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Instructions for Authors

1. Scope

"Acta Orthopaedica et Traumatologica Hellenica (AOTH)" is the official journal of the Hellenic Association of Orthopaedic Surgery and Traumatology, (HAOST) first published in 1948. The current edition of Acta Orthopaedica et Traumatologica Hellenica (AOTH) is published in English, online, without any article processing charges (APCs). It offers a compact forum of communication to orthopaedic surgeons and related science specialists. It publishes only peer reviewed articles. The peer review process is the established method for research validation in science whereby a work is critically assessed by expert referees demonstrating both the right level of knowledge in the field of the work, while being fully independent from it. Acta Orthopaedica et Traumatologica Hellenica (AOTH) follows a blind peer review process mediated and ensured by the Editor-in-Chief and the Editorial Board members. Aiming for clinically pertinent, scientifically correct, ethical, original and review quality research, only scientifically sound articles, deemed of high enough interest and originality that will receive favorable reports from our Editors/Reviewers Board will be accepted for publication.

2. Types of papers

The journal accepts and publishes the following types of articles:

Original articles: Original articles are encouraged. They should provide novel insights and contribute to continuous medical education and transfer of knowledge. They should include a clear rationale, and the findings/conclusions need to be sound and supported by statistical analysis. When the accuracy of a diagnostic test is assessed, following the Standards for Reporting of Diagnostic Accuracy (STARD) flow diagram (http://www. stard-statement. org) is suggested. A structured abstract of 250 words (divided into Background, Materials and Methods, Results and Conclusions), 3-5 keywords, text up to 4,500 words, figures up to five, tables up to six, and references up to 50 are recommended. (It is at the Editor's discretion to allow differences in the above numbers).

Review Articles: All types are allowed including narrative reviews, systematic reviews, meta-analyses, literature reviews, mini reviews, monographs, and historical reviews on orthopaedic heritage. They should be extensive, educative, informative, adequately illustrated, and appropriately cited with up to date quality citations. An unstructured abstract of 150-250 words, 3-5 keywords, text up to 8,000 words, figures up to eight, tables up to six, references up to 100, and a maximum of six authors are recommended. (It is at the Editor's discretion to allow differences in the above numbers).

Case Reports: Case reports should be didactive and educative, exceptional (or unique) and add to the current literature on an interesting topic, diagnostic criteria or therapeutic methods. An unstructured abstract of 150-250 words, 3-5 keywords, text up to 6,000 words, figures up to six, tables up to 4, references up to 80, and a maximum of six authors are recommended. (It is at the Editor's discretion to allow differences in the above numbers).

Pictorial Essays (Images papers): The purpose of pictorial essays is to provide a teaching message through high quality images. A brief text (e.g., the history of the patient shown in the illustration) followed by a brief discussion are required to accompany the images. An unstructured abstract of 150-250 words, 3-5 keywords, text up to 4,000 words, figures up to four, tables up to two, references up to 20, and a maximum of four authors are recommended. (It is at the Editor's discretion to allow differences in the above numbers).

Letters to the Editor: Letters to the Editor, Editorials, Communication to the editor are welcomed and will be published if they offer pertinent and constructive comment on articles previously published in Acta Orthopaedica et Traumatologica Hellenica (AOTH). These papers are usually solicited on a topical topic. No abstract, text up to 4,000 words, figures up to four, tables up to two, references up to 20, and a maximum of four authors are recommended. (It is at the Editor's discretion to allow differences in the above numbers).

3. Language

English is the official language of the journal. All submitted manuscripts should be written in English. The authors are encouraged to consult English speaking authors and services for correct English grammar and syntax.

4. Manuscript Submission

Submissions should be done through the journal's website at https://eexot-journal.com. Manuscripts should be send to aothjournal@gmail.com. Submission should adhere to the journal's instructions with respect to the authorship, abstract, introduction (rationale of the paper), materials/methods, results, discussion, conclusions, references (format), illustrations and tables. Submissions not adhering to the journal's instructions will be send back to the authors for corrections that will delay the peer review process.

After submission, the Editorial office and the Editor-in-chief will check the submitted files and if appropriate will assign to section Editors or invite Reviewers. The time allocated for reviewers to assess the manuscript and submit their recommendation is 3 weeks. By that time the Editor-in-chief will make his final decision for publication.

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Submission of a manuscript implies that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The Editors, the journal, and the Publisher will not be held legally responsible should there be any claims for compensation.

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6. Conflict of interest disclosure statement

Each author needs to disclose any type of financial interest that is related to the study and might create a potential conflict. Funding of the study, if any, needs to be disclosed. If there is no conflict of interest, this should be stated in the manuscript before the Reference section as follows: "The authors declared no conflicts of interest".

7. Permissions and plagiarism

Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Plagiarism, as evidenced by appropriate dedicated software, will not be accepted. If excessive, the manuscripts with plagiarism will be returned to the corresponding author without consideration for peer review.

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A manuscript must contain the following files for submission:

Cover letter: Each manuscript should be accompanied by a cover letter signed by the corresponding author on behalf of the rest of the authors stating that the the work submitted has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. Any other information such as solicited paper, paper submitted for a special issue, letter to the Editor, etc should be communicated to the Editor in the Cover letter. In case of article resubmission a point-by-point answer to the reviewer's comments needs to be submitted with the cover letter.

Title page: It includes the title of the manuscript (concise, informative and capture of the message), the names of the authors, the affiliations of the authors, and the name, affiliation, address, e-mail address, and telephone number of the corresponding author.

Blinded manuscript: The manuscript should be blinded i.e. it should not include authors; names and affiliations.

Abstract and Keywords: An abstract and Keywords are required, as indicated above depending on the manuscripts types.

Text structure: the text of the Original Articles needs to be organized as follows: Introduction, Materials and Methods, Results and Discussion. Review Articles should include sections and subsections with appropriate headings depending on the topic; too many headings and subheadings should be avoided because they complicate reading. Case reports should include an Introduction, Case presentation, and Discussion. Pictorial Essays (Images papers) should include an Introduction and Discussion section only.

Abbreviations: Abbreviations should be used as minimum as possible, and should include only widely known and accepted abbreviations such as ORIF (open reduction and internal fixation), ICU (intensive care unit), etc. When used, they should be defined the first time they are used, followed by the acronym or abbreviation in parenthesis.

Acknowledgements, sponsorships and grants: Acknowledgements should be added at the end of the manuscript before the References section. It should read as follows: "The authors thank… or acknowledge….".

Measurement Units: All measurements should be mentioned in international units (SI). The full stop should be used as a decimal (i.e. 3.5 cm). Spaces should be added around the plus/minus symbol (i.e. 13.6 ± 1.2). There should not be any spaces around range indicators (i.e. 15-20) or equality/inequality symbols (i.e. r=0.37, p<0.005).

Figure and Tables: Figures and tables should be cited in the text consecutively in the order in which they appear. They should be cited in parentheses at the end of the respected sentence, and not be referred to in the text. They should be counted in Arabic numbers: i.e. (Fig. 1) and (Table 1), and any Figure parts should be identified with lower case letters, i.e. (Fig. 1a).

Figures need to be of high quality (minimum resolution of 1,200 dpi) in TIFF or JPEG format.

Patient anonymity should be ensured and patient identifying images such as intraoperative or clinical photographs should be avoided. All identifying data (name, identification numbers, initials) must be removed from text, images and tables.

Figures and Tables legends should be explanatory and appropriate (what the figures and tables show). The legends should be listed at the end of the text, after the References section. The Figures and Tables should not be embedded in the text, but they should be uploaded in separate respective files, named respectively, i.e. (Fig. 1a).

Studies cited in the Tables should be cited according to the references list of the manuscript.

