture, two different clinical identities with many treatment options

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ABSTRACT

Sacral fractures have always been a challenging treatment pathology, as they mostly concerned high-energy traumata with several coexisting fractures and injuries. In recent years, however, as the population ages more but remains active, diagnostic options have become more popular and widely used, leading to the appearance of the terms sacral insufficiency fracture or low energy sacral fracture in clinical practice. Although the terms refer to the same bone, the injury mechanism, complications, and treatment options do not overlap with high energy sacral fractures. This article reviews the two different fracture identities and suggests treatment options.

KEY WORDS: Sacrum fracture, insufficient sacrum fracture, spinopelvic dissociation, fragility fracture

Introduction:
Sacral fractures (SF) are a peculiar type of injury with certain problematics. The main issues are the coexistence of other injuries with high morbidity rate, the missed or delayed diagnosis, the lack of an unique classification system with corresponding treatment algorithms and the overlapping fields of specializations of medical professionals (spine-surgeons, neurosurgeons, orthopaedic-surgeons and trauma-surgeons) [1, 2]. Epidemiologically, SF appear in two patient groups: the first group suffers high-energy (HE) trauma, like motor-vehicle-collisions and falls from height and comprises mostly younger patients; the second group comprises either older patients with primary osteopenia which predispose to pathological fractures, or patients with local bone alteration due to radiotherapy or tumor with or without minor trauma (MT) [3, 4].

Diagnosis:
In the HE group isolated SF appears about 5% [5]. Pelvic or abdominal bleeding, significant soft tissue injury (open fractures or Morel-Lavallee lesions) and neurologic deficit (present up to 50%) are common associated injuries that define mortality rate at these patients (17% mortality rate within a year) [5, 6, 7]. Plain radio-

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graphs of the pelvis with anteroposterior, inlet/outlet views provide the first information about the fracture severity (Fig. 1) but can be insufficient with up to 50% misdiagnosis. CT-scan remains essential for patients, who are admitted to the ER with a known HE-trauma [8]. Nevertheless MRI can diagnose bone bruises and occult fractures where the cortical bone remains intact, which is even more clinical relevant at the MT group [4]. The sensitivity of CT-scan reaches a 77% compared with MRI with a sensitivity of 96,3% [9].

By the MT group a spectacular trauma is missing and the patients mostly complain about low back pain, radiculopathy and hip/inguinal pain that misguides the clinical diagnosis and leads to misdiagnosis or delayed recognition [10]. The most common diagnostic method to raise suspicion of a sacral insufficiency fracture (SIF) is the lumbar MRI, which leads to further investigation through CT-scan [10]. SIFs are associated with increased mortality rate, which can reach 25.5% at 3 years post event, similar to hip fracture at 5 years follow up [12, 13]. Neurologic deficits can appear approximately at 2% of the MT group, as cauda equina syndrome or L5-S1 nerve root paresis [14]. Continuing bleeding with hemodynamic instability is rare, but could occur in elderly patients who receive an antithrombotic therapy [15]. An isolated fragility fracture of the anterior pelvis with a pubic and/or an ischial rami fracture at the radiograph is rare (3%) and a co-fracture of the sacrum should be excluded with a CT-scan [16].

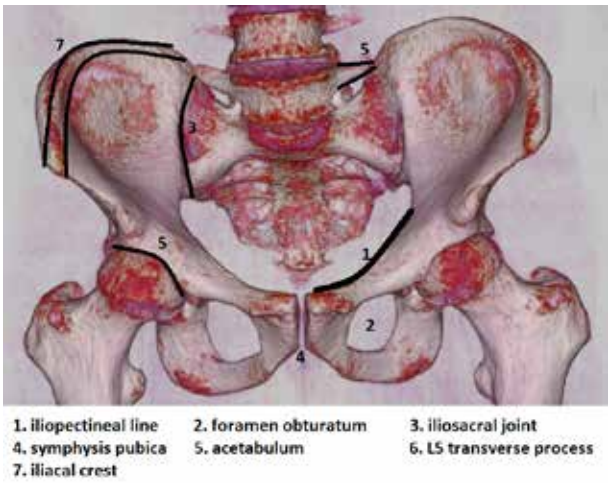

Fig. 1: *Pelvic X-ray interpretation:*

Classification:

There are several classifications used, each one of these deals with the fracture from a different point of view:

a. Pelvic ring fractures:

• AO-modified Tile classification does not refer only to SF but to pelvic ring fractures. It divides them into three types: stable, rotationally stable, vertically and posteriorly stable, and rotationally, vertically and posteriorly unstable [17] (Fig. 2).

• Young-Burgess classification also refers to pelvic ring fractures and describes the different displacing vectors: lateral compression, anterior-posterior compression, and vertical shear [18] (Fig. 3).

b. Longitudinal or vertical sacral fractures (90%) [19]:

• Dennis isolated sacrum fracture classification, based on the sacral foramina, defines 3 longitudinal fractures zones at the oblique view. Zone I lies lateral of the sacral foramina, at sacra ala. Zone II goes through the neural foramina and zone III medial of the foramina. The risk for neurological deficit increases from lateral to median from 6%, to 28%, up to 60%. At zone III fractures there is a high rate of 76% for urinary bladder and sexual dysfunction [20] (Fig. 4).

• Isler classification deals with Dennis-Zone II fractures, meaning through the neuroforamina, but raises the issue of the L5/S1 facet joint: stable Type I is lateral of the L5/S1 facet joint, unstable Type II is through the joint and highly unstable Type III is medial to the facet [21] (Fig. 5).

c. Transverse SF (3-5%) [22] :

• Modified Roy-Camille classification evaluates transverse fractures and displacement of the upper sacrum in Dennis-Zone III in the sagittal plane. Depending on the kyphosis angle there are 3 types, where the 4th Type is a S1 burst fracture, without any angulation [23] (Fig. 6).

d. Mixed longitudinal and transverse fractures classification (3-6%) [24]:

• They are described by an alphabet letter according to the fracture-morphology, which includes the H, U, λ and the T-form, depending on the shape of the fracture line. They represent fractures of the sacrum complicated with spinopelvic dissociation (Fig. 7) [25].

e. Fragility fracture of the pelvis (FFP) [26]:

• This classification differentiates the MT from the

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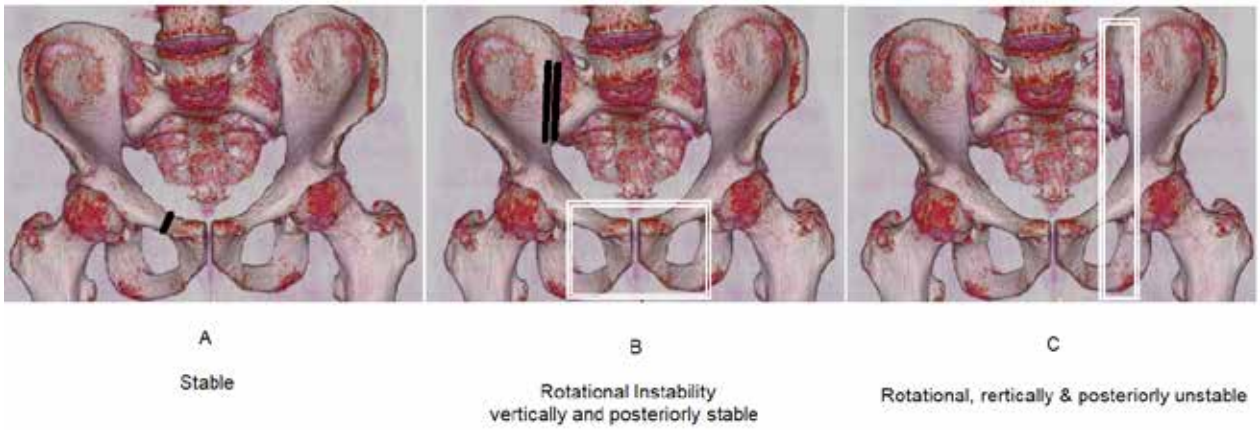


Fig. 2: *The AO/Tile Classification: black lines stand for region with a stable fracture and white frames for region with an unstable fracture*

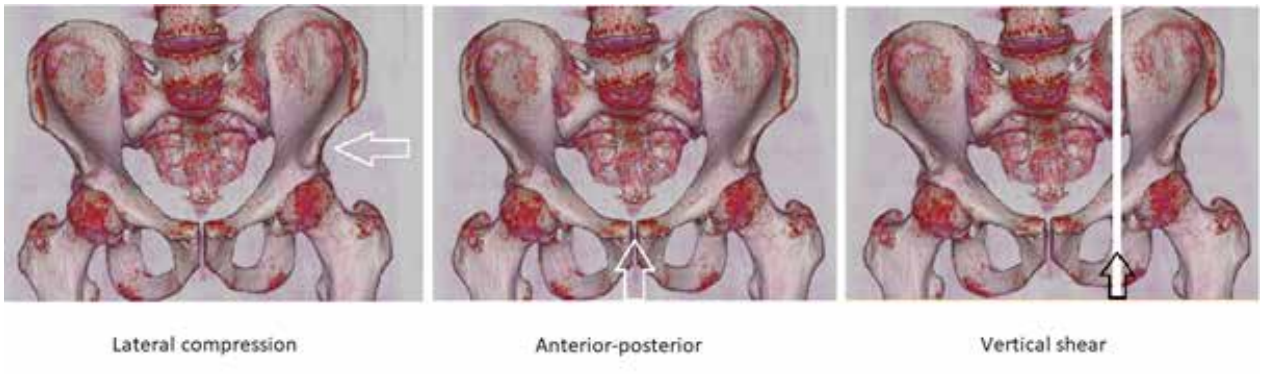
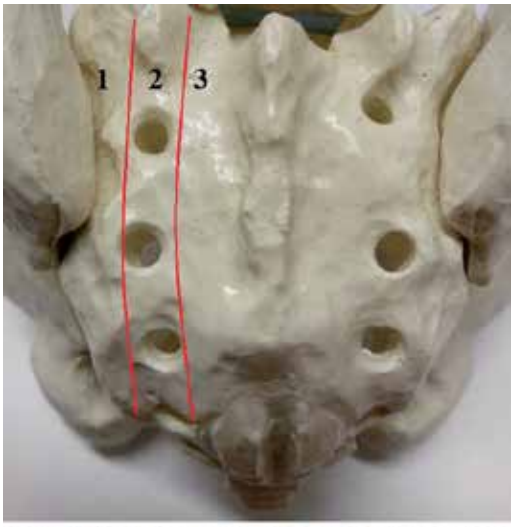


Fig. 3: *The Young-Burgess classification with arrows showing the applying force vector.*

HE sacral and pelvic ring fractures. There are 4 Types described: Type I with isolated fractures of the anterior pelvic ring, Type II with a non-dislocated posterior pelvic ring fracture, Type III with dislocation-fracture of the posterior ring and Type IV with dislocated bilateral fracture of the posterior pelvis ring.

General treatment:

The management of SF depends on the patient group. In the HE group the mortality rate can reach up to 40% for patients with a hemodynamic unstable pelvis fracture [27]. Initially ATLS and institution specific protocols provide cardiopulmonary and hemodynamic stability. If an active bleeding is suspected an external pelvis stabilization should be placed either with a sheet, a binder, a pelvic C-clamp or an external fixator in order to decrease the pelvic volume and minimize the blood loss. In addition, an urgent angiography and



Foramina Sacralia separate sacrum in 3 fracture Types:
Type I, medial of the foramina
Type II, through the foramina
Type III, lateral of the foramina

Fig. 4: *The Dennis classification has 3 fracture zones*

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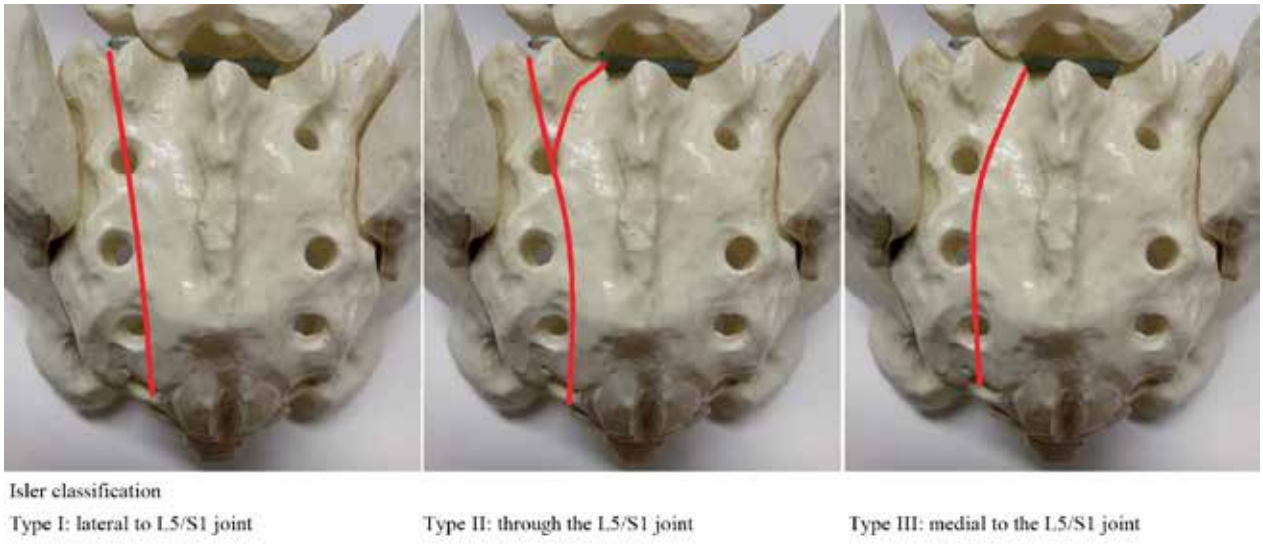

Fig. 5: *The Isler classification considering the L5/S1 facet joint*

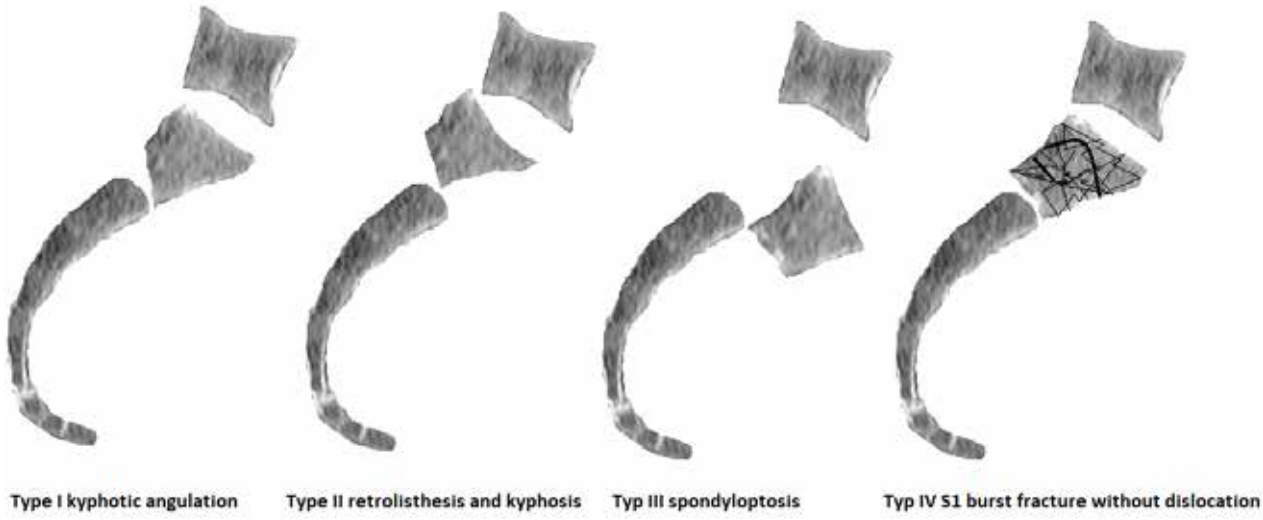

Fig. 6: The modified Roy-Camille classification:

embolization should be performed [28]. Additional specialists should also be counselled if hematomas or active bleeding are present at the urogenital tract or the rectum [29]. If the patient is conscious, a short neurological examination is essential.

In case of stable pelvis fracture, lack of neurological deficit and limited soft tissue injury conservative treatment is indicated with better functional, emotional and mental results [30]. FFP Type IIa fractures could be treated conservatively with painkillers and early mobilization and only in case of pain resistance, operation should be reconsidered. Treatment of the primary disease, in most occasions osteoporosis, with Vitamin D, bisphosphonates and teriparatide, not only prevents further fractures but improves pain relief and enhances the fracture healing [31, 32]. Unstable fractures with or without neurological deficit require an operative treatment [33]. Such are displaced AO-Tile Type B and C, displaced vertical, transverse Roy-Camille Type II-IV, U-shaped fractures as well as dislocated lateral compression injuries (<10mm) [34-38]. FFPs Type III-IV are also considered unstable and a surgical fixation is mandatory [32]. Neurological deficits can be treated either indirectly by reducing the fracture or directly by

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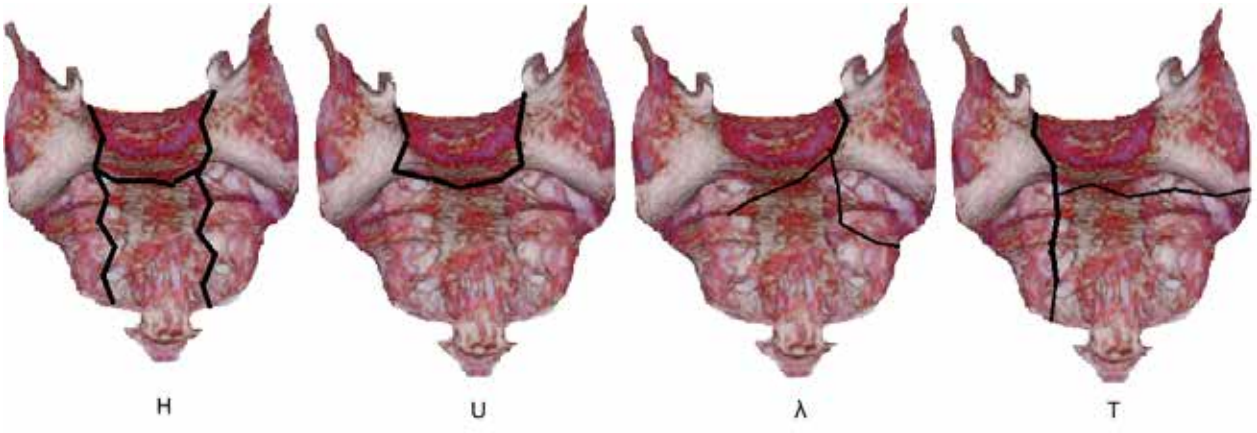

Fig. 7: *The alphabetic fracture classification of the sacrum:*

decompression and laminectomy within 24-72 hours, with controversial outcomes [39, 40].