9. References

References section is not an afterthought but a continuum of the paper. They should be up to date and of acceptable quality. Their accuracy is the responsibility of the authors. They should be cited in the text in the order in which they appear. The numbering needs to be in Arabic numbers and formatted in superscript in the respective areas of the text, after the punctuation (i.e. .[1]).

All authors should be listed for all references of a manuscript.

When a book chapter is cited, the authors and title of the chapter, editors, book title, edition, city and country, publisher, year and specific chapter pages should be mentioned.

For Online Document, the following should be mentioned: authors (if any), title of page, name of institution or owner of Web site; URL; dates of publication, update, and access.

References examples:

Journal article:

Mavrogenis AF, Altsitzioglou P, Tsukamoto S, Errani C. Biopsy Techniques for Musculoskeletal Tumors: Basic Principles and Specialized Techniques. Curr Oncol. 2024;31(2):900-917. doi: 10.3390/curroncol31020067.

Sun J, Mavrogenis AF, Scarlat MM. The growth of scientific publications in 2020: a bibliometric analysis based on the number of publications, keywords, and citations in orthopaedic surgery. Int Orthop. 2021;45(8):1905-1910. doi: 10.1007/s00264-021-05171-6.

Kolovos S, Sioutis S, Polyzou M, Papakonstantinou ME, Karampikas V, Altsitzioglou P, Serenidis D, Koulalis D, Papagelopoulos PJ, Mavrogenis AF. The risk of DDH between breech and cephalic-delivered neonates using Graf ultrasonography. Eur J Orthop Surg Traumatol. 2024;34(2):1103-1109. doi: 10.1007/s00590-023-03770-0.

Book chapters:

Mavrogenis AF, Antoniadou T, Dimopoulos L, Filippiadis D, Kelekis A. Metastasis (Chapter 26). In: Textbook of Musculoskeletal Disorders. Vincenzo Denaro, Umile Giuseppe Longo (Eds). © Springer Nature. 2023. ISBN 978-3-031-20986-4.

Online document:

Copyright Registration Guidance: Works Containing Material Generated by Artificial Intelligence Available at: https://www.federalregister.gov/documents/2023/03/16/2023-05321/copyright-registration-guidance-works-containing-material-generated-by-artificial-intelligence. Published Feb 2023. Accessed on Jan 27, 2024.

10. Review and Proof reading of manuscripts

The Reviewers comments will be communicated to the Authors. The Authors should make proof corrections within 3 weeks. All comments should be addressed point-by-point in a cover letter with Authors' responses to Reviewers' comments. Upon acceptance, the authors will receive a proofs pdf document of their paper for proofs reading. Then, the Authors will be asked to check the integrity of the text (importantly the authors' names and affiliations), accept any grammar or spelling changes and check if all the Tables and Figures are included and properly numbered. This should be done promptly, preferable within 72 hours. Once the publication is online, no further changes can be made. Further changes can only be published in form of Erratum.

Call for Papers/Publish in
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Dear Colleagues,

Acta Orthopaedica et Traumatologica Hellenica (AOTH), the Official Journal of the Hellenic Association of Orthopaedic Surgery and Traumatology, is published since 1949 and is devoted to dissemination of news and information on all aspects of orthopaedic surgery.

Beginning from 2025, **all papers published in Acta Orthopaedica et Traumatologica Hellenica (AOTH) will acquire a DOI (Digital Object Identifier)**. Each published article will be given a specific DOI.

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Sincere thanks,
Andreas F. Mavrogenis
Editor-in-Chief, Acta Orthopaedica et Traumatologica Hellenica (AOTH)

For Authors

Writing for Acta Orthopaedica et Traumatologica Hellenica (AOTH)

Andreas F. Mavrogenis

Editor-in-Chief, Acta Orthopaedica et Traumatologica Hellenica (AOTH)

This article is addressed to the curious readers who may benefit of some simple rules on how to write a scientific paper. It offers advices and tips on medical writing for the junior authors and the less experienced in medical writing on how to prepare a quality submission. These tips apply to any author and any journal, and it is the Editor's personal view and experience in medical writing. Before starting the paper, search the related literature; choose quality papers that are electronically available; provide appropriate correct citations for any material previously published to avoid plagiarism. Before writing the paper, read the authors' instructions. These instructions will need to be met in any case.

Authorship

The number and the order of the authors' names should be fair by reflecting their contribution and the order of their contribution to the manuscript. Those who authored should be listed as authors of the manuscript. Those who have contributed to the work, but not enough to merit their inclusion in the authorship, should be acknowledged in the acknowledgment section. Authorship is not a way to thank a colleague for support, access to resources, or mentorship. Scientific misconduct (fraud) in authorship includes a gift or complimentary authorship, ghost authorship, and coercion authorship.

Title

It should be short and concise; it should capture the message. Titles raising or answering questions will far be more appealing than titles merely pointing to the topic. Do not use run-on (long and busy) titles.

Abstract

It should include all the important information from each section that is the background, questions/purposes, materials/methods, results, and conclusions. The readers should be able to understand the total paper by just reading the Abstract. Some read only the Abstract (e.g., because they do not have the time or access to the full text). Keywords are important for indexing and should be chosen carefully.

Introduction (approximately 500 words)

It is the most critical section. It should start with focus on the topic. General and irrelevant information should be avoided. The first paragraph should present the background. The second paragraph should present what is important on the topic. Appropriate citations (the related studies) should be added. These studies should be further discussed at the discussion section.

The section should end with a clear rationale. Questions to be asked when formulating the rationale are the following: (1) What is missing from the literature for this study to merit publication? (2) How does this study add to the related literature? (3) Does it confirm or reject previous reports? After the rationale, the purposes of the study (study questions or hypotheses) should be listed. The purposes may be primary (the most important) and secondary (the least important). Writing should be clear and concise.

Materials and Methods (approximately 1000–1500 words)

The section should start with the Materials in brevity and clarity. An example could read as follows: *"We present ….. patients admitted and treated at the authors' institution with …… from 2000 to 2024. There were … men and … women with a mean age of … years (range, ….. years)"*. These two sentences provide almost all basic demographic information of the materials of the study. Follow-up is materials and should be provided here; the same for loss to follow-up including the reasons for the loss. Clinical reports must state inclusion and exclusion criteria and whether the series is consecutive or selected; if selected, criteria for selection should be stated. These should inform the readers for any sources of bias.

When reporting clinical studies, the authors must state informed consent (where appropriate) and approval of the institutional review board or ethics committees of their institution. These should be added at the first paragraph of the Materials and Methods sections as follows: *"All patients gave written informed consent for their data to be included in this study. This study was approved by the Institutional Review Board (IRB)-Ethics Committee of the authors' institution"*. Alternatively, *"Informed consent was not necessary for review articles" or "IRB and Ethics Committee approval was not necessary at the authors' institution for retrospective studies"*.

The Methods should contain adequate detail for another investigator to replicate the study. The authors should clearly present what they did and how they did it in the study and analysis. The Methods should be validated with appropriate citations such as for a used score, method, classification, etc.

If authors use statistical analysis, a paragraph should appear at the end of Materials and Methods stating all statistical tests used. When multiple tests are used, the authors should state which tests are used for which sets of data. The level of statistical significance is 0.05 in most cases.

Results (approximately 500 words)

It should be the answers to the study questions in the same order as formulated in the rationale at the last paragraph of the Introduction section. it is easier and more informative to format the study answers (results) in paragraphs. Each paragraph should start with a key statement of the most important result, and then the description and statistical analysis should follow.

The authors should provide which group/method/ analysis is more significant compared to another and parenthetically state the p-value immediately after the comparative terms. Provide the actual p-values instead of p-values greater or lesser than 0.05. Parenthetic reference to all figures and tables enables easier interpretation of the data. Avoid too many numeral data in tables because it complicates and fatigues reading.