Surgical treatment:

If conservative treatment fails or in case of fracture instability, surgical intervention is advised, either minimally invasive/percutaneously (MIS) or with open reduction and internal fixation (ORIF).

MIS procedures are:

a. Sacroplasty with or without balloon kyphoplasty
b. Transiliac sacral screws (TIS)
c. Indirect sacral fixation with iliac screws or
d. Minimally invasive plating
e. Sacral bars
f. Percutan spinopelvic fixation

For fragility fractures of the pelvis such methods are preferred in order to reduce the risks of cardiovascular and lung complications, as well as infection and wound healing problems. FFP Type I and IIa fractures are primarily treated conservatively, however the latter could end up needing an operative treatment because of posterior ring instability. If mobilization under painkillers fails, CT imaging should be performed in order to exclude a fracture displacement [41].

For Type IIa fractures, sacroplasty with or without balloon is a minimally invasive method of preference for stabilization of the fracture and significant pain relief. The patients can be mobilized early and regain their quality of life. The procedure can be performed under fluoroscopy or CT-guided in a prone position [42, 43]. Complications like cement leakage have been described, however major complication rate was reported at 0,3% [44]. There are two recommended techniques: the short and the long axis technique. With the short axis technique the needle is placed over the S1 and/or S2 ala, lateral of the neuroforamina and median of the iliosacral joint. With the long axis technique the needle has a caudocranial direction, entering the sacrum between the inferior margin of the iliosacral joint and the S3 neuroforamen (Fig. 8). Advantages of the long axis technique are better cement distribution and decreased chance of anterior cortex violation [45]. Preoperatively the landmarks of the anatomic relationships have to be studied in order to avoid false positioning of the needles (Fig. 9).

TIS is an established method for treating the posterior pelvic ring fracture, not only for FFP Type II fractures but also for HE trauma as vertically unstable pelvic fractures and U-shaped SF with simple fracture pattern [41, 46]. The screws are placed under fluoroscopic imaging with the patient in prone or supine position. One or two distally-threaded screws are inserted in S1 or one in S1 and a second screw in S2 body [46]. The use of a washer at the screw head reduces the iliac cortex perforation [47]. Using cement augmentation through the cannulated screws can reduce the risk of screw loosening (Fig. 10), even combined with balloon kyphoplasty [48, 49, 50]. Correct positioning of the screws demands proper study of the individual anatomy of each patient at the preoperative CT-scan [51]. Intraoperative use of fluoroscopy with lateral, inlet and outlet pelvic views and identification of the sacral safe zones are mandatory elements of the procedure (Fig. 11) [52].

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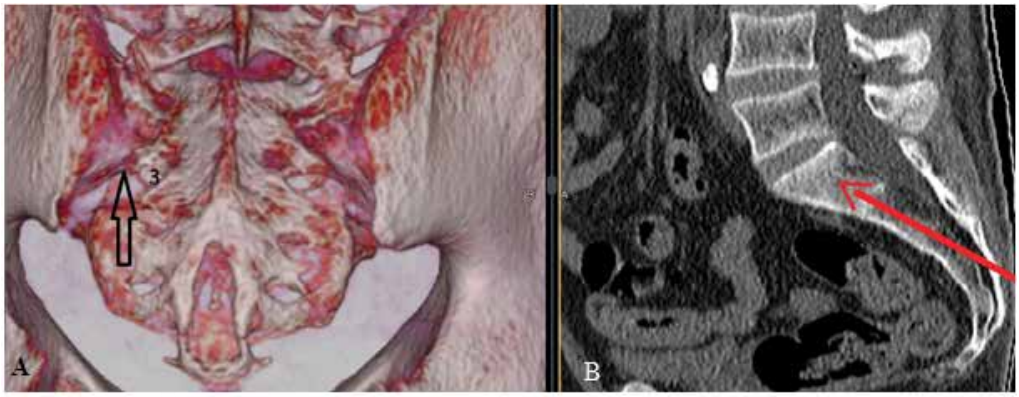
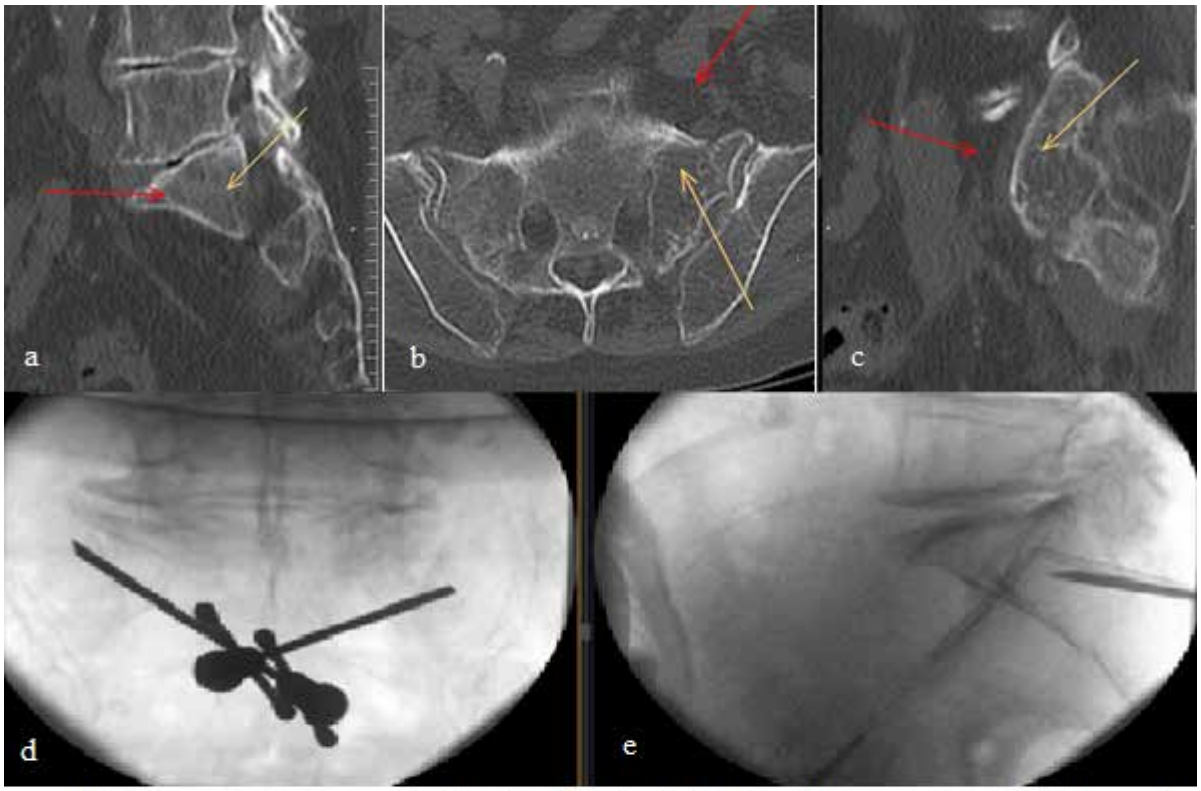


(A) Entry point is between S3 neuroforamen and the iliosacral joint (ap view),
(B) Aiming posteriorly of S1 centre (lateral view).

Fig. 8: *Landmarks for needle placement at the long axis technique:*



a-c: CT-scan compating correct (yellow) to false (red) placing of the cement-needle: The needle should not be targeting for the promontorium at the lateal view, otherwise it will end up too far anteriorly, in the small pelvis.

d-e: Intraoperative needle placing using the short axis, aiming at the lateral view just posteriorly of the S1 center.

Fig. 9: *The short axis technique:*

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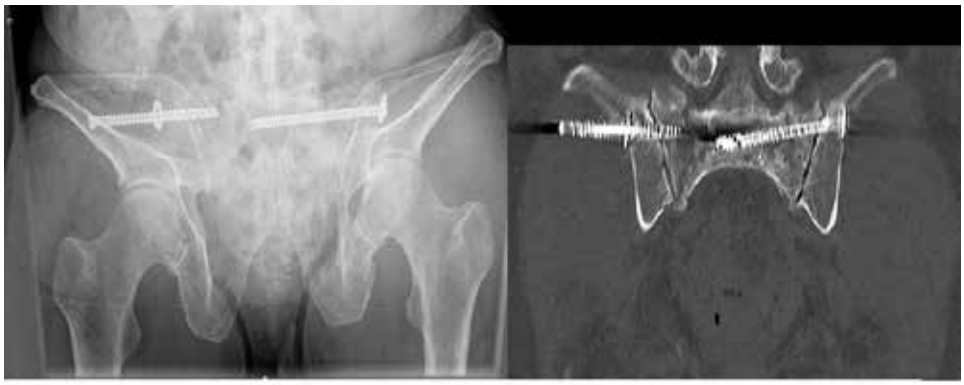
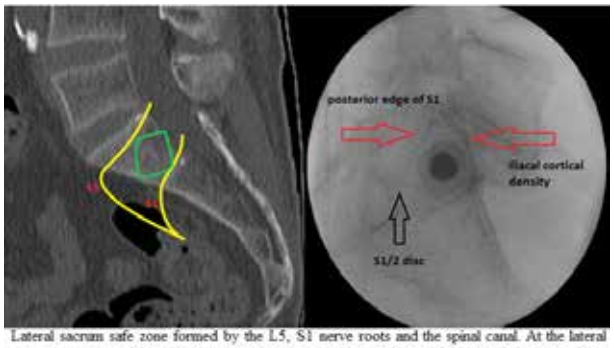


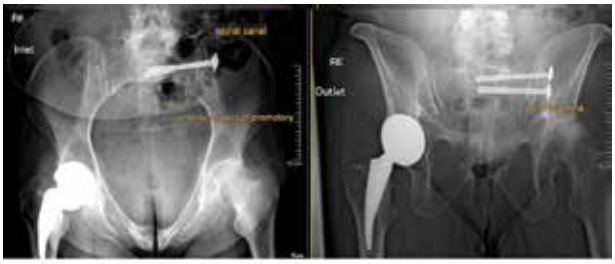
X-ray and CT-scan of a 82years old female patient, showing screw loosening on the right side, 2 months after TIS-treatment

Fig. 10: *Complication after treatment with TIS screws:*



Lateral sacrum safe zone formed by the L5, S1 nerve roots and the spinal canal. At the lateral view, the screw should stay posteriorly of the iliacal cortical density, above the S1/2 disc and in front of the posterior edge of S1 vertebra.

Fig. 11a: *TIS screw placement: lateral view*



1) Inlet view with spinal canal (A) and anterior aspect of promotory (B). 2) Outlet view with S1 foramina

Fig. 11b: *TIS screw placement: inlet and outlet view:*

Other MIS techniques are bridging constructs, which connect the iliac bones bilaterally, posteriorly of the sacrum but do not provide compression at the fracture zone. These procedures can be used at unilateral and bilateral fractures of the sacrum regardless of bone density because of the good anchorage provided by the iliac screws (Fig. 12) [53, 54]. The iliac screw can be inserted posteriorly through the skin, by targeting for the teardrop landmark at the obturator outlet view, over the foramen ischiadicus major at the lateral view and over the acetabulum at the anteroposterior view (Fig. 13). The use of a 5 to 6mm threaded transsacral bar has also been described. It is inserted percutaneously through the S1 body and provides compression at the fracture site by tightening the nuts bilaterally [54]. Both the bridging as well as the transsacral bar technique could be combined with TIS screws for additional rotational stability [47, 56].

When spinopelvic dissociation, vertical instability or complex fracture patterns are addressed, the use of spinopelvic fixation reaches better biomechanical stability. It is recommended for FFP Type III and IV, but also for U and H-shaped fractures (Fig 14) [46, 57, 58]. The construct bridges with screws the lower lumbar spine with the posterior ilium over a vertical rod. The screws can be inserted minimally invasive, uni-or-bilaterally. A S2-Alar-Iliac screw can alternatively be used instead of an alar iliac screw with similar biomechanical features [59]. Spinopelvic fixation combined with a TIS screw for accessorial rotational stability is named triangular osteosynthesis.

Residual instability at the anterior pelvic ring can cause pseudarthrosis and implant failure posteriorly. Depending on the fracture's characteristics, MIS retrograde transpubic screw insertion or ORIF by plate or screws is recommended (Fig. 15) [60, 61].

Conclusions:

SF used to be a concern at trauma center hospitals,

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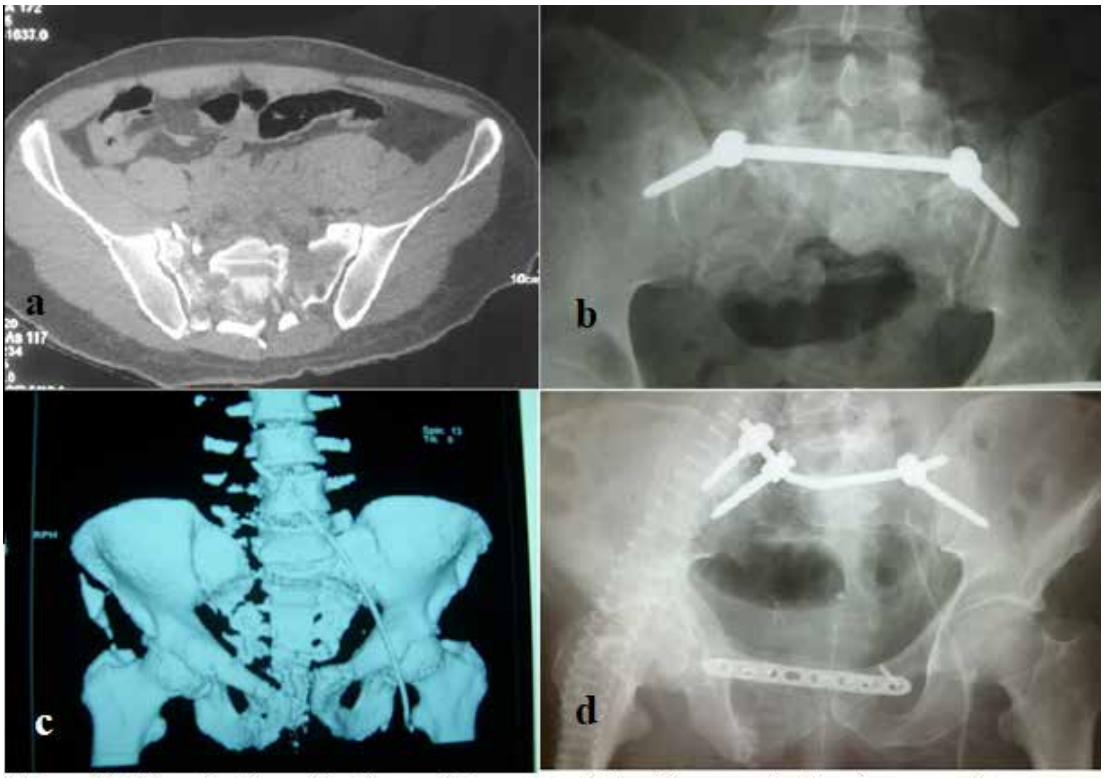
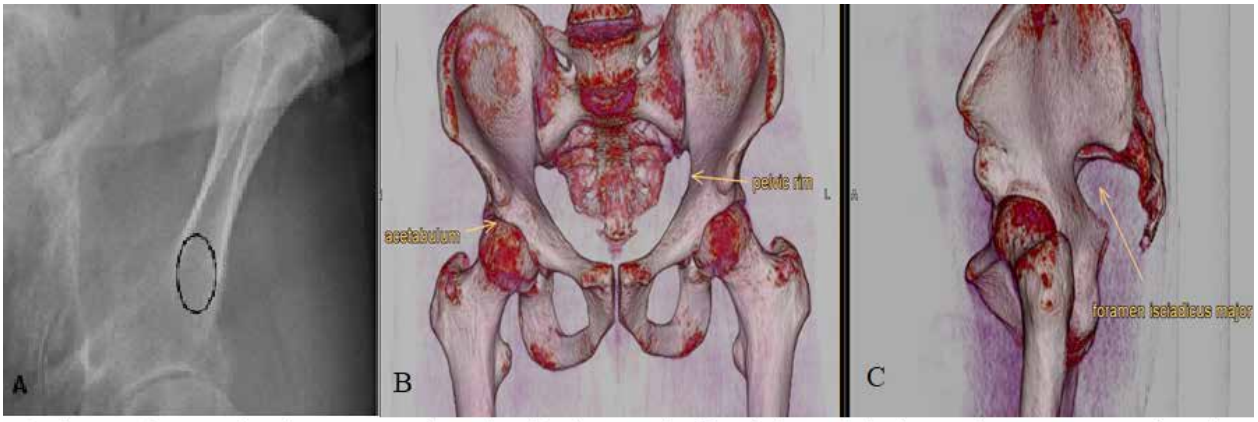


Bilateral (a+b) and unilateral (c+d) sacral fractures stabilized by posterior iliacal screw-rod system

Fig. 12: *Bridging iliac screw-rod constructs for unstable sacral fractures*



a) The teardrop at the obturator outlet view b) the acetabuli and the pelvic rim at the anteroposterior view
c) the foramen ischiadicus major at the lateral view

Fig. 13: *Landmarks for placing iliac screws:*

where high-energy injuries were admitted. Nowadays, the clinical entity of the fragility fractures of the pelvis raises the necessity that also medical specializations such orthopedic- and neurosurgeons be acquainted with the treatment of SF as well.