Discussion (approximately 1500-3000 words)

The Discussion should start with a restatement of the problem or question in brief for emphasis, followed by the study findings and a synthesis of the comparison and the author's new data to arrive at conclusions.

The second paragraph should be the limitations. I prefer the readers should be informed early for the limitations of the study. Failure to explore the limitations suggests the authors either do not know or choose to ignore them, potentially misleading the reader.

In the next paragraphs the authors should discuss their findings in comparison to the literature. They should synthesize their data with that in the literature. The text should be formatted in paragraphs respective to the study questions/ answers. Appropriate and quality studies should be used. Generally, many of these reports will include those cited at the Introduction section. A Table that summarizes the results of the most important published related studies would be useful here (refer to papers with similar tables for the format).

The ultimate paragraph of the section should be the conclusions. The conclusions should be based solely on data that come out of the paper. Conclusions irrelevant of the study findings should not be used. General and philosophical statements

should be avoided. Statements such as "need for further research" or "need for future studies" should be avoided because they underpower the study.

References

Choose quality references, and read the most important papers in full text; approximately 25% of the references used in the references list of a paper are actually read by the authors when writing the paper. References should be accurate and up-to-date. Electronically available citations should be preferred; abstracts and submitted articles (pending publication), newsletters, proceedings, and meetings syllabus should not be used because many in these categories ultimately do not pass peer review because it is not possible to be traced and cited. Use citations from the journal to submit your paper; this will gain the Editor that you are aware of the journal; it will increase the visibility of the paper and the impact of the journal.

Figures and Tables

Figures and tables should complement not duplicate material in the text. They present information that would be difficult to describe in text form. Well-written papers contain one or two tables or figures for every study question/purpose posed in the Introduction. The legends should be explanatory and concise; what the figure/table show.

References

1. Brand RA. Writing for clinical orthopaedics and related research. Clin Orthop Relat Res. 2008;466(1):239-47. doi: 10.1007/s11999-007-0038-x.
2. Mavrogenis AF, Auffret Babak I, Caton JH. Writing for SICOT-J. SICOT J. 2021;7:E1. doi: 10.1051/sicotj/2021042.
3. Mavrogenis AF, Scarlat MM. Writing for "International Orthopaedics": authorship, fraud, and ethical concerns. Int Orthop. 2021 Oct;45(10):2461-2464. doi: 10.1007/s00264-021-05226-8.

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Acta Orthopaedica et Traumatologica Hellenica

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Editorial

The AO Trauma and AO Trauma Greece: mission, history, and perspectives

Theodoros H. Tosounidis MD, PhD
Associate Professor of Orthopaedics and Traumatology
Department of Orthopaedic Surgery, Medical School, University of Crete, 71110 Heraklion, Greece.
Chairperson AO MID Trauma Europe and South Africa
Chairperson AO Trauma Greece

email: ttosounidis@yahoo.com

Abstract

AO Trauma is the world's biggest universal trauma and orthopedic community promoting excellence in the surgical management of trauma and disorders of the musculoskeletal system. It is part of the AO and is the biggest global group of dedicated orthopedic and trauma surgeons, operating room personnel and researchers, committed to excellence and volunteering for a common goal. It offers an unparalleled route to education, research and community development opportunities related to fracture management and orthopaedic trauma surgery. Becoming a member of AO Trama unveils new horizons in young orthopaedic surgeons' careers, and we encourage all of them to become members and actively participate in the numerous activities of this exceptional community (https://www.aofoundation.org/trauma/membership).

AO Trauma is the world's biggest universal trauma and orthopedic community promoting excellence in the management of trauma and diseases of the musculoskeletal system[1]. It is part of the AO - Arbeitsgemeinschaft für Osteosynthesefragen, i.e. "Association for the Study of Internal Fixation". It is the most renowned global group of orthopedic and trauma surgeons, operating room personnel and researchers, dedicated to excellence and volunteering for a common goal.

AO Trauma History

The Orthopaedic Trauma management, related education and research were not always in their best form. It is not a long time ago when the management of fractures was mainly nonoperative, empirical, guided by experts' opinion and taught only on a personal face-to-face basis, not substantiated by any educational approach or method.

In the late 1940s, the biology of bone healing had not been scientifically investigated and knowledge was sparse. Maurice Muller an enthusiastic young surgeon from Switzerland was fascinated by the work of the Belgian Surgeon Robert Danis, as this was published in the book titled 'Théorie et Pratique de l'Ostéosynthèse' in 1949. After Mullers visit to Danis in 1950, a small group of three Swiss surgeons Robert Schneider,

Hans Willenegger, Martin Allgöwer, and Walter Bandi was formed. In November 1958, the AO Foundation was established at the Hotel Elite in Biel in Switzerland.

AO Milestones

- At the beginning, AO founders looked for a suitable place to conduct research. Davos was selected as the location and the Laboratory for Experimental Surgery (LECD, Labor für experimentelle Chirurgie Davos) was the first place that AO operated in 1959 under the leadership of Allgöwer.
- In 1984, the Charter of the AO Foundation was signed in Davos, Switzerland, formally establishing the AO as an international organization with Martin Allgöwer as its first president.
- The official opening of the AO Center took place in 1992 and at the same time the AO's headquarters, known as the AO Center, opened in Davos, Switzerland.
- In 2005, the Clinical Priority Program (CPP) Fracture Fixation in Osteoporotic Bone (FFOB) commenced.
- The AO Surgery Reference was introduced in 2006. AO Surgery Reference (https://surgeryreference.aofoundation.org) is an online resource for the management of fractures, which is used daily by thousands of surgeons in everyday clinical practice.
- In 2008, the AO celebrated its 50th anniversary and AO Trauma was created serving as the main pillar of the AO Foundation.
- The new AO Trauma membership program took place in 2010.
- The second Clinical Priority Program (CPP) Bone Infection was established in 2012.
- In 2013, the first education curricula for basic principles and advanced principles courses and introduction of the Skills Lab into the basic principles course were launched.
- In 2014 the global evaluation and assessment package for all principles courses and, later, for all AO Trauma courses was presented.
- In 2017 AO Trauma's fellowship community programme was introduced.
- In 2017 the Clinical Priority Program (CPP) Patient Outcome was set in motion.

Figure 1: *The practical exercises session of an AO Advanced Principles of Fracture Management Course offers an unparalleled hands-on experience to participants.*

- In 2018 AO Trauma celebrated its tenth anniversary

AO Trauma Mission

Following its core values AO trauma, the basic mission statements of the organization are to

1. Educate surgeons, researchers, and ORP.
2. Curry out and fund clinical and translational research.
3. Offer membership to a distinguished international network that provides members with rich opportunities for dialogue, knowledge-sharing, professional development, and collaboration across the AO Trauma community worldwide.
4. Focus to empowering and developing its contributions to the entire orthopedic trauma community, and further develop our membership by providing great support, so that we can make a significant impact to improve patients' lives

The key activities of AO trauma can be summarized as education, research and membership-related activities. AO Trauma conducts more than 400 educational events every year around the world. More than 34.000 participants attend these events, and more than 5.000 faculty members voluntarily contribute to knowledge, skill and attitude education. These events include

Figure 2: *Group photo of the AO TESA Subregional courses, May 2025, Larisa - Greece. More than 30 faculty members, 100 participants are experiencing the unique AO spirit.*

courses and seminars, webinars and webcasts and hospital-based education.

The Basic and Advanced Principles of Fracture Management Courses constitute the core of education events and focus on delivering the fundamental principles of fracture management to young orthopaedic and trauma resident surgeons (Figure 1). At the same time courses dedicated to sub-speciality orthopaedic trauma education are taking place mainly at regional and international level. These more advanced, master-level courses explore subspeciality topics include: Foot and ankle, Orthogeriatrics, Pediatrics, Hand and wrist, pelvis and acetabulum, Operating room personnel, periprosthetic fractures, upper extremity, lower extremity and soft tissue management. The content and the structure of these courses are developed based on the AO Trauma's competency-based curricula, promoting education that is dedicated to addressing patient problems and improving patient care.

The AO Davos Courses https://www.aofoundation.org/aodavoscourses is the organization's premier educational event. For many surgeons, Davos courses constitute a unique experience that serves as a window to a world of lifelong education and networking experience. Evey year more than 300 faculty members interact with more than 1000 participants sharing experience and knowledge.

Organization

AO Trauma is active around the globe, nurturing self-directed regional research and educational activities. AO Trauma's boards and commissions are responsible for implementing AO Trauma's strategy. The AO Trauma International Board is the highest governing body of AO Trauma. The Board works in close collaboration with the regional trauma-related AO Trauma organizations to ensure a solid global vision and strategy. It supports harmonization between the different regional organizations and the central AO functions and services. Global AO Trauma has five distinct regions: a) Europe and Southern Africa, b) Asia Pacific, c) Latin America, d) Middle East and Northern Africa and e) North America.

Country Chapters were introduced to facilitate the representation of the various needs of national groups and provide local members the opportunity to get involved with the most fundamental activities of AO Trauma. In most regions, AO Trauma Country Chapters are in an advanced stage of development, and they are managed by elected Councils comprised of AO Trauma officers.

AO Trauma Greece

The AO Trauma Greek Chapter was established in 2008 and thrived under the leadership of Prof. Minos Tylianakis from Patras University, who successfully organized the first and subsequent events and established the chapter as the leading organization of trauma education in Greece. AO Trauma Greece is part of AO MID (Middle Europe), which was established in 2005. AOMID was created by representatives of the following countries (in alphabetical order): Hungary, Israel, Poland, Slovenia and Turkey. It was essentially an effort of South and East European Countries to group and to ensure that the educational needs of the countries were recognized and served from the respective educational activities. This effort is one of the many success stories within the AO Foundation. AO

MID has grown from the original 5 members in 2005 to the current 23 member countries. It has become the forum in which the country members can gather together, discuss common problems and find shared solutions organizing more than 40 courses each year.

In 2018, Prof. George Babis from the National and Kapodistrian University of Athens took over as the Chair of AO Trauma Greece. Under his leadership, the chapter grew even further, and new faculty members joined, thus ensuring the continuity of the educational process. Theodoros Tosounidis is the current Chair of AO Trauma Greece and the Chair of AO MID (East Cluster of Trauma Europe and South Africa) since 2022. AO Trauma Greece has successfully managed to organize at least two courses every year, a) the Basic and b) the Advanced Principles of Fracture Management Courses. Our primary focus is to communicate the fundamental principles of fracture management to young residents of Greece. We conduct our courses in the English language to ensure the participation of esteemed international faculty and also to attract attendees from around the globe. Our courses have been highly evaluated and have attracted people from around Europe and also countries like United States, Singapore, Peru, Saudi Arabia, Israel, Australia etc. AO Trauma Greece has also organised sub-speciality master level events and has also succefully fostered two regional events of outmost importance in 2024 and 2025 in Larisa, Greece. These international events attracted participants from more than 30 countries, thus confirming the organizational and educational capabilities of the AO Trauma Greek Chapter (Figure 2). Today the chapter has more 80 active–paying members and it is one of the biggest and strongest at the East Cluster of AO Trauma Europe and South Europe. In addition to the aforementioned local and regional events, the chapter annually organizes a very well-attended community development event that serves to strengthen the bonds between its members and empower the Greek trauma community.

Membership and community

Members of the AO Trauma community share a spirit of volunteerism and camaraderie along with a desire to advance the care of musculoskeletal trauma patients around the globe. AO Trauma members enjoy access to exclusive privileges, including educational resources, member discounts, and research grants. They have the opportunity to connect with a lively community of surgeons, researchers, and experts from around the world, all working together to formulate the perspectives of trauma care. AO Trauma offers routes to assist you in your professional network, track fellowships, and be involved as a faculty member in various educational activities. Members gain free access to:

- myAO
- AO Trauma video hub
- AO Surgery Reference
- AO/OTA Classification
- AO Trauma e-learning
- AO PEER research knowledge platform (selected content)
- AO Access learning journey
- AO Trauma Orthogeriatrics App
- OSapp interactive osteosynthesis learning platform
- Podcasts
- Discount on Anatomy.tv - 3D Human anatomy software

In addition, member Privileges include:

- Free AO e-books and book discounts
- Online journals
- AO Trauma fellowship opportunities
- Discount on selected AO courses
- AO Member Directory
- Member networking events
- AO research grants
- Faculty development opportunities
- Discount on AO PEER Online course—Principles of clinical research
- AO PEER research knowledge platform (full access)
- Free 6 months trial of AMBOSS medical knowledge platform (Language: German)
- Exclusive discounts on SYNBONE models
- Faculty Development Essentials online modules

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Review

Antibiotic prophylaxis in orthopaedic surgery: A review of evidence and best practices

George A. Komnos[1], Efstathios Konstantinou[2], Nikolaos Stefanou[3], Sokratis Varitimidis[4]

[1]*Department of Orthopaedic Surgery, Faculty of Medicine, University of Thessaly, Larissa, Greece*
[2]*Department of Orthopaedic Surgery, Faculty of Medicine, University of Thessaly, Larissa, Greece*
[3]*Department of Orthopaedic Surgery, Faculty of Medicine, University of Thessaly, Larissa, Greece (Corresponding Author)*
[4]*Department of Orthopaedic Surgery, Faculty of Medicine, University of Thessaly, Larissa, Greece*

Abstract

The use of prophylactic antibiotics in Orthopaedic and Trauma surgery is well-established. Superficial and periprosthetic joint infections are dreaded complications that increase morbidity, disability, and mortality. Despite the various guidelines and the wide employment of antibiotics, there is still controversy about their optimal use. The main factors that have to be taken into account are the choice of the most effective antibiotic, the timing of administration, and the duration of the treatment. This review deepens into the evidence behind commonly argued topics in antibiotic prophylaxis and highlights the fundamental aspects that lead our current practice.

Keywords

Antibiotics; prophylaxis; surgical site infection; orthopaedics

Corresponding author

Nikolaos Stefanou
nikvsteph@gmail.com

Introduction

Infection is one of the most disastrous complications in Orthopaedic surgery. It is associated with increased morbidity, disability, and mortality.[1] The use of antibiotics against infections, which was once considered a panacea, remains an integral part of Orthopaedic practice as it has been proved that antibiotic prophylaxis is effective in reducing the incidence of surgical site infection (SSI) subsequent to arthroplasty from roughly 4% to 1%. SSIs can result in extended hospital stays, increased healthcare expenses, and patient discomfort.[2]

Infection control methods have been extensively disseminated, but guidelines are frequently disregarded. The World Health Organization (WHO) has recommended a 19-item surgical safety checklist to reduce complications before any surgical procedure, which includes prophylactic antibiotics.[3] Nevertheless, the antibiotic resistance that has arisen due to inconsiderate use presents a major threat and the WHO has warned about a new era in which trivial infections and minor injuries will once again threaten human life.[4]

Despite the widespread acceptance of antibiotic prophylaxis in Orthopaedic surgery, significant variability in practice patterns persists.[5] Discrepancies in adherence to guidelines, debates over the most effective antibiotic choices, and concerns about the optimal timing and duration of administration highlight a need for clarity.[6] This review aims to compile the latest research and guidelines to support evidence-based practices in Orthopaedic antibiotic prophylaxis, addressing areas of controversy and emphasizing the need for consistency and compliance in clinical practice.