AOSpine/Trauma concluded that a new global classification should be generated [62]. Lehmann et al. proposed a scoring system for evaluating injury severity and developed an algorithm for clinical decision making and surgical management [63].

Summarizing, cement augmentation or TIS should be considered for FFP Type II fractures. For Type

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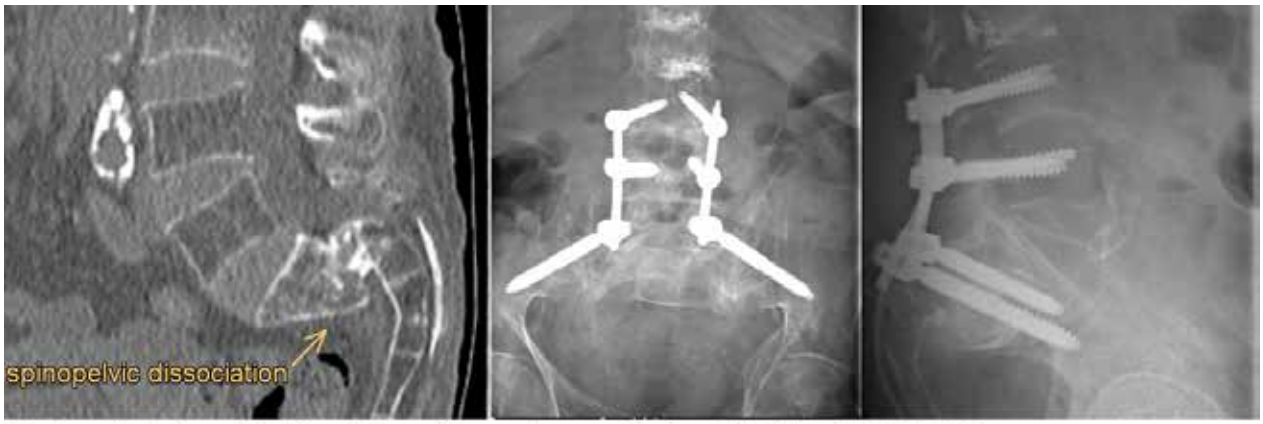

Fig. 14: *Treatment of spinopelvic dissociation*

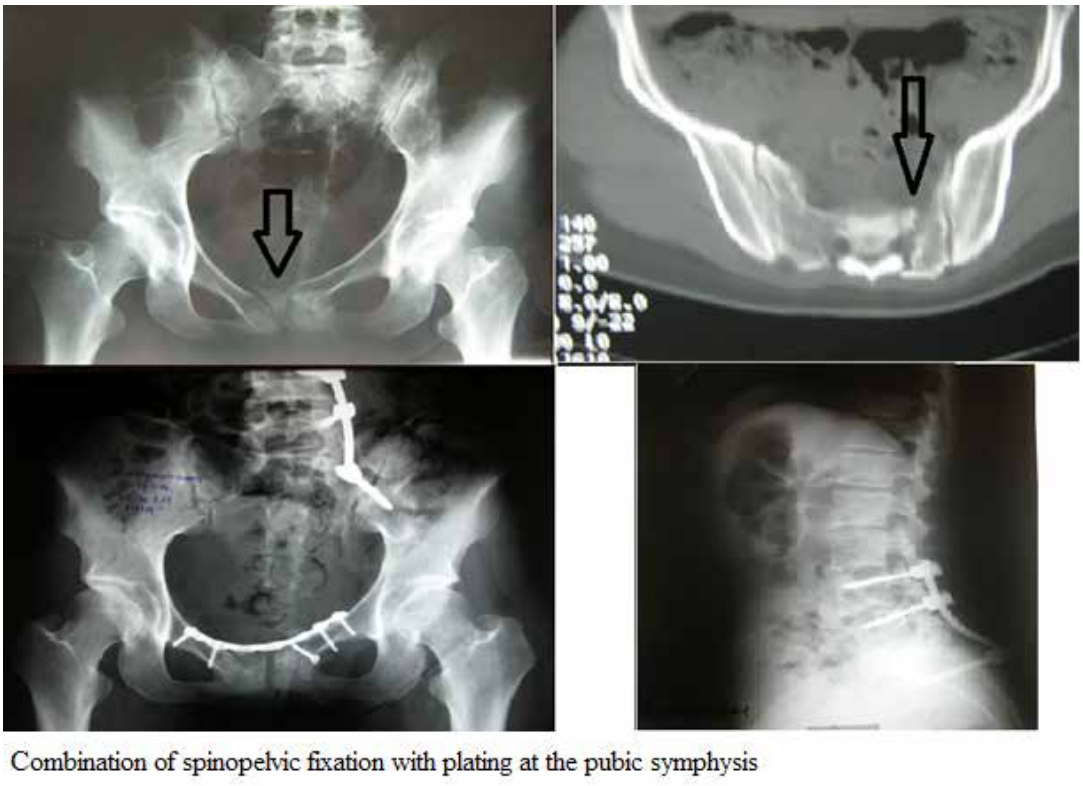

Fig. 15: *38years old female patient with motor vehicle collision: fracture of the symphysis pubis and unilateral vertical sacral fracture on the left side*

III lesions open surgical reduction will be needed in most cases. In Type IV fractures spinopelvic fixation is required [61]. Simple vertical fractures could be treated with TIS, where complex ones are more suitable for triangular fixation. Unstable transverse fractures and spinopelvic dissociation as may occur at U-and H-fractures demand more rigid osteosynthesis, which involves iliolumbar fixation [64, 65, 66].

Conflicts of Interest

The authors declare that they have no conflicts of Interest.

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REVIEW ARTICLE

Infections of the spine: Current concepts and a literature review

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ABSTRACT

Infections of the spine comprise a wide spectrum of different clinical manifestations depending on the exact anatomical structure involved. Spinal infections pose an essential health problem, the treatment of which requires a multidisciplinary approach. Diagnosis is based on clinical symptoms, radiologic evidence, laboratory tests and biopsy. The most common pathogens are bacteria; most of which spread hematogenously. Current treatment involves a combination of antibiotic agents. Sometimes, surgery is required to eradicate the infection or to treat its complications. In all cases, thorough and repetitive clinical examination and laboratory tests are of paramount importance for optimal outcomes.

KEY WORDS: Spine Infections, Spondylitis, Spondylodiscitis, Pathogenesis, Clinical Presentation, Back pain

1. Introduction

Infections of the spine and their various clinical manifestations consist a group of challenging medical conditions which necessitate a team of specialists for optimal diagnosis, treatment and recovery. The responsible pathogens are usually bacteria, however, fungi and even parasites can be encountered. Spinal infections can be classified as pyogenic (bacterial), granulomatous (tuberculosis or fungal) or parasitic (Echinococcosis).[1] Alternatively, an anatomical classification can be used. [2]. Depending on the route of spread of the pathogens, spinal infections can be divided in those that spread hematogenously, from adjacent tissues, or through direct inoculation. This is a review of the literature regarding infections of the spine. We also describe and summarize the epidemiology, pathogenesis, clinical manifestation, diagnosis and management of spinal infections.

2. Epidemiology

Spinal infections are relatively rare with an estimated incidence around 22 cases per million per year. [3] Vertebral osteomyelitis is responsible for about 0.15% to 5% of all osteomyelitis cases.[4] Despite being a rare entity, vertebral osteomyelitis is the most frequent form of osteomyelitis spreading hematogenously in older patients. [5]

The most commonly diagnosed spinal infection is primary pyogenic spondylodiscitis [2],[6]. The causative pathogens are Gram positive bacteria especially Staphylococcus Aureus.[7] The disease has a male: female ratio of 1.5.[3],[8] It usually affects people in their 50s or 60s.[9] An exception is younger intravenous drug users.[10] Prior to the use of antibiotics, spondy-

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lodiscitis had a mortality ratio of 25–71%. The current rate is 2–12% [11]

The spine can be extensively affected with multifocal or adjoining lesions (common in TB osteomyelitis) or present as an isolated site of infection as in pyogenic cases. [12] The most common region affected is the lumbar spine followed by the thoracic spine. [4], [6] A distinct entity, tuberculous spondylodiscitis has predilection for the thoracolumbar region.[13] Sacral osteomyelitis has been described, usually as a complication of infected pressure ulcers in bedridden patients.[14] The infection may expand posteriorly forming epidural or subdural abscesses, or laterally, forming most commonly psoas abscesses.[15] Facet involvement has been described as septic facet joint arthritis.[16]

In terms of epidemiology, certain risk factors predispose to spinal infection; immunocompromised in particular are in great danger.[5] Another category, intravenous drug addicts incur high likelihood of infection from repetitive injections.[10] Likewise, people with common clinical conditions like diabetes, malignancy, renal or hepatic failure sustain a higher risk for spinal infection.[17],[18] A distinct category of patients with increased likelihood for regional infection are those who had spinal surgery and those with orthopedic or other implants.[19] Moreover, immigrants from third world countries, inmates, and those of low socioeconomic level are exceptionally vulnerable. [20]

3. Pathogenesis

There are two possible routes of dissemination: the hematogenous and the non-hematogenous; the latter is further divided to direct inoculation and contiguous spread. In hematogenous spread bacteria due to simple events like tooth brushing related microtrauma or more serious, like urinary tract infections circulate in the bloodstream.[21] A common source of bacteremia are various kinds of medical implants. Hematogenous spread allows bacterial seeding the metaphysial and cartilaginous end-plates and afterwards into the adjacent tissue.[22] The characteristic vascular anatomy and physiology of the region provides the appropriate circumstances (slow blood flow, lack of valves) for pathogen adherence and proliferation. The hematogenous route is the most common route of dissemination and perfectly describes the pathogenesis of pyogenic spondylodiscitis. Once microorganisms enter the vascular arcades in the metaphysis, the infection spreads. The disc is destroyed by bacterial enzymes.[23] Tuberculous infection stems from Batson's paravertebral venous plexus. Tuberculous spondylitis characteristically encompasses early obliteration of the anteroinferior part of vertebral bodies and may then expand beneath, involving the anterosuperior aspect of the inferior vertebra.[12] However, tuberculous spondylitis does not destroy the disc until late disease.[24].

There are two additional, less frequent, ways of pathogen dissemination in spinal infection. The first is direct inoculation, commonly due to regional trauma or recent surgery in the spine or surrounding tissue. [25],[26] The second is contiguous spread from adjacent foci as the aorta, the esophagus or the bowel.[27]

Children and adults manifest differences regarding pathogenesis. In children, the spread of infection is rapid, because vessels supply both the end plates and the intervertebral discs, whereas in adults, intra-osseous arteries are end-arteries; septic emboli may occlude the circulation, resulting in broad destruction. [28]

4. Clinical presentation

Awareness of the clinical presentation is crucial in the recognition of spinal infection.[29] Nonetheless, this can be particularly difficult due to the non-specific, and often mild symptoms of spondylodiscitis, especially in early disease. Thus, initial diagnosis delays more than three months after development of the first symptoms in about 50% of the patients. [30]

Idiopathic back or neck pain has often been described as the predominant symptom.[31] Paravertebral muscle tenderness and spasm, and limitation of spine movement represent the predominant signs in spondylodiscitis. [32] Pain should be differentiated from the common back pain. This can be achieved by looking for concomitant "red flags", for instance fever, malaise, neurological deficits, and persistent symptoms with minimum or no improvement. However, fever is rarely present in patients with mycobacterial, brucella, or fungal spondylodiscitis and may be absent in patients taking analgesics.[33]

Clinical examination is necessary and can be very helpful. Inspection of the patient can detect the cause

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TABLE 1.

Table 1: Parenteral Antimicrobial Treatment of Common Microorganisms Causing Native Vertebral Osteomyelitis (Ryang, Y.-M., Akbar, M., 2020.)

Microbiology [77], [78]	Incidence (%)	Route of infection
Staphylococcus aureus	20–84	Most common pathogen; 1.7–6% of bloodstream infections complicated by VO
Coagulase-negative staphylococci	5–16	Device-related bacteraemia or direct inoculation in post-operative infections
Streptococci and enterococci	5–20	Haematogenous spread. Associated with infective endocarditis in 26%
Enterobacteriaceae	7–33	Haematogenous spread from urinary tract infections in older population. Commonly Escherichia coli, Proteus, Klebsiella, Enterobacter spp
Anaerobes	<4	Contiguous spread from pelvic or intra-abdominal foci. Cutibacterium acnes direct inoculation from implants
Polymicrobial	<10	Contiguous spread

(scars due to trauma or previous operations). Paravertebral tenderness and masses (muscle spasm or rarely abscess formation) may be palpated. [34]

The role of neurologic examination is crucial because it can unveil neurologic deficits. In such cases, common findings are muscle weakness, sensory impairment or loss and sphincters incompetence.[54]

5. Diagnosis

Any delay in diagnosis increases the risk for abscess formation and confer increased morbidity and mortality.[29] Co-existing medical conditions, previous surgeries and drug use can raise the suspicion for spinal infection or elucidate the primary cause. [11],[18]

Laboratory work up includes White Blood Cells count (WBC), Erythrocyte Sedimentation Rate (ESR) and C - reactive protein (CRP). WBC is slightly elevated or normal in about half the patients with spondylodiscitis, thus is relatively nonspecific. ESR is a more sensitive inflammatory marker, found elevated in > 90% of patients.[36] CRP seems to be the most important blood test, being very sensitive and normalizing in response to treatment.[35] However, these markers remain relatively nonspecific.[37] Blood cultures should be part of routine laboratory evaluation. However, cultures often fail to identify a specific pathogen. [38] Quantification of interferon-gamma (IFN-γ) based tests for tuberculous infection detection or serologic tests for Brucella can be utilized in patients from endemic areas.[39]

The next step is the use of radiologic modalities. Even though radiographs have low specificity, they remain a valuable, low-cost, diagnostic tool with high sensitivity.[40] Radiographic signs suggesting spondylodiscitis are narrowing of disc space, loss of definition and irregularity of the vertebral endplate. Pedicle, lamina and spinous process involvement is rare in pyogenic spondylodiscitis and should alert for tuberculous infection. [41] Destruction of intervertebral disc is indicative of pyogenic infection.[4], [42]

MR imaging is the modality of choice with 96% sensitivity, and 94% specificity.[43],[44],[45] MRI offers details about paravertebral soft tissue involvement, abscess formation, nerve root and spinal compression. Although gadolinium-enhanced MRI scans are highly sensitive and specific they often overestimate the presence and extent of infection. [46]

Computerized Tomography (CT) can be utilized whenever MRI is contraindicated. Indicative findings of vertebral infection are end-plate erosion, paravertebral fat reduction, disc hypodensity and bone necrosis or pathological calcification. [37], [42]

Technetium or leucocyte labelled bone scintigraphy, although relatively sensitive (90%), has low specifity,

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TABLE 2.

Parenteral Antimicrobial Treatment of Common Microorganisms Causing Native Vertebral Osteomyelitis (Barberi et al., 2015)

Microorganism	First Choice[a]	Alternatives[a]	Comments[b]
Staphylococci, oxacillin susceptible	Nafcillin[c] sodium or oxacillin 1.5–2 g IV q4–6 h or continuous infusion or Cefazolin 1–2 g IV q8 h or Ceftriaxone 2 g IV q24 h	Vancomycin IV 15–20 mg/kg q12 h[d] or daptomycin 6–8 mg/kg IV q24 h or linezolid 600 mg PO/IV q12 h or levofloxacin 500–750 mg PO q24 h and rifampin PO 600 mg daily [86] or clindamycin IV 600–900 mg q8 h	6 wk duration
Staphylococci, oxacillin resistant [87]	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	Daptomycin 6–8 mg/kg IV q24 h or linezolid 600 mg PO/IV q12 h or levofloxacin PO 500–750 mg PO q24 h and rifampin PO 600 mg daily [86]	6 wk duration
Enterococcus species, penicillin susceptible	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses; or ampicillin sodium 12 g IV q24 h continuously or in 6 divided doses	Vancomycin 15–20 mg/kg IV q12 h (consider loading dose, monitor serum levels) or daptomycin 6 mg/kg IV q24 h or linezolid 600 mg PO or IV q12 h	Recommend the addition of 4–6 wk of aminoglycoside therapy in patients with infective endocarditis. In patients with BSI, physicians may opt for a shorter duration of therapy. Optional for other patients [88], [89]. Vancomycin should be used only in case of penicillin allergy.
Enterococcus species, penicillin resistant[e]	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	Daptomycin 6 mg/kg IV q24 h or linezolid 600 mg PO or IV q12 h	Recommend the addition of 4–6 wk of aminoglycoside therapy in patients with infective endocarditis. In patients with BSI, physicians may opt for a shorter duration of aminoglycoside. The additional of aminoglycoside is optional for other patients [88], [89]
Pseudomonas aeruginosa	Cefepime 2 g IV q8–12 h or meropenem 1 g IV q8 h or doripenem 500 mg IV q8 h	Ciprofloxacin 750 mg PO q12 h (or 400 mg IV q8 h) or aztreonam 2 g IV q8 h for severe penicillin allergy and quinolone-resistant strains or ceftazidime 2 g IV q8 h	6 wk duration Double coverage may be considered (ie, β-lactam and ciprofloxacin or β-lactam and an aminoglycoside).