Risk factors for infection in Orthopaedic surgery

Infections in orthopaedics remain a significant concern, as SSIs can significantly affect patient recovery and healthcare costs.[7] Advances in surgical techniques and the increased use of implants, while improving outcomes, have also increased the risk of SSIs.[8] Factors such as diabetes mellitus and hypertension are well-established risk factors, with diabetic patients being six times more likely to develop infections.[9] Hypertension has similarly been linked to higher SSI risk.[10] Additionally, the influence of age on infection rates is debated; while younger patients may face lower risks, older adults often experience higher susceptibility due to weaker immune system and existing chronic comorbidities.[11] Surgical factors, including the type of incision, also play a crucial role; fresh, open wounds present the highest risk, while clean, sterile incisions are associated with the lowest infection rates.[12]

Moreover, complex and prolonged surgeries increase the likelihood of SSIs, highlighting the need for surgical precision and strict adherence to infection control protocols.[13] Operating room conditions, such as proper air filtration and use of laminar flow systems, contribute to maintaining a sterile environment. Finally, the presence of multidrug-resistant organisms adds another complicated burden, making targeted antibiotic prophylaxis essential. Despite extensive research, inconsistency in identifying specific SSI risk factors remains a challenge.[14] Improving our understanding of these variables can result in more effective preventative strategies and decreased SSI rates in Orthopaedic patients, thus improving outcomes and reducing healthcare costs.

Surgical site infection

Orthopaedic procedures, such as joint replacement or fracture fixation, include bone and soft tissue manipulation, and often implantation of prosthetic devices. These procedures are threatened by the likelihood of surgical site infections, which can result in serious complications such as implant failure, septic arthritis, and osteomyelitis. This risk is mitigated by antibiotic prophylaxis, which prevents the colonization and subsequent infection of the surgical site by bacteria introduced during surgery.[15]

Airborne organisms and patient microbiota are the most prevalent causes of SSIs, frequently acquired in the operating theater. Staphylococcus aureus and coagulase-negative staphylococci such as Staphylococcus epidermidis are the most common infectious agents.[2]

It has been demonstrated that the overall incidence of SSI following hip fracture surgery is approximately 5%, with roughly one-third of these cases involving a deep infection.[16] Within a year, approximately fifty percent of patients who develop an SSI after hip fracture surgery will pass away.[17] Around twenty-three percent of revisions after total knee arthroplasty (TKA) and between 7% and 13% of revisions after total hip arthroplasty (THA) in elective surgery is caused by infection with the mortality rates associated with prosthetic joint infection (PJI) ranging between 2% and 18%.[18,19,20]

Timing of antibiotic administration

The minimum inhibitory concentration (MIC) of antibiotic levels must be exceeded throughout the duration of the operation for prophylaxis to be effective against bacterial growth.[21] The majority of studies support that prophylactic antibiotics should be administered 30–60 minutes prior to skin incision. Antibiotic concentrations in blood and bone usually arise within 20 and 60 minutes, respectively, and must be maintained until skin closure above the MIC.[22] When antibiotics are administered after tourniquet application, prophylaxis is probably ineffective. Therefore, the extremity remains without high antibiotic prophylaxis for an extended period of time. To prevent this unfortunate circumstance, the antibiotics should be administered at least 10 minutes prior to the incision and tourniquet inflation; they should have a sufficient half-life to maintain MIC throughout the procedure, and they should be effective against the most common pathogenic organisms.[23]

Generally, the initial two hours following an incision or contamination are the most crucial for preserving antibiotic concentration and the antibiotics should ideally be administered within an hour of the incision; however, some authors argue that the administration within two hours is acceptable.[24] Surgical site infection incidence increases two- to six-fold when we fail to provide antibiotic prophylaxis during this 2-hour timeframe.[25]

In the case of an open fracture, where contamination precedes treatment, it is not plausible to administer antibiotics to the surgical site prior to exposure to likely pathogens. The standard recommendation for patients with an open fracture is to administer antibiotics within three hours; nonetheless, in a retrospective study conducted by Lack et al., an interval of >66 min was identified between fracture and antibiotic administration as a major independent risk factor for surgical site infection in Gustilo-Anderson Grade III fractures. Urgent antibiotic prophylaxis and soft-tissue coverage within five days were independently correlated with a lower rate of deep infection; the timing of early surgical debridement had no effect on subsequent infection rates.[26]

Another parameter that might additionally impact the administration time frame is the type of antibiotic applied. For instance, vancomycin, which can be administered to patients with a β-lactam allergy, those colonized with MRSA, and those hospitalized in departments experiencing recent MRSA outbreaks, should be dispensed over a period of minimum 60 minutes due to the potential risk of anaphylactic adverse effects.[27] On this particular topic, no definitive recommendation can be implemented; however, the efficacy of antibiotic therapy has been demonstrated, and it should be administered as soon as possible.

Choice of antibiotics

The selection of antibiotic prophylaxis in Orthopaedic and Trauma surgery should prioritize cost-effectiveness, safety, and broad-spectrum coverage. While there is substantial evidence supporting the general use of prophylaxis, there is no clear consensus favoring one specific antibiotic over another. The most common pathogens causing SSIs are Gram-positive organisms, particularly Staphylococcus aureus and Staphylococcus epidermidis, both of which are part of the skin's natural flora. Therefore, β-lactam antibiotics, such as cephalosporins and penicillin derivatives like cloxacillin, are frequently used.[19] Among these, cefazolin has been the standard choice in Orthopaedic and Trauma surgeries, including arthro-

Table 1. Antibiotic Selection and Indications in Orthopaedic Surgery

Antibiotic Class	Common Agents	Coverage	Advantages	Limitations	Indications
1st Generation Cephalosporins	Cefazolin	Gram-positive, limited Gram-negative	High safety profile, good bone penetration	Limited coverage for Gram-negative, ineffective against 90% of coagulase-negative staphylococci	Standard for orthopaedic and trauma surgeries, including arthroplasty
2nd Generation Cephalosporins	Cefuroxime	Broader Gram-negative, maintains Gram-positive coverage	Better Gram-negative coverage than 1st generation	Less effective against a wider range of Gram-negative organisms	Broader Gram-negative coverage
3rd Generation Cephalosporins	Ceftriaxone	Gram-negative, some Gram-positive	Broader spectrum	Associated with Clostridium difficile infections, leading to reduced use	Maybe in open fractures
Penicillin Derivatives	Cloxacillin, Flucloxacillin	Gram-positive (Staph. aureus)	Good safety profile	Ineffective against MRSA and 90% of coagulase-negative staphylococci	Commonly used in orthopaedic trauma
Macrolides / Lincosamides	Clindamycin	Gram-positive, anaerobes	Excellent bone penetration	Ineffective against aerobic Gram-negative bacteria	Alternative for β-lactam allergic patients, suitable for Grade I and II open fractures
Glycopeptides	Teicoplanin, Vancomycin	Gram-positive (MRSA, MSSA)	Effective against MRSA, good bone penetration	Risk of resistance with vancomycin, potential nephrotoxicity	Used in β-lactam allergic patients, added to bone cement in arthroplasty
Fluoroquinolones	Ciprofloxacin	Broad-spectrum (Gram-positive and negative)	Excellent oral bioavailability	High resistance risk, Clostridium difficile risk	Not used as first-line due to resistance risk
Beta-lactam Combinations	Co-amoxiclav	Broad-spectrum (Gram-positive, negative, anaerobes)	Effective for open fractures		Recommended for open fractures
Local Antibiotics	Gentamicin (in PMMA)	Broad-spectrum (local high concentration)	Effective local delivery, minimizes systemic side effects	Systemic coverage is limited	Used in bone cement, beads for open fractures

plasty, due to its proven efficacy.[21]

Second-generation cephalosporins, like cefuroxime, are increasingly favored for their broader spectrum compared to first-generation cephalosporins. They provide enhanced coverage against Gram-negative organisms while maintaining effi-

cacy against key Gram-positive pathogens. This makes them a suitable alternative for prophylaxis in certain surgical settings, particularly where Gram-negative coverage is a concern.[28,29]

Cephalosporins, in general, have a favorable safety profile, excellent penetration into bone and muscle tissues, and are recommended by the American Academy of Orthopaedic Surgeons (AAOS) for arthroplasty patients.[30] However, they are less effective against a wider range of Gram-negative bacteria and only cover about 10% of coagulase-negative staphylococci.[31] Concerns over third-generation cephalosporins' association with Clostridium difficile infections have led to their reduced use as first-line prophylactic agents, particularly in the United Kingdom, where about half of NHS hospitals have transitioned to flucloxacillin to target Staphylococcus aureus.[32,33]

For patients with a β-lactam allergy, alternatives such as clindamycin are effective against Gram-positive and anaerobic bacteria, though they lack efficacy against Gram-negative organisms, making them unsuitable for higher-grade open fractures.[34] Vancomycin and teicoplanin are effective antibiotics for Gram-positive bacteria, including MRSA and MSSA, making them suitable options for patients with β-lactam allergies.[11] However, vancomycin requires cautious use due to concerns over resistance and potential nephrotoxicity, limiting its recommendation for routine systemic administration.[35,36,37] In specific clinical contexts, such as arthroplasty and contaminated open fractures, vancomycin can be utilized locally. It can be added to bone cement for arthroplasty prophylaxis, used in antibiotic nanoparticles to prevent infections in open fractures, and employed in spinal surgeries or ACL reconstructions by soaking the graft in a vancomycin solution.[5,38,39] These localized approaches aim to deliver high antimicrobial concentrations directly to the surgical site while minimizing systemic side effects. Similarly, gentamicin-loaded bone cement is commonly used to provide effective local antibiotic delivery in procedures at high risk of infection.[38,40]

The decision to use dual antibiotic prophylaxis against periprosthetic joint infections (PJIs) remains controversial due to potential risks like acute kidney injury. Thus, considerations regarding antibiotic resistance, cost-effectiveness, and patient-specific factors should guide the choice of prophylactic regimens.[41] In clinical practice, antibiotics targeting Gram-negative organisms are reserved for high-risk joint replacements, provided the patient's renal function allows it. Quinolones, despite their broad-spectrum coverage and good oral bioavailability, are avoided as first-line agents due to increased resistance risks and Clostridium difficile concerns.[5] For open fractures, co-amoxiclav, a combination of amoxicillin and clavulanic acid, remains a favored option due to its wide coverage of Gram-positive, Gram-negative, and anaerobic bacteria.[5]

Duration of antibiotic prophylaxis

The controversy over antibiotic chemoprophylaxis duration in Orthopaedic surgery arises from inconsistent guidelines recommending anywhere from a single dose to 14 days. This variation results from insufficient high-quality evidence, as decisions are frequently influenced by expert opinion and institutional practices rather than reliable clinical data.[23,42,43] Overall, there is a trend toward a decrease in the necessary doses of prophylactic antibiotics. The American Academy of Orthopaedic Surgeons (AAOS) recommends that chemoprophylaxis should not exceed 24 hours[14], and even stricter, the 2017 U.S. Centers for Disease Control and Prevention (CDC) guideline advises against administering antibiotic prophylaxis after surgical site closure in clean or clean-contaminated operations. In the orthopaedic setting, this includes procedures such as elective joint replacements without existing infections (clean) and minimally invasive surgeries with minor exposure to sterile areas (clean-contaminated), to prevent antibiotic overuse and resistance.[44] Williams and Gustilo found no difference in the infection rate between those who received prophylaxis for one and three days, in a retrospective study of patients undergoing total hip and knee arthroplasty.[45] A randomized controlled trial (RCT) reinforced the previous results, as no dif-

ference in the incidence of SSI between patients who received prophylaxis for 24 hours or seven days after THA or TKA was observed.[46]

In both elective and trauma surgery, evidence suggests that a single dose of antibiotic prophylaxis may be adequate;[47,48] however, the recommendation to shorten prophylaxis remains controversial, especially in high-risk situations like surgeries involving wound drainage or prosthetic implants, where the consequences of a SSI could be severe. Patients with total hip or knee arthroplasties who were not given extended oral antibiotic prophylaxis were up to five times more likely to develop periprosthetic joint infection (PJI), according to a retrospective analysis.[49] Long-term use was linked to drug-resistant pathogens, drug-induced hepatic/nephropathy, and burdensome healthcare costs.[1] The optimal duration of postoperative antibiotics is not yet clearly established, although the majority of reports indicate that prophylactic antibiotics administered for more than 24 hours postoperatively provide virtually no extra benefit.[50,51,52,53]

The authors' experience and everyday clinical practice contain the application of antibiotics for 24 hours in soft tissue procedures and for 48 hours when implantation of prostheses is performed. This clinical practice has led to significantly low infection rates, without severe side effects for many years. An individualized approach is of paramount importance, though.

Conclusion

Without a doubt, the utilization of surgical prophylactic antibiotics is of great importance in everyday orthopaedic practice. Regarding the timing, choice, and duration of prophylactic antibiotics in Orthopaedic surgery, general guidelines exist but an ongoing debate is also present. As a general rule, we could summarize that the current trend and the authors' proposal are to administer mainly cephalosporins (first or second-generation), but also vancomycin, clindamycin or penicillin-derivatives as prophylactic antibiotics 30 minutes to one hour prior to skin incision, preferably via intravenous infusion for 24 hours to three days postoperatively, depending on the type of the procedure and the patient characteristics. Exact antibiotic selection should be decided depending on cost, availability, allergies and local microbiology characteristics. A dual antibiotic scheme could be considered in selected cases.

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AOTH

Review

Novel selective MMP-13 inhibitors are associated with reduced joint damage and increased cartilage regeneration during osteoarthritis progression

Angelos Kaspiris[1], Olga Savvidou[2], Vasileios S. Nikolaou[3], Panagiotis Koulouvaris[2]

[1]*Third Department of Orthopaedic Surgery, School of Medicine, National and Kapodistrian University of Athens, KAT – General Hospital of Athens, Nikis 2, Kifissia, Athens 145 61, Greece*
[2]*First Department of Orthopaedic Surgery, School of Medicine, National and Kapodistrian University of Athens, "ATTIKON" University General Hospital, Athens 124 62, Greece*
[3]*Second Department of Orthopaedic Surgery, School of Medicine, National and Kapodistrian University of Athens, "Konstantopoulio-Patission Hospital", Konstantopoulou 3-5, Nea Ionia, Athens 142 33, Greece*

Abstract

Osteoarthritis (OA) is a common degenerative disease characterized by the destruction of articular cartilage and chronic inflammation of surrounding tissues. Matrix metalloproteinase-13 (MMP-13) plays a pivotal role in cartilage degradation through its ability to cleave type II collagen comprising an attractive target during OA progression. New classed of very potent and highly selective MMP-13 inhibitors showed increased capacities in the blockage of IL-1/OSM induced type II collagen degradation in bovine explants and human OA cartilage samples indicating potential chondroprotective and regenerative efficacy. The elucidation of the pathophysiological processes and the understanding of the mechanisms of MMP-13 regulation in OA and the development of MMP-13 selective inhibitors may provide a potential target therapeutic option for OA cartilage prevention and regeneration.