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Enterobacteriaceae	Cefepime 2 g IV q12 h or ertapenem 1 g IV q24 h	Ciprofloxacin 500–750 mg PO q12 h or 400 mg IV q12 hours	6 wk duration
β-hemolytic streptococci	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or ceftriaxone 2 g IV q24 h	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	6 wk duration Vancomycin only in case of allergy.
Propionibacterium acnes	Penicillin G 20 million units IV q24 h continuously or in 6 divided doses or ceftriaxone 2 g IV q24 h	Clindamycin 600–900 mg IV q8 h or vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	6 wk duration Vancomycin only in case of allergy.
Salmonella species	Ciprofloxacin PO 500 mg q12 h or IV 400 mg q12 h	Ceftriaxone 2 g IV q24 h (if nalidixic acid resistant)	6–8 wk duration

Abbreviations: BSI, bloodstream infection; IV, intravenous; PO, take orally; q, every.
[a] Antimicrobial dosage needs to be adjusted based on patients' renal and hepatic function. Antimicrobials should be chosen based on in vitro susceptibility as well as patient allergies, intolerances, and potential drug interactions or contraindications to a specific antimicrobial.
[b] Recommend Infectious Diseases Society of America guidelines for monitoring of antimicrobial toxicity and levels [136]
[c] Flucloxacillin may be used in Europe.
[d] Vancomycin should be restricted to patients with type I or documented delayed allergy to β-lactams.
[e] Daptomycin, linezolid, or Synercid may be used for vancomycin-resistant enterococci.

thus it is not routinely used. A plethora of novel nuclear imaging modalities exist such as 111 In, Gallium spine scan and strepteridin scintigraphy. These modalities are very sensitive and specific, however, the requirement for specialized facilities and personnel, limits their role.[47],[48],[49] Fluorine-18 (F-18) fluorodeoxyglucose-positron emission tomography (FDG-PET) has shown promising results for both acute and chronic infection, being particularly useful in patients with metallic implants because FDG uptake is not hampered by metallic artifacts.[50], [51]

When blood cultures fail to identify a pathogen, biopsy is considered; open or percutaneous. While open biopsy is a last resort option, percutaneous biopsy is routinely executed.[52],[53],[54] In addition to bacterial cultures, mycobacterial, brucella and fungal cultures should be obtained.[55], [56] If the results are inconclusive, a second CT-guided needle biopsy may be performed before open biopsy is finally required.[57] In either case PCR should be used. Molecular diagnostic tools have improved the yield of microbiologic diagnosis via tissue biopsy.[58],[59] Use of antimicrobial agents before biopsy remains a highly debatable topic. We recommend adhering to the classical approach and withholding initiation of treatment when this is feasible.[60],[61],[62] In patients with neurologic compromise or hemodynamic instability, we recommend immediate surgical intervention plus empiric antimicrobial therapy.[63]

6. Differential diagnosis

Diagnosis of spinal infection based on clinical signs and symptoms is very challenging. Initial differential diagnosis consists of common causes of back and neck pain such as trauma, disc herniation, osteoporosis, rheumatic diseases and pathologic conditions as malignancies.

A distinction between mechanical causes and pathologic conditions can be presumed clinically. Back pain that resolves with bed rest and limitation of physical activity points towards mechanical causes. On the other hand, pain of insidious onset with evolving neurologic deficits, prolonged pain, aggravating at night or with rest and accompanied by other general signs and symptoms should raise awareness for pathologic conditions. Imaging and biochemical, microbiological and histopathological evaluation should be considered.

7. Microbiology

Epidemiology of the causative pathogens of spinal in-

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fections varies. Vertebral osteomyelitis can be polymicrobial, albeit usually one pathogen is responsible.[23] The infectious microorganisms are bacteria, fungi or rarely parasites; bacteria remain the predominant cause of the disease. Specifically, gram positive cocci are responsible for the most common type of spinal infection: pyogenic vertebral osteomyelitis, whereas in the past, tuberculous osteomyelitis was the commonest.[64] Although uncommon in Western world nowadays, TB remains an important cause of spinal infection in endemic countries. Patients with tuberculous spinal infection, not coming from an endemic area typically are immunocompromised or elders, possibly reflecting reactivation of a latent infection.[65] In extreme cases, spondylodiscitis is a complication of intravesical BCG (bacillus Calmette-Guerin) instillation in people treated for bladder cancer.[66] Staphylococcus aureus is the most common isolated bacterium, responsible for 20% to 84% of all spinal infections.[7],[67] Staphylococcus lugdunensis has been associated with deep-seated infections and may mimic S. aureus.[68] Staph. Epidermitis, related with iatrogenic or periprosthetic infection, has been linked with cases of spondylodiscitis.[69] Streptococci and Enterococci related spinal infections represent 5% to 20% of cases.[40] Enterobacteriae species follow with about the same incidence (7-33%). They are strongly related with concomitant urinary tract or gastrointestinal infections. Salmonella species have been linked with vertebral osteomyelitis in children, particularly those with sickle cell disease[70] . Another causative pathogen for spinal infection in children is Kingella Kingae, however, it is not routinely isolated. [71] Pseudomonas aeruginosa, a rare pathogen, is found in 0% to 6% overall positive bacterial cultures.[72],[73] IV drug abusers are more likely to be infected with Pseudomonas.[74] Cutibacterium Acnes has been implicated as causative pathogen for spinal infection, despite previously considered iatrogenic contaminant. Implant associated contamination during orthopedic surgeries is another way of seeding.[75],[76]

Brucella species should be considered in endemic areas, accounting for 30% of spinal infections.[3], [79],[80] Fungal spinal infection is rare and can occur in patients in endemic areas or certain host risk factors such as immunocompromised (Aspergillus), intravenous drug users or indwelling intravenous catheters (Candida, Aspergillus). [81],[82] Parasitic infections are extremely rare globally but common in endemic areas. Specifically, spinal echinococcosis, due to Echinococcus granulosus, is found in sheep breeding areas of the Eastern and Southern countries of Mediterranean sheep breeding. Thus, awareness and clinical suspicion is necessary in patients coming from these regions.[83]

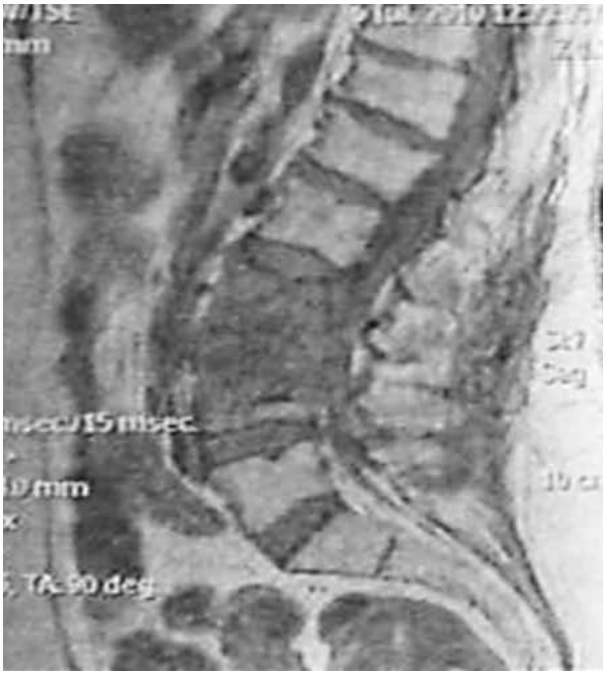

Figure 1. *Pyogenic spondylitis of the L3 and L4 vertebrae after facet joint ingections successfully treated with debridement and antibiotics.*

8. Conservative treatment

The next step is appropriate therapeutic management. Conservative treatment is the treatment of choice in uncomplicated spondylodiscitis and those who are not candidates for surgical operation. Conservative treatment involves antibiotics, analgesics, special spinal braces, physiotherapy and immobilization. The goal is pain suppression, infection eradication and ensuring the stability of the vertebral column.[84]

Regarding immobilization, usually a period of bed rest (1-2 weeks) followed by a period of patient ambulation using special rigid braces is applied. Prolonged bed rest (up to six weeks) is associated with complications such as thrombi and pulmonary emboli, thus should be applied only when necessary. Generally, early ambula-

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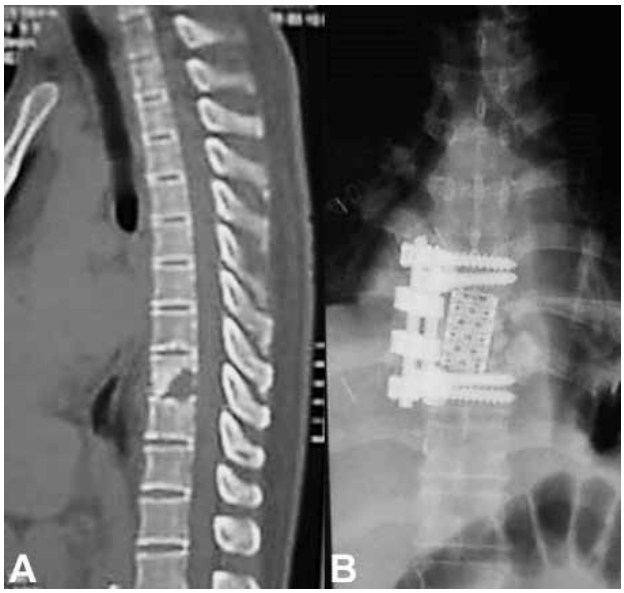

Figure 2. *(A) TBC spondylitis of the T9 vertebra (B) successfully treated with vertebrectomy and fusion, and antituberculous medication for 12 months.*

tion with spinal braces should be encouraged. [85]

Antibiotics are used invariably in the clinical management of patients with spinal infection. Generally, in patients with hemodynamic instability, progressive or severe neurologic symptoms empirical antimicrobial therapy is initiated, whereas in stable patients selective antimicrobial therapy based on the specific pathogen and susceptibility tests is applied.[61] According to IDSA 2015 guidelines, empiric regimen should cover for staphylococci, including MRSA, streptococci, and gram-negative bacilli. Such regimens include a combination of vancomycin and a third- or fourth-generation cephalosporin. In case of allergy or intolerance, daptomycin and quinolone are reasonable alternatives.[23] Common therapeutic regimen are shown in the following table:

Treatment of spinal tuberculosis necessitates a complicated combination of antimicrobial agents.[91] A commonly used protocol constitutes of isoniazid, rifampicin, ethambutol, and pyrazinamide.[92] Brucella spondylodiscitis is treated with a combination of either streptomycin plus doxycycline or rifampin plus doxycycline.[11] Management of patients with fungal spinal infection involves a variety of drugs; azoles and amphotericin B are the most common choices.[93],[94]

Prolonged antibiotic treatment is recommended due to the limited bone penetration of most antimicrobials.[95],[96] Nevertheless, the optimal duration remains a debatable topic with most studies suggesting a 6-8 week regimen.[97] Accordingly, the 2015 IDSA guidelines recommend a 6 week antibiotic therapy.[23] This is mainly based on a randomized clinical trial that showed that 6 weeks of antibiotic treatment is noninferior to 12 weeks. The 6-week recommendation is, also, supported by another retrospective study in which the first group was treated for less than 6 weeks and the second for more than 6 weeks. The outcomes, rates of relapse and deaths were comparable between the two groups.[84]

Treatment can be discontinued after 6 weeks in most patients with clinical improvement. However, those diagnosed with Brucella, Tuberculous or fungal infection should continue their therapy for the targeted duration.[4],[98] In case of complications such as abscess formation, the duration of treatment is prolonged.[99] Pediatric patients should receive intravenous antibiotics for about two weeks, followed by oral antibiotic for another one to three weeks if there is clinical and laboratory improvement.[99]

There is controversy regarding the switch from parenteral drug administration to oral. Intravenous antibiotics are used initially for 2 to 4 weeks in most cases.[30], [100] Recent studies argue that an early switch to agents with great oral bioavailability has similar efficacy to prolonged intravenous drug administration.[62],[101]

Discontinuation of antimicrobial therapy is considered in neurological deterioration with imaging tests indicating progressive destruction. Furthermore, a different approach should be considered if the expected clinical improvement is not achieved.[100] In either case, attempts to isolate a pathogen should be made.

9. Surgical management

A surgical approach is deemed necessary in case of failure of conservative measures.[102] Other indications for surgery are symptoms persistence, onset or progression of neurologic deficits, spinal instability, abscess larger than 2.5 cm, signs of ischemia or compression and deformities such as kyphosis or scoliosis.[103],[104] Urgent operation is indicated in septicemia

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TABLE 3.

Criteria for absolute and relative surgery indications. (Saeed et al., 2019)

Indication for surgery	Absolute	Relative
Neurologic deficit	+	-
Spinal instability/ deformities (e.g. Kyphosis)	+	-
Spinal core compression/ cauda equina	With neurologic deficit	Without neurologic deficit
Space occupying/ non drainable abscess	+	-
Sepsis	+	-
Conservative treatment failure	-	+
Extensive spread of the infection	Antibiotics non responsive, clinical, laboratory, imaging deterioration with positive cultures	Without laboratory and clinical deterioration

or rapid clinical deterioration with no response to drug treatment.[30],[99]

Thorough surgical debridement and maintenance or restoration of vertebral stability are the principal goals. Open surgery with extensive debridement of the infected tissue is most times recommended while minimally invasive surgery is an alternative method. [105]

Anterior approach is indicated for anterior debridement and stabilization ,whereas the posterior approach is indicated for decompression of a primary posterior epidural abscess with concomitant posterior spinal instrumentation.[106] A combined anterior-posterior approach has been occasionally used.[105],[107]

Thorough debridement may result in extensive tissue loss endangering the vertebral column's integrity. Therefore, instrumentation and bone grafting are used to stabilize the spine. However, some authors believe that metallic implants are possible foci for bacterial adherence.[103] Nevertheless, spinal instrumentation provides stability and increased fusion rates.[107] Moreover titanium alloy implants are less prone to colonization than stainless steel ones. [108] Additionally, less time of patient immobilization is required. [109]

In postoperative spinal infections with metallic implant involvement, implant removal is most times mandatory.[67] However, stable grafts adherent to native bone should be left in place. If implant removal results in fracture of the fusion mass, bone grafting should be done to ensure alignment of the vertebral column.[110]

10. Conclusion

Spinal infection is a well-documented disease which predominantly affects people with certain risk factors and people from endemic areas. The most common pathogens are bacteria, especially Staphylococcus species. Diagnosis is quite challenging, requiring collaboration of physicians from different fields of medicine. Appropriate management remains an area of controversy. Most evidence-based guidelines along with experts' opinion recommend a conservative approach of antimicrobial drugs and patient immobilization. Surgical treatment may be considered in infection persistence, and extensive disease. Surgery involves broad debridement, bone grafting and spinal stabilization. Publication of more studies is crucial to ensure optimal diagnostic evaluation and disease management.

Conflicts of Interest

The authors declare that they have no conflicts of Interest.

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REVIEW ARTICLE

Current Concepts in Hematogenous Septic Spondylodiscitis

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ABSTRACT

Hematogenous Septic spondyloDiscitis (HSD) is a rare but serious infectious disease which affects in an increasing rate immuno-compromised patients. The most common clinical symptom in HSD is a constant and increasing nocturnal axial spinal pain, while consequently different degrees of residual neurological symptoms from nerve roots and/or spinal cord may appear. The most frequent causative agent is Staphylococcus Aureus followed by the second most common to be Gram(-) bacteria. Since the disease course is chronic and clinical symptoms are not specific, surgeons should be aware that the time between the onset of the infection and final diagnosis is prolonged. MRI is mostly used to investigate HSD, however F-18 FDGPET has been recently proved to be more accurate than MRI in the detection of HSD. A delayed HSD diagnosis potentially increases morbidity and mortality while the final diagnosis is mainly based on biopsy and blood culture results. Conservative treatment is the mainstay in cases with no residual neurological symptoms consisting of antibiotic therapy and immobilization. Surgical treatment is used in patients with neurological deficit, spinal instability or drug resistance, comprising of conventional open approaches such as anterior, posterior or combined and transcutaneous approaches. The use of metallic implants does not interfere with favorable outcome and recurrence rates. The overall mortality rate ranges from 1.5%-38%. Rates of disability of up to 31% have been reported with residual spinal dysfunction or persistent pain after recovery followed by spinal infection. The outcome of treatment is influenced by the type of infection, age, comorbidities and the degree of neurologic compromise before treatment.

KEY WORDS: Spine infections; Spondylitis; Spondylodiscitis; Hematogenous Spondylitis

Introduction

Hematogenous septic spinal infection consists of several pathologies such as spondylodiscitis, primary epidural abscess, pyogenic facet arthropathy, diskitis or spondylitis [1]. It is an uncommon disease with an estimated incidence of 0.2 to 2.4 cases per 100,000 people per year [1].

Hematogenous Septic sponyloDiscitis (HSD) is a relatively rare condition that makes up 2% to 7% of spinal infection cases. The incidence of HSD has been increased in the recent years mostly because of the prolonging of average age, malnutrition, immuno-suppression (AIDS, chemotherapy, diabetes mellitus, chronic renal failure, etc) [2]. Hospital in-

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fections nowadays are a common source of HSD, with 1/3 of these infections to be catheter-related, with higher mortality and relapsing rates [3].

Discussion

The main causative microorganisms include Gram(+) bacteria, especially Staphylococcus aureus, which are responsible for the 40-60% of the cases [1] and on the other hand Gram(-) bacilli for the 15–23% of the HSD cases [1]. Staphylococcus aureus was reported to be the main causative agent that promotes abscess formation [1, 4, 5-11]. MSSA is more likely to be associated with epidural abscess than Gram(-) bacilli [4, 6, 7, 10]. Enterococcal HSD is frequently (26%) associated with endocarditis, therefore, patients with enterococcal HSD should undergo a cardiac ultrasound.

In countries with an increased frequency of brucellosis, Brucella varies from 33% to 44% of HSD cases [1, 12].

Gram(-) bacteremia was much more common in the elderly than in younger patients mostly because of the increased urinary tract infection on elders [11]. Although most of the HSD are caused by a single organism, polymicrobial infection was reported by the 1-10% of the patients [13].

The clinical symptoms of HSD are non specific including axial spinal pain and paravertebral muscle spasm. The rate of patients that present with neurological involvement ranges from 10% to 50%. The reported delay between the onset of initial symptoms of HSD and the final diagnosis ranges from 2 to 6 months [3, 13].

Clinical manifestations of HSD in elderly or immuno-compromised patients may be associated with absence of localized symptoms [14]. The most common localization of HSD is the lumbar (49%), while the least common is the cervicothoracic spine (2%) [13].