Keywords

Osteoarthritis; Matrix Metalloproteinase-13; selective inhibitors; chondroprotection; cartilage regeneration

Corresponding author

Dr. Angelos Kaspiris MD, MSc, PhD
angkaspiris@hotmail.com, angkaspiris@med.uoa.gr

Introduction

Osteoarthritis (OA) is the major cause of disability in the adult population affecting more than 7% of the global population, corresponding to 500 million people worldwide. The prevalence of OA is high among the elderly (≈70%) and can lead to aggravated pain and progressive dysfunction. Although in the past it was considered as a primary disorder of articular cartilage, it is now generally considered a disease of the whole joint (panarthritis), including the calcified cartilage, subchondral cortical and trabecular bone, joint capsular tissues and the synovium.[1] It must be highlighted that the structural support and the biological cross-talk between bone and cartilage, make subchondral bone and cartilage become a closely functional unit that cannot be separated[2]. Early structural abnormalities of OA are characterized by the progressive reduction of the proteoglycan aggrecan, that can be detected by the loss of the sarfarin O staining, generalized degeneration and fibrillation of the cartilaginous tissues and the ultimate brakeage of cartilage and sclerosis of the underlying subchondral bone.[1]

Moreover, OA is accompanied by abnormal neurovascular invasion at the osteochondral junctions, the regulatory mechanisms of which remain poorly understood. The invasion of nerves and vessels in the osteochondral unit is one of its hallmarks and is the primary reason for aggravated pain.[3] Many cytokines, including semaphorins,[4] netrins[5] and growth factors, such as vascular endothelial growth factor (VEGF) and nerve growth factor[6], have been found to have significant contribution in angiogenesis process. Recently, several therapeutic strategies, such as platelet-rich plasma (PRP), hyaluronic acid (HA), and mesenchymal stem cells (MSCs), have been applied to improve OA-related symptoms, enhancing the regenerative potential of the osteochondral tissue. Additionally, molecular target therapy has demonstrated promising experimental results as it was associated with stabilization or delayed progression of the OA degeneration process and, in many cases, with restoration of the normal cartilage and subchondral bone, as observed by objective assessment methods like imaging techniques or histological and immunohistological examinations).[7-8]

The matrix matalloproteinases (MMPs) are a family of 23 proteolytic enzymes that share several structural and functional characteristics with different substrate specificities. MMPs degrade proteins of the extracellular matrix and they have been considered the main enzymes responsible for degradation of collagens in OA cartilage.[9] MMP-13, also known as human collagenase-3, is thought to play an important role in type II collagen degradation in articular cartilage and especially in OA.[10] Type II collagen is the preferred substrate for MMP-13. Expression and contents of MMP-1 (collagenase-1) and MMP-13[11], expression of MMP-8 (collagenase-2), and collagenase activity are upregulated in human OA cartilage[11]. Additionally, increased expression and collagenase activity of MMP-13 was detected in mice.[12] Similarly, upregulation of MMP-1 and MMP-13 are also noted at OA lesions in guinea pigs, accompanied by increased collagenase activity.[13]

However, no effective treatment to reverse the degenerative process of articular cartilage has been discovered yet. Despite the profound limitations, the low selectivity and side effects of the up-to-date MMP selective inhibitors, the extensive experimental knowledge of MMP-related mechanisms of action and the urgent requirement in the development of effective therapies for OA therapeutic approaches led the researchers to evolve potent inhibitors of MMP-13 displaying an increased rate of selectivity over other MMPs.[14]

The aim of our study is to summarize the main molecular pathophysiological mechanisms of MMPs and MMP-13 that are implicated in cartilage and subchondral bone degenerative alterations in OA and to unveil possible target therapeutic options of novel MMP-13 selective inhibitors in the restoration and regeneration of the destroyed osseous cartilaginous tissues *in vivo*.

Matrix Metalloproteinases and Osteoarthritis

The cartilage extracellular matrix (ECM) is mainly composed of collagen fibers polysaccharides, secreted enzymes and proteoglycan molecules. It acts as a protective structure for cartilage against elastic and shear loadings, but it also regulates the chondrocyte behavior via matrix–cell interactions.[15] Moreover,

the collagenous proteins display critical structural and mechanical activity in the connective and bony tissues that are mainly composed by types I, III and V collagen. Collagen fragmentation is mediated by two distinct pathways. In the first, collagen degradation is mediated by secreted or membrane proteases. In the second, the collagen turnover occurs intracellularly through the urokinase plasminogen activator receptor-associated protein uptake (uPARAP/Endo180). After the uPARAP-induced turnover, collagen fragments are delivered to the lysosomes, where they are degraded by cathepsins B, L, N, and K under acidic conditions.[16-17] Matrix metalloproteinases (MMPs) are involved in both processes.[18]

Matrix metalloproteinases are a family of at least 24 zinc-dependent endopeptidases, capable of degrading all ECM components. In humans, the MMP family consists by 24 genes encoding 23 MMPs.[18] MMP-23 is coded by two identical genes at chromosomal 1 (MMP-23A and MMP-23B).[18] The classification of MMPs is based on a) their location in the ECM matrix (soluble) or on the cell membrane (insoluble), b) their structural appearance and substrate affinity.[18] According to this classification they divided into six subgroups. The collagenases (MMP-1, MMP-8 and MMP-13), gelatinases (MMP-2 and -9), stromelisins (MMP-3, -10 and -11), matrilysins (MMP-7 and -26), membrane type ones (MMP-14, -15,,-16,-17 and -24) and finally others (MMP-12, -18, -19, 20, -21, -22, -23, -27 and -28), c) their chronologically discovery.[18] Matrix metalloproteinases -4,-5 and -6 are not included, because they have identical structural and functional similarities with other members of the list.[18] Most MMPs are secreted into the extracellular space immediately after synthesis as proenzymes (pro-MMP) and are activated by proteolytic cleavage in the extracellular space. Specifically, the pro-MMPs are activated by proteolytic cleavage of the zinc-thiol interaction between the cysteine on the pre-domain and the Zn+2 on the catalytic domain by serine proteases or active MMPs, denominated as the "cysteine-switch mechanism".[19] The spherical catalytic domains share the same structural organization: three α-helixes, five β-sheets, connected by eight loops. Additionally, they contain a catalytic zinc ion coordinated by three histidine residues, a structural zinc ion, and three structural calcium ions required for enzyme stability.[19] The specificity of the MMP-substrate interaction depends on specific subsites or pockets (S) within the MMP molecule that interacts with corresponding substituents (P) in the substrate. The pockets localized on both sides of the catalytic zinc ion (Left: S1, S2, S3, ... Sn; Right: S10 , S20 , S30 , ... Sn') confer binding specificity to the substrate P1, P2, P3, . . . Pn and primed P10 , P20 , P30 , ... Pn' substituents, respectively.[19] Of these pockets, the S10 is the most variable in both the amino acid makeup and depth of the pocket. The S10 pocket may be shallow (e.g., MMP-1 and MMP-7), intermediate (e.g., MMP-2, MMP-8 and MMP-9), or deep (e.g., MMP-3, MMP-11, MMP-12, MMP-13 and MMP-14).[18-19] The large hydrophobic S10 pocket of MMP-13 has a highly flexible "S10 specificity loop (Ω-loop)" consisting of residues 245–253, which has been suggested to be a determining factor for the selective binding of inhibitors of MMP-13.[19]

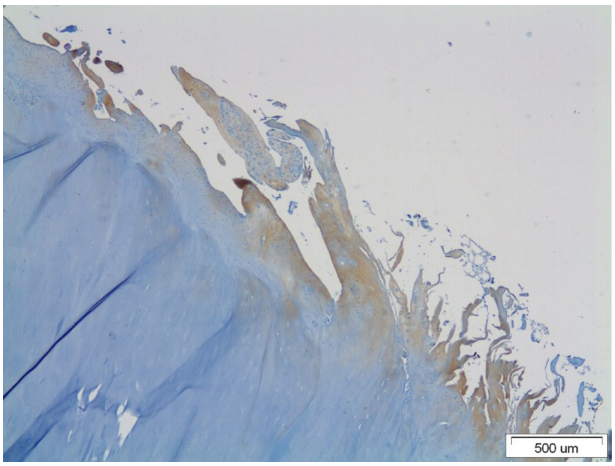

***Figure 1**: Increased immunolocalization of MMP-13 in the cartilage and subchondral bone of an immunohistological section in OA patient with Mankin score 8 (Magnification 4X)*