Plain radiographs have low sensitivity in the early stages of HSD, as abnormalities usually are developed later on. CT-scans are sensitive in detecting signs of HSD but they do not demonstrate the soft tissue with high accuracy. Abnormalities in the CT-scans are visible in the first 2 weeks in about 50% of the patients. Magnetic resonance imaging (MRI) is the most sensitive for confirming an early HSD diagnosis and it possesses the highest importance in diagnostic procedure. With 96% sensitivity, 94% specificity and 92% accuracy, MRI can show details in anatomically pathological alterations [15, 16]. However, disadvantages of MRI contain artifacts due to metallic implants, occasional similarities between spondylodiscitis, degenerative disease [15-17] and reduced sensitivity in patients with short duration of symptoms [15-17]. A recent meta-analysis revealed that F-18 FDGPET has better diagnostic accuracy than MRI for the detection of HSD [18].

Increased ESR and CRP are common findings in greater than 90% of HSD cases. Leukocytosis occurs in <50% of the cases. CRP is superior to ESR in the evaluation of HSD as it rises more quickly and is less influenced by other plasma factors [3].

Blood cultures can be very useful in the diagnosis of HSD and present a positive identification in about 50% of the cases [3]. Biopsy provides positive cultures in >75% of the cases [3, 13] however, the proportion of HSD with negative culture result ranges from 21% to 34% [13]. If polymicrobial infection is suspected, biopsy is mandatory [3, 13].

False negative blood culture or biopsy results are frequently found in patients, who were treated with empirical antibiotics before microbiological diagnosis; therefore, a second biopsy should be performed when the initial culture results are negative [13].

Common complications of HSD are axial pain, instability, segmental kyphotic deformity, neurological impairment like radiculopathy and paraplegia, paravertebral or primary epidural abscess which is reported to occur at rates ranging from 5.7% to 29% [1] or secondary epidural abscess that is more frequent and ranges from 38% to 94.2% [3, 13] associated with significant morbidity and mortality [3, 13].

The management of HSD firstly includes the identification of the causative agent and antibiotics administration [19, 20]. Early treatment of HSD may decrease morbidity and mortality. Most of the uncomplicated HSD cases can be treated with immobilization and intravenous antibiotics. Most guidelines recommend 6-12 weeks of parenteral antibiotic treatment for HSD [20]. Optimal duration of parenteral antibiotic therapy and of subsequent oral ther-

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apy still remains unclear [20, 22-24].

Surgical indications include failure of conservative treatment, intractable axial pain, instability, neurological deficit and abscess formation. Anterior, posterior, or combined approaches for debridment, decompression and stabilization in single or 2-staged procedures have been described [25-30].

The most important advantages of the anterior procedure are that it does allow radical resection of the infectious focus (disc, endplates, abscess evacuation, etc) and does enable satisfactory interbody fusion. Subsequently, patients have rapid infection resolution, early and frequent bony fusions. Laminectomy has a limited role in the decompression of HSD because the pathology is located anteriorly in the vertebral body and thus a posterior decompression is difficult to access the lesion and it may also cause instability because the posterior elements will be removed; therefore it is contraindicated [1, 13, 25-30].

The anterior approach decreases the postoperative pain and provides early ambulation and protects posterior ligamentous structures. Thoracotomy provides a good exposure from T5 to T12, while the contralateral hemithorax must be chosen for patients, who had previous chest operation to prevent approaching related complications such as bleeding, atelectasis or pneumothorax [25]. However, some authors reported on a 55.5%-87% fusion rate via posterior approach surgery and instrumentation [13].

Restoration of the destructed anterior spinal column is paramount for both restoration of stability and infection healing through fusion. Most authors recommend a double approach including anterior debridement with vertebrectomy supplemented with posterior instrumentation and fusion. This combined surgery seems to be well tolerated by patients with comorbidities, who suffer from HSD and it results in pain reduction, faster spinal fusion, reduction of associated segmental kyphotic deformity and maintenance of correction with little loss of correction and early patient mobilization [13].

A quite recent study that systematically reviewed on 50 articles and 4173 patients showed that conservative management remains the first-line treatment of HSD justifying previous case series. Decompression with instrumented fusion was the most commonly performed intervention reported (79%), compared to decompression alone (22%). Combined with anterior and posterior approach was performed in 33% and staged surgery was performed in 26% of surgical patients. Repeated surgeries were necessary in 13% of patients among the surgery-specific series. This review concluded that surgery may be indicated: 1) for progressive pain 2) for persistent infection on imaging 3) for neurologic deficits. If surgery is required, reported literature shows potential for significant pain reduction, improved neurologic function and a high number of patients returning to a normal functional/work status [31].

Various autografts and allografts have been used to reconstruct the anterior column. Because of the complications and morbidity associated with harvesting iliac bone autografts and the recent enthusiastic outcomes with metallic implants, vertebral body replacement with titanium mesh cages with autogenous bone graft has emerged as a viable option for reconstructing a deficient anterior spinal column contributing this way to infection healing [13, 28, 30].

Although previously spine surgeons were reluctant to the instrumentation of an infected spine, because metallic implants may hinder the antimicrobial treatment, recent studies focusing on the issue of Titanium implants have shown the usefulness, stability, and safety with minimal recurrence rate of internal fixation in eradication of an active spinal infection [13, 28, 30].

Minimally invasive surgical techniques can be used to provide temporary stabilization in some cases that spinal instability occurred [26]. These techniques diminish the major surgical stress and provide early and safe mobilization avoiding complications related to immobilization of sick and elderly patients.

A recent retrospective study [27] concluded that mini-open anterior debridement and lumbar interbody fusion in combination with posterior percutaneous fixation via a modified ALIF approach results in little surgical trauma and less intraopera-

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tive blood loss, acceptable postoperative complications, and is effective and safe for the treatment of single-level lumbar pyogenic spondylodiscitis. This approach could be an alternative to the conventional open surgery.

The overall mortality rate of HSD patients ranged from 1.5% to 38% [13, 32]. The large variance in these reported mortality rates may be attributed to different follow-up periods, varying in-hospital 6-month or 1-year mortality rates, and different causative microorganisms such as drug-resistant bacteria [13, 33-36].

There is little published data regarding the long-term neurologic and functional outcome or quality of life, in patients with HSD, managed operatively or non-operatively. Rates of disability of up to 31% report on residual spinal dysfunction or persistent pain after recovery following spinal infection and diagnostic delay to be associated with poor prognostic outcome. Poor functional outcome following HSD is common at long-term follow up, even in patients with apparent full neurologic recovery. This suggests under-reporting of poor outcome in series using neurologic deficit solely in order to qualify poor outcome [33-36].

Conclusion

The incidence of HSD is progressively rising due to the availability of more efficient imaging and the increase in vulnerable patients (elderly, immune-compromised, etc). Although MRI is the most sensitive examination for confirming an early HSD diagnosis, recent research showed that F-18 FDGPET has higher diagnostic accuracy than MRI for the detection of HSD. There is still some controversy regarding the best treatment of HSD. Although the mainstay of treatment for HSD is long-term antibiotic therapy and bracing, surgical intervention is recommended in cases of complicated HSD (spinal instability with vertebral destruction, paravertebral and/or epidural abscess formation, and/or associated neurologic deficits). Minimally invasive surgical techniques have been successfully used to provide debridment of infection and stabilization, in some cases in elderly and immuno-suppressed patients who cannot withstand an open major surgery. Spinal decompression and instrumentation via anterior, posterior or combined approach is indicated in most of the patients with complications even those with mild or medium severity comorbidities. Moreover, the use of titanium instrumentation does not increase the risk of infection or resistance to antibiotics. High rates of mortality and disability have been reported in HSD patients with increased comorbidity and preoperatively existed neurologic impairment.

Conflicts of Interest

The authors declare no conflict of interest.

The authors declare that no funding has been received for this research.

The authors declare that the research was performed according to the ethical standards as described by the Declaration of Helsinki and that an informing statement consent for participation in the study was obtained from all subjects.

The authors declare that the Hospital Ethics Committee approved this research.

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ORIGINAL ARTICLE

Surgery Improves Pain and Quality of Life in Multiple Myeloma Patients with Symptomatic Osteolytic Spinal Lesions

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ABSTRACT

Purpose: A prospective study that aims to present the functional outcome and the survival of 21 consecutive selected Multiple Myeloma (MM) patients who underwent 25 surgeries for symptomatic vertebral body osteolysis.

Methods: 25 wide spectrum surgeries including percutaneous augmentation, hybrid fixation and circumferential decompression were performed for symptomatic vertebral body osteolysis in 21 selected patients with MM. Tomita osteolysis classification, Karnofsky disability scale, ASIA neurological impairment scale and VAS pain scale were used. Survival analysis was performed.

Results: All patients were followed for a minimum of 6 months postoperatively. Karnofsky Index improved from 66%±20% preoperatively to 81.3%±15%, onemonth and 83%±10% one year postoperatively. VAS score significantly reduced in all patients from 7.08±2 preoperatively to 3.35±1.5 at the latest evaluation. One patient with ASIA grades D and 2 with ASIA grades C improved postoperatively to ASIA E. The one-year survival from index diagnosis was 85.2% (95% CI, 60.6% - 96.0%), while it dropped to 55.4% (29.4% - 75.1%) five-year postoperatively. The one-year survival rate from index surgery was 65.9% (95% CI, 38.8% - 83.2%), and dropped to 33.5% (95% CI, 11.1% - 58.0%) five-years postoperatively.

Conclusions: There are several modalities of surgery for symptomatic osteolytic vertebral body lesions in MM patients. Surgery was proved a safe procedure with few complications it reduced pain and improved quality of life. Together with hematological and radiation therapy it may increase the survival of MM patients.

KEY WORDS: multiple myeloma; spinal lesions; kyphoplasty; tumor

Introduction

Multiple myeloma (MM) is a systemic neoplasm of plasma cells that affects 1-4 per 100,000 people per year and is commonly associated with bone pain, usually due to spinal and rib osteolyses, in 70% of this kind of patients [1-4]. Skeletal osteolyses are the most frequent cause of morbidity and mortality in patients affected by this pathology [5].

Spinal involvement can be the initial clinical

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presentation of the disease in 34-64% of the MM patients, leading often to intractable pain and/or neurological complications due to spinal cord or cauda compression [6], [7]. In the one third of the patients, MM is diagnosed after a pathological spinal fracture has occurred[8], moreover new vertebral body fractures occur in approximately 15-30% of patients with MM annually [5].

Recent advances in therapeutic approaches, such as autologous stem cell transplantation, radiotherapy and chemotherapy, bracing and surgery in certain cases, helps towards lessening the occurrence and severity of adverse effects of this disease, as well as managing associated complications [7], [9-14]. Although medical treatments & radiation help towards slowing down the natural history of MM [5], they do not correct any structural vertebral destruction that may have already been occurred, either as osteolysis or as a fracture and wedge deformity in up to 70% of all patients with MM [15-17]. In vertebral body osteolyses and/orvertebral body fractures, the main goal of surgical intervention is pain relief, reduction of angular deformity for prevention of potential neural element compression and spinal canal decompression. In the last few years, percutaneous Minimal Invasive Surgery (MIS), vertebral augmentation techniques such as Vertebroplasty (VP), Balloon Kyphoplasty (BK) and KIVA [18], are well tolerated and drastically decrease pain while simultaneously improve patient's quality of life [15], [16], [17], [19]. Radiofrequency-targeted vertebral augmentation was recently developed to address potential adverse issues reported with VP and BK [2], [20], [21], [22]. However, in patients with vertebral body osteolyses with involvement of the posterior vertebral body wall some authors have raised concerns regarding the high leakage rates associated with low viscosity polymethylmethacrylate (PMMA) bone cement [23], [24], [25], [26].

Survival after MM is highly variable; however, recent studies of various drug therapies have led to promising outcomes and reported survival beyond 10 years [12-13].

The aim of this prospective study is to present the functional outcome and survival rates following surgical treatment in 21 consecutive selected MM patients, who underwent a total of 25 surgeries, by a single senior orthopedic spine surgeon, in one tertiary institution and to review the relative literature.

Materials and methods

Twenty-one consecutive selected patients (7 women, 14 men) suffering from MM with established spinal involvement and associated intractable pain, who were surgically treated between 2004 and 2012 in the authors' Orthopaedic institution by a single spine surgeon (Table 1), were prospectively evaluated. The average±SD age of the patients at the index surgery was 70±21, range 49-90 years. The Tomita classification [31] was used to grade the extension of vertebral bodyosteolytic lesions, (Table1). VAS (0-10 scale) [28] and ASIA neurological classification [29] were used for evaluation of patients' pain level and neurological function. The quality of life was evaluated with the Karnofsky Index [30]. The inclusion criteria and indications for surgical intervention were MM or solitary spinal plasmocytoma with symptomatic spinal involvement (painful osteolysis±spinal fracture, neurological impairment or potential or progressive neurological impairment due to vertebral body fracture), intractable spinal pain resistant to conservative treatment (pain killers, brace, etc). Our surgical strategy was as follows: Patients neurologically intact and osteolysis in≥1 non-contiguous vertebral body (-ies) were treated with vertebral augmentation solely; in patients with multilevel contiguous cervical spine involvement vertebrectomy, mesh cage plus posterior fixation was made; patients with neurologic impairment were treated with posterior MIS reduction, pedicle screw stabilization plus vertebral body augmentation; patients with posterior cord/cauda compression (posterior spinal elements involvement) were treated via wide laminectomy and posterior pedicle screw fixation. Patient survival, using all-cause mortality as event of interest, was estimated with the Kaplan-Meier method [32]. Survivals from: a) index MM diagnosis and

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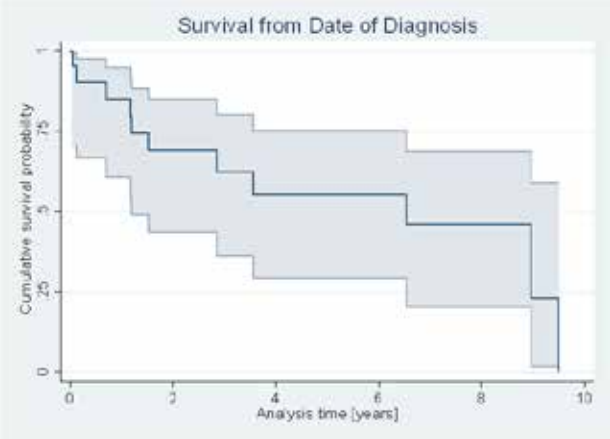

Fig. 1: *SURVIVORSHIP. The one-year survival from the index diagnosis was 85.2% (95% CI, 60.6% - 96.0%), while the 5 year survival dropped to 55.4% (95% CI, 29.4% - 75.1%), see Figure 1.*

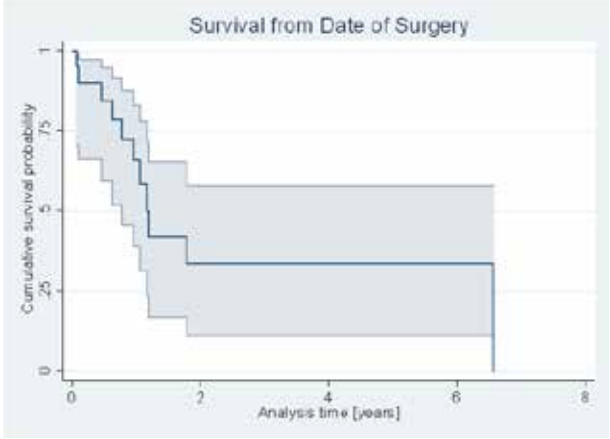

Fig. 2: *The one-year survival from the index surgery, was 65.9% (95% CI, 38.8% - 83.2%), while the five year survival dropped to 33.5% (11.1% - 58.0%), see Figure 2.*

b) index surgery were calculated.

Results

The most common spinal location of vertebral body osteolysis was the thoracolumbar junction (16/25 cases), and the less common was the cervical spine with only1 case (4%). Multilevel spinal localization was observed in 9/25 cases (Table 1).

Percutaneous augmentation was performed in the majority of the cases: 13/25 (52%); followed by hybrid MIS in 7/25 cases (28%); and posterior pedicle screw fixation in 4/25 cases (16%). Combined open anterior decompression corpectomy and mesh cage implantation supplemented by posterior lateral mass stabilization for multi-level cervical osteolytic lesions and associated kyphotic deformity was performed in one female patient (4%) for cervical kyphosis and potential for cervical spinal cord compression (Table 1).

Four from the 21 patients, were re-operated at different spinal levels for new symptomatic vertebral bodyosteolyses and/or associated fractures (Table 1). One patient (cases No. 6.1 & 6.2, Table 1), with previous augmentation of T11-vertebra was re-operated 6 months later because of pain in two adjacent vertebrae (T9 and T10), (Table 1). In one additional patient (cases No. 12.1 & 12.2,Table1), a cephalad extension of an already existed posterior pedicle screw construct was made for new T2 vertebral body osteolysis, 24.5 months following primary decompression and posterior stabilization for severe osteolytic lesion in a lower level (Table 1).

Five patients (cases 2, 9, 15, 18.1 & 19) were treated with MIS with or without simultaneous vertebral augmentation (Table 1).

The time lapsed from the index diagnosis to index surgery, for the 17/25 (68%) cases for which the diagnosis was already preoperatively known was 40±6.15 months (range 0.25-105).

Functional results

Daily performance (Karnofsky Index) was significantly improved from 66%±20% before surgery to 81.3%±15% one month following surgery and 83%±10%, one year after surgery in survived patients, (Table 2).

VAS score was reduced from 7.08±2 preoperatively to 3.35±1.5 at the time of last postoperative evaluation.

No neurological deterioration was observed postoperatively in 18/19 patients with preoperative ASIA grades E and D. One patient (case 5, Table 2) with preoperative ASIA grade D and 2 patients, cases 12.1 & 21.2, with ASIA C grades improved postoperatively to ASIA E, Table 2.

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TABLE 1.

Table 1: Cumulative data on 21 MM patients who underwent 25 surgeries for painful vertebral osteolyses. Four patients underwent two subsequent surgeries for other level osteolyses. Patients no 6, 12, 18 & 21 were operated twice. (F=female & M=male)

Cases NO	AGE AT SURGERY	GENDER	TOMITA OSTEOLYSIS GRADE	NEUROLOGICAL IMPAIRMENT ON ADMISSION	LOCATION OF OSTEOLYSES (Fractures are indicated)	SURGICAL TREATMENT	SURVIVAL FROM DIAGNOSIS (days)	SURVIVAL FROM SURGERY (days)
1	65	F	TYPE 6	NO	C3, C5, C6	COMBINED STAGED 360O (POST. C2-C6 & ANTERIOR DECOMPRESSION C3, C5, C6 WITH MESH CAGE)	2386	2401
2	83	F	TYPE 6	PARAPARESIS INCOMPLETE	L3, L4, L5	MIS POST. STABL3-L5	559	650
3	73	M	TYPE 7	NO	FRACTURES in T5, T8, T9, T10, T11	AUGMENTATION: T5, T8, T9, T10, T11	2566	2570
4	73	M	TYPE 7	NO	FRACTURES in T7, T12, L1, L2	AUGMENTATION: T7, T12, L1, L2	432	385
5	53	M	TYPE 7	PARAPARESIS INCOMPLETE	FRACTURES in T8, T10, L1, L2, L3	HYBRID FIXATION AUGMENTATION: L1, L2, L3, DECOMPRESSION & POST. STAB. T7-L3	508	498
6.1	68	F	TYPE 1	NO	T11	AUGMENTATION: T11	2990	414
6.2	69	F	TYPE 6	NO	T9, T10, T11	AUGMENTATION: T9, T10	2990	217
7	73	F	TYPE 6	NO	FRACTURES in L2, L3, L4	AUGMENTATION: L2, L3, L4	3486	339
8	63	M	TYPE 6	NO	L2-L5	AUGMENTATION: L2, L3, L4, L5	1299	226
9	78	F	TYPE 7	PARAPARESIS INCOMPLETE	FRACTURES inT11, L1	HYBRID FIXATION AUGMENTATION: T11, O1 MIS POST. STAB. T12-L2	38	31
10	81	M	TYPE 7	NO	FRACTURES in T11, T12, L4, L5	HYBRID FIXATION AUGMENTATION: T11, T12, L4, L5 DECOMPRESSION & POST. STAB. T10-L2	422	349
11	70	M	TYPE 6	NO	L1, L2, L3, L4	AUGMENTATION: L1, L2, L3, L4	1222	553

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12.1	49	M	TYPE 4	PARAPARESIS INCOMPLETE	FRACTURE in T6 WITH EPIDURAL METASTASIS	DECOMPRESSION & POST. STAB. T3-T8	1043	897
12.2	51	M	TYPE 6	NO	FRACTURE in T2	EXTENSION OF POST. STAB. TO T1	1043	165
13	65	M	TYPE 7	NO	FRACTURES in T11, T12, L2, L3, L4	AUGMENTATION: L2, L3, T11, T12, L4	1293	617
14	83	F	TYPE 7	PARAPARESIS INCOMPLETE	FRACTURES in T12, L1, L4, L5	AUGMENTATION: T12, L1, L4, L5	3276	425
15	77	M	TYPE 3	NO	FRACTURE in L3	HYBRID FIXATION AUGMENTATION: L3 MIS POST. STAB. L2-L4	3471	435
16	78	F	TYPE 6	NO	FRACTURES in T12, L1	AUGMENTATION: T12, L1	414	420
17	75	M	TYPE 7	NO	FRACTURES in L1, L2 OSTEOLYSES in T10, T11, T12, L3	HYBRID FIXATION AUGMENTATION: L1, L2 POST. STAB. T8-L5	968	687
18.1	64	M	TYPE 3	NO	FRACTURE in L3	HYBRID FIXATION AUGMENTATION: L3 MIS POST. STAB. L2-L4	3236	3250
18.2	69	M	TYPE 6	PARAPARESIS INCOMPLETE	FRACTURE in L5, OSTEOLYSES in S1, S2	AUGMENTATION: L5, S1, S2	3236	1295
19	78	M	TYPE 7	PARAPARESIS INCOMPLETE	FRACTURES in L2, L3, T7, T8, WITH EPIDURAL EXTENSION	HYBRID FIXATION AUGMENTATION: L2, L3, T7, T8 MIS POST. STAB. T12-L4	14	21
20	90	M	TYPE 6	NO	FRACTURES in L2, L3	AUGMENTATION: L2, L3	249	286
21.1	63	M	TYPE 7	NO	T2, T7, T8	AUGMENTATION: T7	1732	1760
21.2	64	M	TYPE 7	PARAPARESIS INCOMPLETE	FRACTURES in C7, T2, T3, T6, T7, T10, T11, L1	POST. STAB. C5-T4	1732	1534

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Survivorship

The one-year survival from the index diagnosis was 85.2% (95% CI, 60.6% - 96.0%), while the 5 year survival dropped to 55.4% (95% CI, 29.4% - 75.1%), see Figure 1.

Discussion

The reported median survival time from the index diagnosis has increased from an average of 2.5 to 4.5 years[21], [33]. The one-year survival in our patients from index diagnosis was 85.2% (95% CI, 60.6% - 96.0%), while the five-year survival dropped to 55.4% (29.4% - 75.1%).

Expansible vertebral body osteolyses and fractures with associated wedge deformity and spinal instability are quite often present (75%) in MM patients [34] and may result in compression of spinal cord or cauda leading to neurological impairment. In our study population, neurological impairment was present on admission in 6/21 (28.9%) MM patients, slightly higher than those previously reported (22% to 25%) [11], [13]. All 6 patients with preoperative neurologic impairment improved at least one ASIA grade while no patient deteriorated postoperatively.

The high benefit of surgery in symptomatic MM patients with spinal involvement seems to be the lower surgical complication rate (8%) [43] than the one observed in patients with metastatic spinal disease (19%) [44].

A recent study [43] on the treatment of MM patients suffering from osteolytic vertebral body fractures treated with combined BK and radiofrequency showed a significant reduction of VAS score from 8.1 to 2.5, with an average reduction of preoperative VAS of 5.6 points in 75% of the operated patients. In our series, pain relief was achieved in all 23 cases that survived for more than 30 days postoperatively. VAS was reduced from 7.08±2 preoperatively to 3.35±1.5 at the time of postoperative evaluation.

Choeet al [41] reported on a 4.6% incidence of pulmonary embolism in patients with MM after VP or BK with a high correlation between PMMA in the lungs and paravertebral PMMA leak, independent of treatment type (VP or BK). In no patient in our series lung embolism was clinically evident. However, in our series, complications of lower severity occurred in 3/25 surgeries (12%) -3/21 patients- and included acute renal insufficiency and transient lower limb muscle weakness. Our complication rate is significantly lower to those previously published of approximately 37.5% in [38].

During vertebral body augmentation, surgeons are often facing pulmonary and neurologic complications related to PMMA extravasation. In MM patients, PMMA extravasation rates following VP ranges from 1% to 48%, while it is less common in BK (<2%) [15], [16], [39], [40]. Recently, Julka et al reported cement extravasation in 12/32 (37.5%) patients, all without clinical sequelae [38]. In 52 VPs in 37 MM patients, vertebral augmentation reported in 3/37 (8%) patients with transient nerve root paresis because of cement leakage, while 1/37 (2.7%) patient required nerve root decompression with PMMA removal [42]. In our series, there was only one case with cement leakage into the foramina, in a patient (case 15) with severe (Tomita 3) vertebral body bone erosion that caused temporary nerve root irritation and resolved one month later.

The one-year survival rate from the date of surgery was 65.9% (95% CI, 38.8% - 83.2%), while the five-year survival rate dropped to 33.5% (95% CI, 11.1% - 58.0%). The most common cause of death following palliative surgery was multiple organ failure because of the MM in final stage.

Formal laminectomy alone is usually not recommended for decompression and osteolysis treatment in metastatic or MM patients, because a wide posterior decompression further destabilizes the spine. Laminectomy combined with stabilization was reserved in four patients with posterior spinal canal encroachment due to posterior elements involvement and dural compression. Consistent with previous studies [45], [46], [37], spinal instability due to vertebral body osteolyses, associated with intractable pain and potential for neurologic impairment were the indications for surgery in our patients. Surgery performed in our MM patients, was patient-specific and

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TABLE 2.

Karnofsky Index pre-operatively, 1 month and 1 year post-operatively, ASIA Impairment Scale and VAS Axial Pain Scale pre-operatively and post-operatively & postoperative complications & complications outcome

Cases NO	KARNOFSKY PREOP	KARNOFSKY 1 MONTH POP	KARNOFSKY 1YEAR POP	ASIA PREOP	ASIA POP	PAIN PREOP VAS	PAIN POP VAS	POSTOP COMPLICATIONS	COMPLICATIONS OUTCOME
1	70	80	80	E	E	6	3	Ø	Ø
2	70	80	80	D	D	7	3	Ø	Ø
3	70	80	80	E	E	8	3	Ø	Ø
4	70	80	80	E	E	6	3	Ø	Ø
5	50	70	80	D	E	9	4	ACUTE RENAL INSUFFICIENCY EARLY POSTOPERATIVELY	RENAL RECOVERY WITH MEDICATION
6.1	70	80	Ø	E	E	7	4	Ø	Ø
6.2	70	80	Ø	E	E	8	5	Ø	Ø
7	70	90	Ø	E	E	7	3	Ø	Ø
8	70	80	Ø	E	E	7	3	Ø	Ø
9	50	Ø	Ø	D	Ø	8	Ø	Ø	DIED 31 DAYS AFTER SURGERY (FINAL STAGE PATIENT)
10	70	80	Ø	E	E	7	4	Ø	Ø
11	90	100	90	E	E	5	2	Ø	Ø
12.1	50	80	90	C	E	5	2	Ø	Ø
12.2	70	90	Ø	E	E	6	2	Ø	Ø
13	80	90	90	E	E	7	2	Ø	Ø
14	70	80	70	E	E	7	4	Ø	Ø
15	60	70	80	E	E	8	5	RIGHT L4 MUSCLE WEAKNESS	NEUROLOGICALLY FULLY RECOVERED
16	70	90	Ø	E	E	7	3	Ø	Ø
17	60	70	80	E	E	8	4	Ø	Ø
18.1	70	90	90	E	E	7	3	Ø	Ø
18.2	60	70	90	E	E	8	4	Ø	Ø
19	50	Ø	Ø	C	Ø	8	Ø	ACUTE RENAL INSUFFICIENCY LEFT L2, L3 MUSCLE WEAKNESS	DIED 21 DAYS AFTER SURGERY-DEATH CAUSE: ACUTE RENAL FAILURE-MULTIPLE ORGAN FAILURE SYNDROME
20	60	80	Ø	E	E	8	3	Ø	Ø
21.1	70	80	Ø	E	E	8	4	Ø	Ø
21.2	60	80	80	D	E	5	4	Ø	Ø

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ranged from percutaneous augmentation with PMMA to MIS pedicle screw fixation combined with vertebral augmentation with PMMA, anterior open decompression and combined anterior decompression plus posterior pedicle screw fixation. In MM patients with neurologic impairment due to epidural compression by the MM lesion itself, without structural deficiency of the vertebral body, radiation is often able to diminish the local tumor lesion and the associated axial pain. However, radiation therapy alone cannot treat instability induced by vertebral body osteolysis and associated pathological fractures. Spinal instability resulted from vertebral body osteolysis requires mechanical stabilization to reduce axial pain and simultaneously to prevent potentially secondary neurological impairment due to spinal cord and cauda compression.

There are two strengths in our study. The first strength is the homogenous population with only pure MM patients. In the relative literature, most studies reported on mixed populations of MM and cancer patients [15], [47]. The second strength is that all patients were operated by one senior experienced orthopaedic spine surgeon.

Conflicts of Interest

The authors declare no conflict of interest.

The authors declare that no funding has been received for this research.

The authors declare that the research was performed according to the ethical standards as described by the Declaration of Helsinki and that an informing statement consent for participation in the study was obtained from all subjects.

The authors declare that the Hospital Ethics Committee approved this research.

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ORIGINAL ARTICLE VOLUME 72 | ISSUE 1 | JANUARY - MARCH 2021

How to Avoid Complications in Kyphoplasty - the Rule of Four

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ABSTRACT

Purpose. There is no consensus on the number of levels that may be treated in a single kyphoplasty session; some authorities suggest up to four vertebrae while others have augmented more levels in one session. The purpose of this study is to define the optimal number of vertebrae that may be treated on a single operative session in a safe manner.

Methods. We retrospectively studied the patients that underwent kyphoplasty during a 7-year period (2010-2016) from a single surgeon. 70 consecutive patients were identified (mean 65 years). Overall 224 vertebrae were cemented in 82 operative sessions. Perioperative complications, 10-day morbidity, pain and kyphotic angle were analyzed. We used Stata version 9.1 for statistical analysis.

Results. Three serious (life threatening or lethal) adverse events were encountered during the 10-day perioperative period, related with multilevel prolonged operations (more than 4 levels) ($p<0.001$). The only other factor that was marginally correlated was the presence of vertebrae plana (p: 0.06). Cement leak was observed in 44% (leakage per session not per vertebrae), correlating with the number of augmented levels (23.3% in 1-2 levels, 51.5% in 3 and 64.7% with more levels, odds ratio 2.53, $p=0.005$). Pain improved from 8.2 points to 4.4 points postoperatively ($p<0.001$) and kyphotic angle from 22.9 degrees to 20.8 degrees ($p<0.001$).

Conclusion. Up to 4 levels may be safely treated with kyphoplasty in one session. Augmentation of more vertebrae especially in debilitating patients suffering from pathologic fractures leads to more cement leakage and may predispose to major complications.

KEY WORDS: Rule of Four; Kyphoplasty; Osteoporosis; Vertebral Fractures; Complications

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Introduction

Balloon Kyphoplasty (BKP) and Vertebroplasty (VP) are vertebral augmentation procedures successfully employed in the treatment of osteoporotic or malignant fractures [1-6]. In osteoporotic fractures usually a single level procedure suffices for the reduction and stabilization of the fracture; however in corticosteroid-induced fractures, and in vertebral compression fractures secondary to malignant and metastatic disease, multiple vertebral augmentation may be necessary to address the clinical condition of multilevel involvement [7-11]. Yet, there is no consensus on the number of levels that may be treated in a single session; while some authorities recommend a plateau of 4 levels per session [7, 12], there have been many reports of more than 4 levels being successfully treated in a single session [9, 10, 13-15]. The benefits both to the patient and the treating surgeon are obvious: one trip to the operating theater, less operative time overall and reduced cost (recycling of the same balloon device). However, it has been demonstrated that with increasing levels of augmentation the risk for cardiopulmonary complications rises, as well [16].

The aim of this study is to define the optimal number of vertebrae that may be treated in a single operative session in a safe manner. For this reason perioperative morbidity/ mortality were studied and correlated with the levels treated. Additional factors predisposing to complications were further analyzed.

Materials & methods

We retrospectively studied the patients that underwent kyphoplasty during a 7-year period (2010-2016) from a single surgeon (IP). 70 patients (49 women, 21 men) were identified aged between 22 and 85 years old (mean 65 years). The majority of them were diagnosed with metastatic cancer (40%), followed by osteoporosis (24%), multiple myeloma (23%) and hematologic malignancies (13%). Sixty patients were treated in a single operative session. In nine patients a second session was necessary, and one patient underwent a total of four kyphoplasty sessions. Overall 224 vertebrae were cemented in 82 operative sessions. Single-level BKP was performed in 11 sessions (13.4%); 2-level BKP in 20 (24.4%); 3-level BKP in 33 (40.2%); and 4-level BKP in 15 sessions (18.3%). More levels were augmented in three cases; two patients underwent a 5-level and one patient a 6- level BKP (3.7%). Vertebra plana and intravacuum cleft were observed in 15% and 7% of patients, respectively. In addition epidural spinal cord compression/ spinal stenosis was noted in 22% of patients(without clinical myelopathy which was considered a contraindication for the procedure [17]). Nine of these patients (13%) underwent simultaneous laminectomy (open BKP) without fusion (patients with either open or percutaneous fusion were excluded from analysis). Inclusion criteria for the procedure were pain intensity at least 4/10, recent fracture or edema as seen in the Magnetic Resonance Imaging (MRI) and clinical exam corresponding to the fracture seen on the MRI (pain at percussion at the fractured level) [17]. In cases where the patient was not suitable for MRI a bone scan was performed instead to differentiate between acute and chronic fractures [18].

The perioperative complications and 10-day morbidity were studied, and a correlational analysis was performed for adverse events and independent variables, including age, number of treated vertebrae, diagnosis, spinal cord compression, vertebra plana, intravacuum cleft, concomitant laminectomy (open kyphoplasty), and cement leakage. Cement leakage was also correlated to the number of levels treated. Pain, was evaluated with a numerical rating scale from 0-10, and the pain scores before surgery, as well as 10 days after surgery were analyzed. In thoracic or thoracolumbar fractures kyphotic angle was compared pre and postoperatively. We used Stata version 9.1 for statistical analysis and the level of significance was set to 0.05.

Results. Two life threatening adverse events (hemothorax- figures 1-3 and cardiac tamponade- figure 4) and one death (figure 5) were encountered during the 10-day postoperative period. All major complications were related to multilevel prolonged operations (more than 4 levels). Univariate analysis showed that the occurrence of major complications was correlated with the number of augmented levels (>4 levels, $p<0.001$, Fisher's exact test). The pres-

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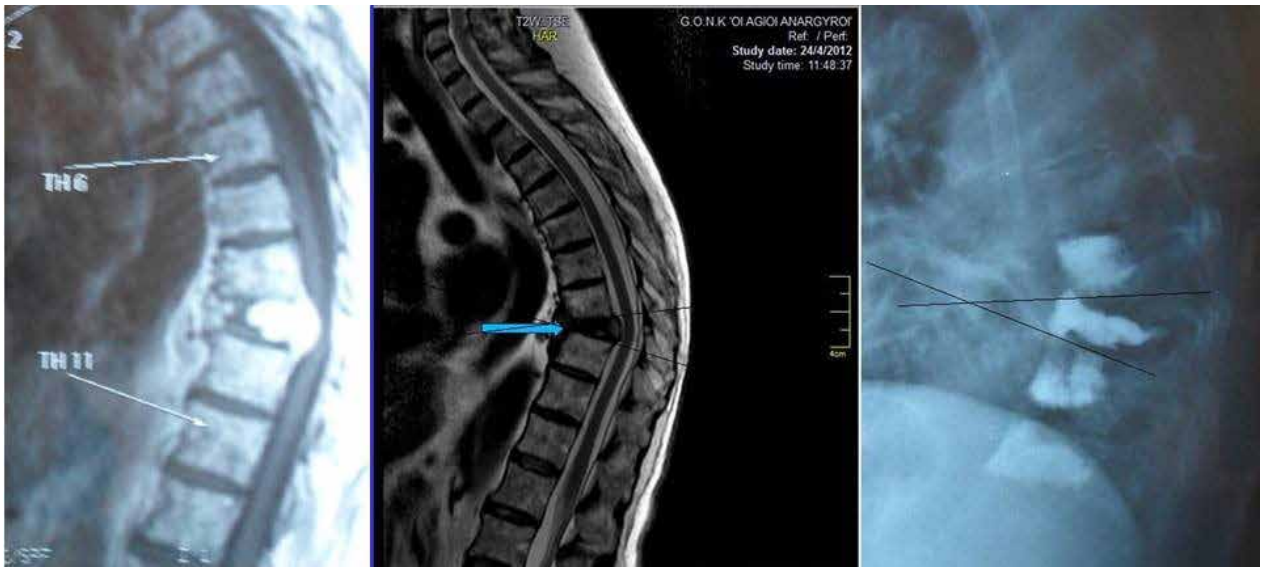

Figure 1. *A 48year old female presented with T9 metastasis from breast cancer and fracture leading to significant kyphosis (1a- sagittal T1 sequence on Magnetic Resonance Imaging- MRI) that was aggravated after radiation therapy (1b- sagittal T2 sequence on MRI). The patient was treated with multilevel open kyphoplasty (1c- lateral xray).*

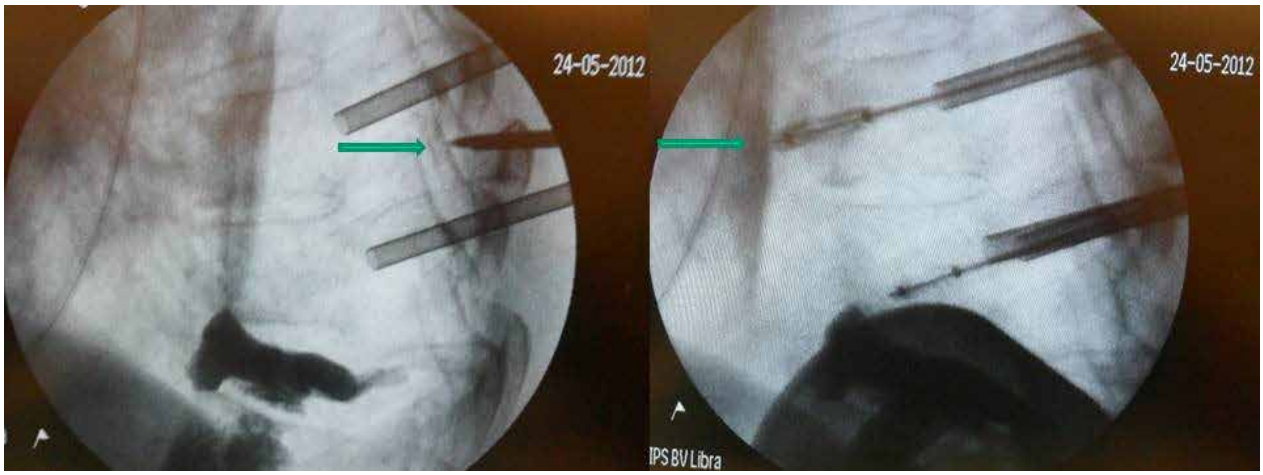

Figure 2. *A 5-level kyphoplasty was attempted instead of fusion due to severe tumor encroachment of the adjacent vertebral bodies. Since decompression was needed, we chose to augment 2 levels above and below the fracture in order to strengthen the kyphotic area and avoid catastrophic collapse. On the left image possible injury of a segmental thoracic vessel is depicted (left C-arm image, green arrow). On the right image, the balloon introducer is placed outside the vertebral body (green arrow) due to significant cancerous destruction of the vertebral body which was left uncemented.*

ence of vertebra plana was marginally correlated with complications, yet did not reach the level of significance (p=0.06, Fisher's exact test). None of the rest factors studied, including age, diagnosis, spinal cord compression, intravacuum cleft, concomitant laminectomy (open kyphoplasty), and cement leakage, were found to predispose to major complications. Logistic regression or multivariate analysis could not be performed in the present patient series, due to the limited number of major complications noted.

Cement leak was observed in 44% of operative sessions. In logistic regression analysis the presence of cement leakage was related to the number of aug-

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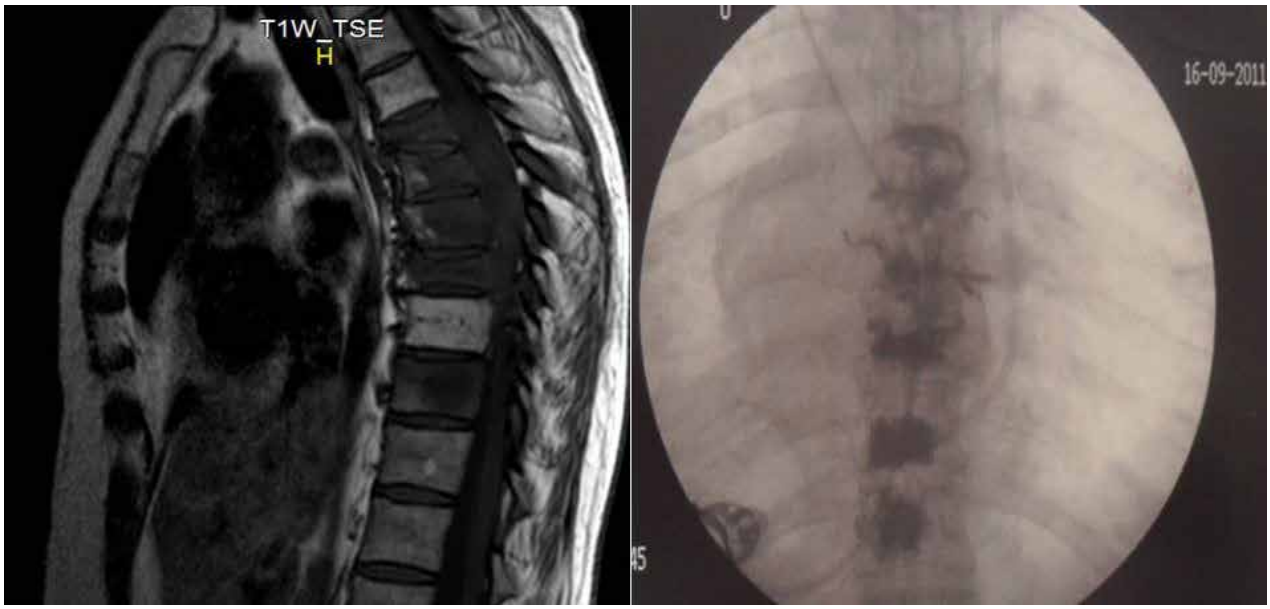

Figure 4. *A 48year old paraplegic female patient with metastasis in multiple thoracic vertebrae (left image- sagittal T1 sequence MRI) treated with 6-level kyphoplasty (right image). She developed atraumatic cardiac tamponade attributed to the prolonged prone position and osmotic exsanguination of pericardiac fluid; she was treated with pericardiocentesis that yielded xanthochromatic fluid.*

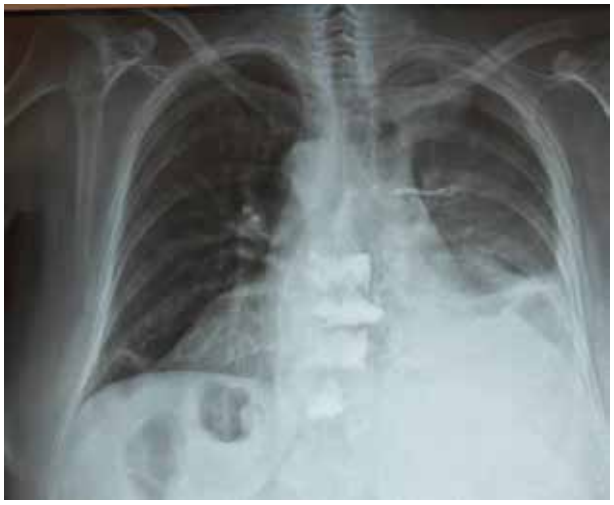

Figure 3. *Postoperative left hemothorax (same patient) that resolved conservatively. The patient is doing well four years postoperatively.*

mented levels (odds ratio 2.53, p=0.005). More precisely, the incidence of cement leakage was 23.3% in single and 2-level procedures, 51.5% in 3-level procedures, and 64.7% in 4-,5- and 6-level procedures. Nevertheless, cement extravasation caused clinical sequela only in two cases; a cement leak into the S1 foramina that caused postoperative sciatica and was surgically treated; and another T5 foramina leak that caused pain and was sufficiently managed with intraforaminal injections and oral analgesics.

Regarding pain relief, the mean score for pain significantly decreased from 8.1 (range, 7-10) before surgery to 4.4 (range, 1-5) after surgery ($p<0.001$, paired t-test).This difference should be considered not only statistically but also clinically important (a minimum difference of 2 points is considered by some authorities the minimal clinical important difference [19]. The mean kyphotic angle also changed significantly, and was decreased from 22.9 degrees (range, 18.4 – 27.4 degrees) before surgery to 20.8 degrees (range, 16.2 – 25.5 degrees) after surgery ($p<0.001$, paired t-test).

Discussion

Multilevel kyphoplasty/ vertebroplasty may be indicated in the context of multiple fractures in cancer/ myeloma patients or corticosteroid induced fractures [7-10]. The maximum number of vertebrae that may be augmented in a single session still remains an issue of controversy; societies like the Myeloma Working Group or the Cardiovascular and Interventional Radiological Society recommend

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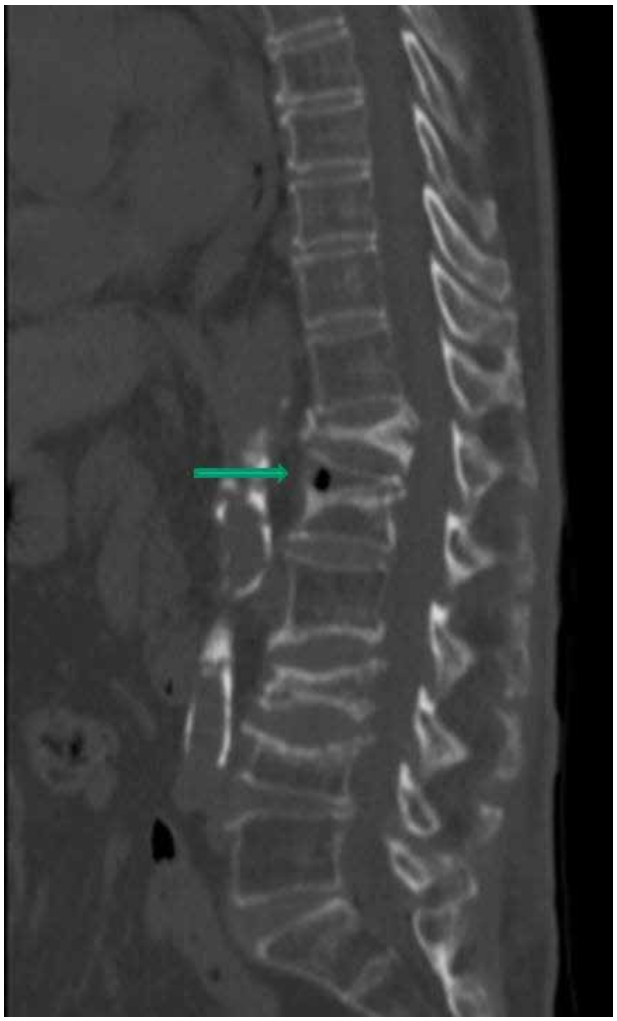

Figure 5. *A 78 year old female with multiple fractures in the thoraco-lumbar and lumbar spine due to multiple myeloma (green arrow denotes a vacuum cleft in L1). A 5- level kyphoplasty (T11-L4) was performed; shortly after the 2.5 hour operation she experienced sudden death attributed to pulmonary embolism or cardiac syncope (relatives did not give consent for necropsy).*

augmentation of up to 4 or 5 levels per session [7, 12, 20], while on the same time, there have been various studies in the literature reporting on successful multilevel vertebral augmentations (of more than 5 levels) in a single operative session [9, 10, 13-15]. Mailli etal in a comparative study of patients undergoing few level (up to three) vs. more than 4 levels found no difference between groups in terms of pain control, performance status, or complication rate including cement leakage [13]. Audat etal studied 14 myeloma patients, who received multilevel augmentation of the thoracolumbar spine (mean of 14.7 levels in a single session). The authors reported on good results, although one patient (7.1%) died from pulmonary embolism the day of surgery, possibly related to the prolonged operation and the large amount of PMMA (Polymethylmethacrylate) instilled [10].

BKP/ VP are considered safe and effective procedures with minimal complications. However silent pulmonary cement embolism may be present in up to one fourth of the patients undergoing VP (VERTOS II study [21]). Asymptomatic cement leakage in prevertebral veins, intervertebral disc or even epidural space happens frequently (on average around 10- 20% [2]). Serious complications are rare although well documented in the literature in the form of case reports. Pneumo/ hemothorax, cardiac tamponade and fatal embolism may ensue [22-28]. A reasonable hypothesis is that multilevel/ prolonged operations may lead to catastrophic results; the FDA back in 2004 highlighted this small risk "especially when multiple vertebral levels are treated in one setting" [29]. This is also suggested by our study.

The detrimental cardiovascular effects of bone cement (Polymethylmethacrylate- PMMA) are well documented in the arthroplasty literature [30-34]. For vertebral augmentation procedures where PMMA is instilled inside the vertebral body, animal studies suggest that cardiovascular parameters deteriorate during cement injection. Aebli etal reported that with augmentation of four vertebrae (VP) there is a significant decrease in mean blood pressure along with hypoxemia and hypercapnia; this is an accumulated phenomenon that becomes more prominent with increasing vertebrae treated, possibly due to increase in intraosseous pressure and fat microembolism; therefore continuous invasive monitoring during VP is recommended [35]. Benneker etal also found that fat embolism along with increase in mean arterial pulmonary pressure was significant in a sheep model after VP, whereas a pulsed jet- lavage technique (that removes intravertebral fat) alleviated this phenomenon [36]. In human studies transient hypotension after VP has also been reported [37]; Kaufmann etal found a statisti-

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cal but not clinically significant drop of oxygen saturation 10 minutes after VP[38]. However, this study included single or 2-level procedures which in general are very well tolerated. On the other hand Uemura and colleagues noticed that PaO2 decreased during percutaneous VP which strongly correlated with the number of treated vertebral bodies. Reasons for this pulmonary compromise include fat or cement emboli, increased oxygen desaturation from prolonged administration of sedative drugs, decrease in functional residual capacity as a result of thoracic compression attributable to the prone position etc [16]. Although we did not measure cardiovascular markers in our patient cohort, we did find that cement leakage is proportional to the number of treated vertebrae, a factor that may theoretically predispose to complications (along with the bigger cement volume instilled). The higher incidence of cement leakage found in our patients, compared to the reported incidence in the literature, is attributed to the higher percentage of malignant fractures which have a higher propensity of leakage than osteoporotic ones [2]. Another factor is that cement leakage was assessed with respect to operative sessions, rather than to levels treated, leading to a factitious higher incidence.

The results of our study are in accordance with the BKP literature regarding pain control and sagittal balance correction. Serious complications were rare and strongly correlated with the number of treated vertebrae. This led us to modification of our therapeutic strategy and we have abandoned the lengthy multilevel procedures. We stop at 4 levels which is translated to a less than 2-hour operation, thereby minimizing our complication rate. To our knowledge, this is the first series to deal with the optimal number of levels that should be augmented on a single session in a more evidenced based way. Vertebrae plana may also predispose to complications since accuracy is needed in the trajectory of the needle, bipedicular approach is fostered most of the times because the lateral pillars of the vertebral body are generally better preserved and penetration of the body/ cement extravasation or encroachment of the foramen or canal is more likely to happen. It is not advisable for unexperienced operators to undertake severely collapsed vertebrae.

The retrospective design, the small number of patients, as well as the small number of complications that were encountered are important limitations that reduce the power of the present study. However, it is a single surgeon series with patients being treated in a uniform way. Additionally, it is our belief that the safety issue hereby studied is rather important and interesting, and guidelines on this matter are missing; surgeons have reported augmenting up to sixteen levels at one session[10]. Larger prospective trials may shed more light on this controversial topic.

In conclusion we believe the surgeon should avoid the temptation of performing more than a 4-level operation and prefer to return subsequent times to the operating theatre. Also meticulous approach and careful planning is needed in severely deformed vertebrae. In this manner, life threatening complications may be avoided.

Conflict-of-interest statement

On behalf of all authors, the corresponding author states that the work presented here is original and has not been concurrently submitted or published in another journal/media. The authors declared no conflict of interest: no benefits have been or will be received from a commercial party related directly or indirectly to the subject matter of this article.

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CASE REPORT
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Management of neurofibromatosis spinal deformity, a case report and review of the literature

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ABSTRACT

Patients with NF-1 present musculoskeletal abnormalities with scoliosis being the most common the management of those disorders are demanding. In the present case report it is presented the operative technique that applied for the correction of the scoliotic deformity of a 12 year old patient suffering from NF1.

KEY WORDS: Neurofibromatosis; Spinal Deformity – operative treatment

Introduction

Neurofibromatosis consists a multisystemic, autosomal dominant genetic disorder defined as a spectrum of multifaceted diseases involving neuroectoderm, mesoderm, and endoderm. The German pathologist Virchow was the first one who introduced the clinical features of the disease in several family members in 1847 [1]. However, 35 years later von Recklinghausen, who was Virchow's student, described the histological characteristics of neurofibromatosis [2].

There are five types of neurofibromatosis that can be presented. These types are neurofibromatosis type 1(NF-1), neurofibromatosis type 2 (NF-2), segmental neurofibromatosis, Legius syndrome and schwannomatosis [3]. The NF-1 is the most common one affecting approximately over two million people around the world. It is the most likely form to be presented with orthopaedic manifestations. The diagnosis of NF-1 is based on the clinical signs of the patient. These include (1) six or more café-au-lait macules more than 5mm in greatest diameter in prepubertal individuals and more than 15mm in postpubertal individuals, (2) two or more neurofibromas of any type or more than one plexiform neurofibroma, (3) freckling in the axillary or inguinal regions, (4) two or more Lisch nodules, (5) optic glioma, (6) a distinctive osseous lesion and (7) a first degree relative with NF-1. The diagnosis is established when at least two of these

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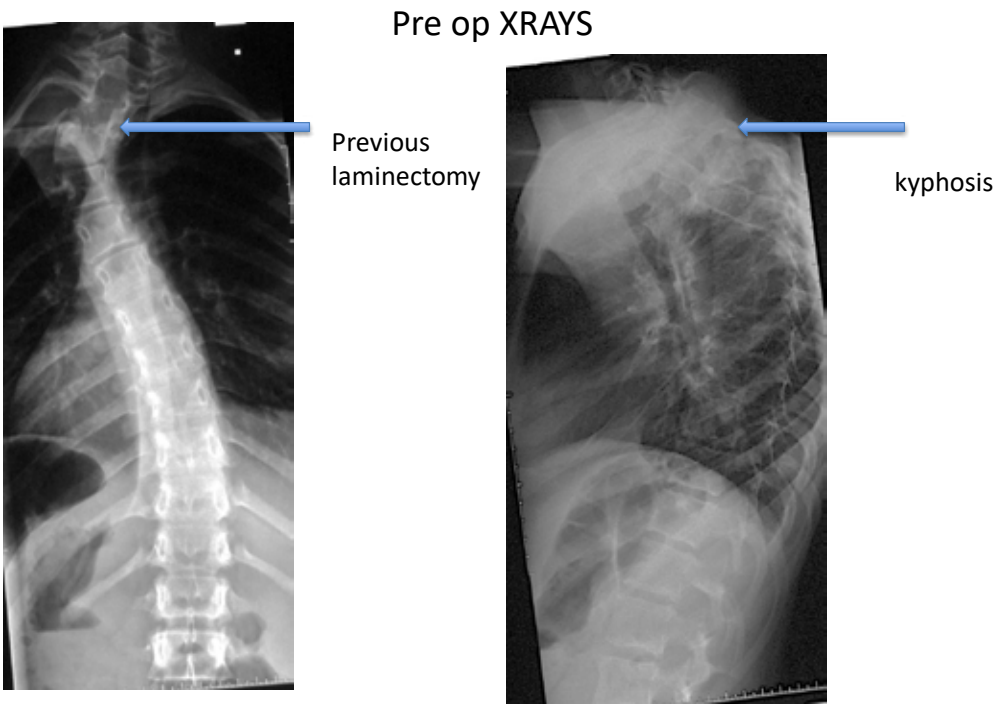

criteria are fulfilled. NF-2 despite the fact that is not associated with primary skeletal disorders, it can be presented with multiple paraspinal and intraspinal tumors. Segmental neurofibromatosis is similar to NF-1 but it involves a single body segment. Patients with Legius syndrome have mild symptoms of NF-1 and schwannomatosis, consists a separate form of neurofibromatosis with multiple schwannomas all over the body.

The epidemiology of spinal deformities in patients with NF-1 varies from 2% to 36% [4,5] and they consist the most frequently presented orthopaedic manifestations in these patients. The characteristic deformity tends to be a short-segmented, sharply angulated curvature that usually involves four to six vertebrae in the upper third of the thoracic spine [6]. The deformities are classified as dystrophic and non-dystrophic according to the coronal plane radiographs. The categorization is based on the coronal plane radiographs and there are certain radiographic criteria for this separation. In total there are nine criteria and if 3 of them are present then the deformity is characterized as dystrophic, otherwise it is non-dystrophic. The non-dystrophic curves have many similarities with the idiopathic scoliosis [7].

Here we present an interesting case report of a 12 year old patient suffering from NF-1 and was operated with a posterior fusion due to spinal deformation.

Case Presentation

A 12 year old female patients with NF 1 presented in the outpatient clinic with spinal deformation. More explicitly the patient suffered from thoracic kyphoscoliosis. The patient was previously operated with laminectomy at T3-T4 level for a plexiform neurofibroma removal. She had been operated twice for plexiform neurofibroma removal. She had a positive history from mother side and she also had cutaneous neurofibromas and typical café au lait spots.

When presented the radiographic examination revealed a kyphoscoliosis deformation of 58 degrees and high grade spondylolisthesis T3-T4. There were not/were neurological defects of the patient. In addition to the plain x-rays a 3 dimensional computed tomography (CT) examination

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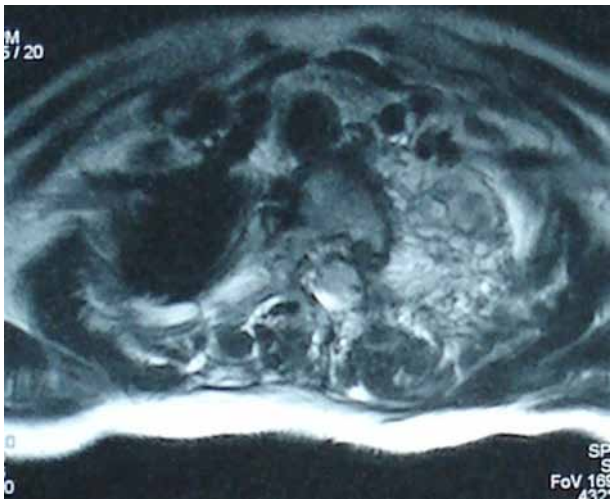
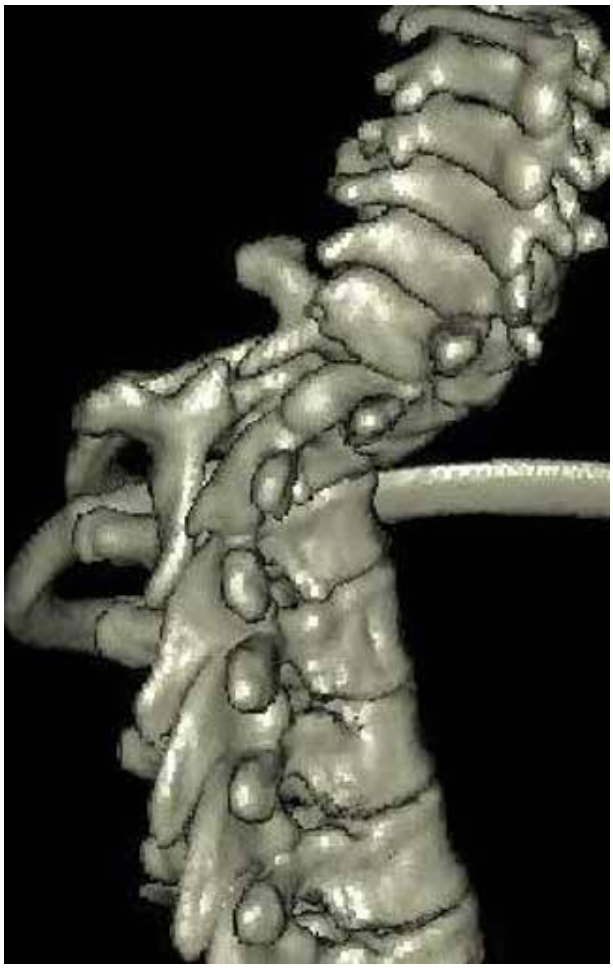


MRI shows the plexiform neurofibroma



CT shows the deformity

was performed for better assessment of the deformity. After reviewing the x-ray and the CT operation was decided. A posterior spinal fusion from C5 to T10 was performed lateral mass screw was used in the cervical spine, Magerl' technique implemented. In the thorasic spine pedicle screws was used. In order to achieve adequate fixation and to avoid the anterior support a transvertabrae screw at the level of T3 –T4 was implanted. . The entry point of the transvertebrae screw was the usual entry point of the pedicle screw of the T4, under fluoroscopy the screw targets the body of the listhetic vertebrae. By doing this approach we destroyed the end plate in order to achieve interbody fusion. Cancelous bone allograft was used the bleeding was controlled with the use of Flo Seal.

The patient had an uneventful postoperative period and she was able to follow daily school activities after the first month.

Three years postoperatively, the patient is functional with a very good alignment with good fixation without signs of pseudarthrosis and implants failure.

Discussion

Patients with NF-1 present musculoskeletal abnormalities with scoliosis being the most common. The management of these disorders in young patients are demanding and require experienced surgeons. Apart from the scoliosis there are also other deformities of the spine associated with NF-1 such as kyphosis, lordoscoliosis , kyphoscoliosis and spondylolisthesis.

In the present case report the 12 year old patient presented with kyphoscoliosis deformation. The definition of kyphoscoliosis is a kyphosis deformity more than 50o which accompanies the scoliotic curve. The deformation of kyphoscoliosis may present in early stages of the disease. In the present case the patient had undergone a previous operation for a neurofibroma removal. Moreover, severe kyphotic deformity is the most common cause of neurological defects even with paraplegia. An explanation for this complication is the elongation of the spinal cord and the deformation after increased

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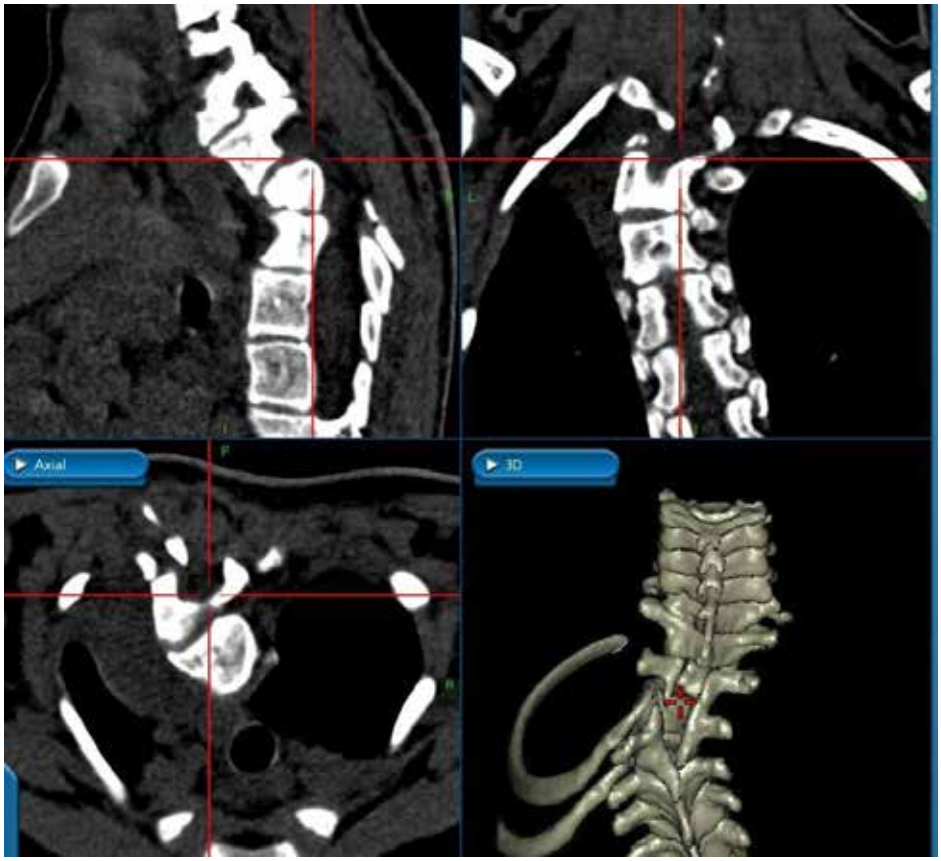

Multiplanar CT reconstruction shows the deformity

spinal flexion such as in kyphoscoliosis [8]. When the angle of the curve surpasses the 50o, the anterior approach for release and fusion is recommended followed by posterior segmental instrumentation one or two levels above and below the end vertebrae [9,10]. In the previously described case a posterior fusion was performed without anterior stabilization. The use of a transvertebrae screw aimed to provide good fixation without anterior support. In such patients even with a combined approach the bony fusion is not always achieved. That is a fact that makes our case even more interesting. Because with the use of posterior approach only, we achieved both adequate fixation and bony fusion as well.

On the other hand, lordoscoliosis is rarer compared to kyphoscoliosis. In such cases it is also recommended anterior release and intervertebral fusion along with posterior instrumented fusion. Spondylolisthesis is also very rare in NF-1 patients. The definition of spondylolisthesis is the pathologic forward progression of the anterior elements of the spine. In a patient with NF-1 the presence of spondylolisthesis is associated with abnormally thin and long pedicles or pars interarticularis by lumbosacral foraminal neurofibromas or dural ectasia [11].

Apart from the thoracolumbar spine deformities in patients with NF-1, there are also cervical spine deformities as well. Kyphosis is the most common deformity in cervical spine and especially in its progressive form. The posterior cervical spine fusion is recommended in such cases where instability is also present. In cases where flexible deformity is present, the use of halo preoperatively is indicated whereas for stiff cases anterior release and after that the use of halo traction and posterior fusion is a common practice [7].

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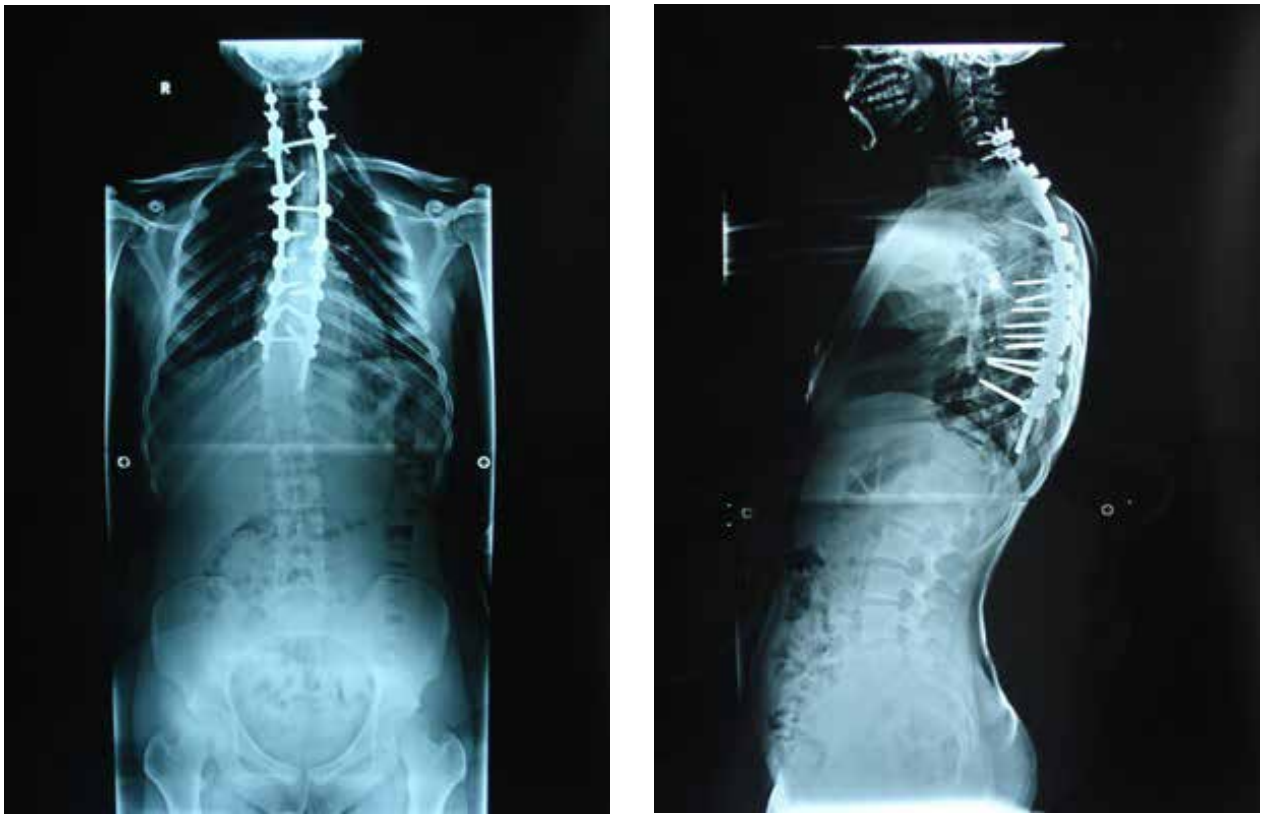

3 yrs post op

The operations for deformity corrections in a patient with NF-1 do not lack complications. Non-union, vertebral column dislocation, rib protrusion and paraplegia are some of them [7]. During the operation the surgeon should take care of the haemostasis and prevent the formation of haematomas. Additionally, erosion of the laminae secondary to dural ectasia may be noted [12]. In the follow-up period, the deterioration of the curves is not rare in combination with pulmonary symptoms. The infection and thromboembolic are also common complications that the surgeon and the patient should be aware of [7].

Conclusion

In conclusion the management of spinal deformities in patients with NF-1 are challenging and require surgeon's experience and expertise in spine surgery. The principles of the corrections of each curve should be followed. The treating physician should be able to make the separation between the non-dystrophic and the dystrophic curves due to the fact that the latter ones may result in scoliosis, kyphosis and kyphoscoliosis. The postoperative management of the patient is also of high importance as well as a multidisciplinary approach in order to minimize the complications.

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READY - MADE CITATION

Samoladas E, Gkiatas I, Gelalis I. Management of neurofibromatosis spinal deformity, a case report and review of the literature. *Acta Orthop Trauma Hell* 2021; 72(1): 118-123.