MMPs and a disintegrin and metalloproteinase production with thrombospondin motifs (ADAMTS) initiate ECM breakdown in OA **(Figure 1)**. Through the bone morphogenetic protein (BMP) pathway, the degradation of type II collagen (Col2A1) promotes the hypertrophy of chondrocytes, accelerating the degenerative alterations of OA.[20]

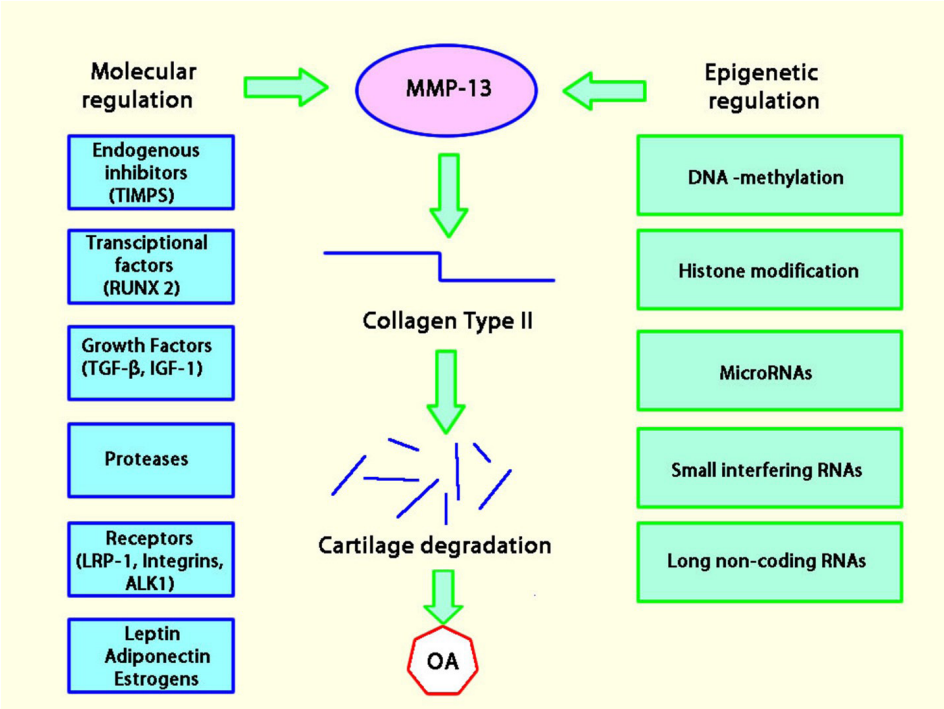

Figure 2: *Molecular and epigenetic regulation of MMP-13 expression*

Moreover, cartilage mineralization has also contributed to the OA development.[21]

The activation of 2A-adrenergic receptor signaling pathway via the extracellular regulated protein kinases 1 and 2 (ERK1/2) and protein kinase A (PKA) pathways stimulate the synthesis of matrix degradation-associated enzymes, such as MMP-3 and MMP-13. The inflammatory agent Osteopontin also triggers the production of MMPs through the NF-κB signaling pathway.[22]

Similarly, the HTRA1–DDR2–MMP-13 axis is essential for ECM breakdown. This procedure begins after the increased expression of high-temperature requirement A1 (HTRA1) and the breakdown of pericellular matrix components, including type VI collagen. Col2A1 can also activate the transmembrane protein Discoidin Domain Receptor Tyrosine Kinase 2 (DDR2) in the absence of a pericellular matrix. DDR2 ultimately triggers MMP-13 leading to OA degenerative changes.[23]

Structure, zymogen activation and regulation of MMP13

MMP-13 typically consists of a highly conserved signal peptide, a propeptide domain, a catalytic domain, a proline-rich hinge region, and a C-terminal hemopexin-like domain.[19-20] The optimum substrate for MMP-13 action is type II collagen, which is cleaved five times faster than collagen I, six times faster than collagen III, and more readily than by other collagenases.[24] The critical implication of MMP-13 in the cleavage of type II collagen is also supported by the excision of the OA medial meniscus animal model when performed in MMP-$13^{-/-}$ knockout mice. Interestingly, MMP-$13^{-/-}$ mice displayed reduced tibial cartilage fibrillation than wild-type mice after 8 weeks post-surgery.[25] Contrariwise, the constitutional expression of active MMP-13 at the joint cartilage was correlated with articular pathology resembling with OA degenerative changes.[26] Therefore, it must be highlighted that MMP-13 is particularly associated with the degradation of articular cartilage in OA by inducing the intense destabilization of type II collagen. Furthermore, MMP-13 it is not only involved in the breakdown of type II collagen, but it also effects the integrity of other ECM molecules, such as collagen type I, III, IV, IX, X, perlecan, osteonectin, and proteoglycan,[27] being

Table 1: Classification, substrates and mechanism of action of Matrix Metalloproteinases (MMPs)

Gene Symbol	Gene Title	Matrix substrates	Other substrates	Increased expression in Osteoarthritis	References
Minimal domain					
MMP-7	Matrilysin, uterine	Proteoglycans, Laminin, Fibronectin, Fibrin/Fibrinogen, Entactin, Tenascin, Vitronectin, Gelatin, Collagen 3-5, 9-11	Decorin, Pro-Tumor Necrosis Factor (TNF)-α, Pro-MMP-1 and -7	Yes	[18-19]
Collagenases					
MMP-1	Interstitial Collagenase	Gelatin, Collagen 1-3,7,10	Perlecan, Insulin-like Growth Factor Binding Protein (IGFBP) -2, -3, Inactive serpines	Yes	[18-19]
MMP-8	Neutrophil Collagenase	Gelatin, Entactin, Aggrecan, Tenascin, Same as MMP-1	Inactive serpines, Pro-MMP-8	Yes	[18-19]
MMP-13	Collagenase 3	Same as MMP-1	Inactive serpines	Yes	[19]
Stromelysins					

MMP-3	Stromelysin 1, Progelatinase	Same as MMP-7	Decorin, Pro-Tumor Necrosis Factor (TNF)-α, Perlecan, Insulin-like Growth Factor, Binding Protein (IGFBP) -2, -3, Pro-Interleukin 1B, Inactive serpines, Pro-MMP-1, 3, 7, 8, 9 and -13	Yes	[18-19]
MMP-10	Stromelysin 2	Same as MMP-1	Pro-MMP-1, 8, 10	Yes	[18-19]
Gelatinases					
MMP-2	Gelatinase A	Aggrecan, Gelatin, Elastin, Laminin, Fibronectin, Vitronectin, Collagen 1, 4, 5, 7, 10 and 11	Pro-Tumor Necrosis Factor (TNF)-α, Pro-Transforming Growth Factor(TGF)-β2, Insulin-like Growth Factor Binding Protein (IGFBP)-3, 5, Fibroblast Growth Factor (FGF)-R1, Pro-MMP-1, 2 and 13	Yes	[18-19]
MMP-9	Gelatinase B	Same as MMP-2	Bioavailable Vascular Endothelial Factor (VEGF), Pro-Interleukin 1B	Yes	[18-19]
Other					
MMP-28	Epilysin	Casein	Pro-Transforming Growth Factor(TGF)-β2, Pro-Tumor Necrosis Factor (TNF)-α	Yes	[18-19]

involved in ECM turnover in healthy cartilage.

Nevertheless, MMP-13 expression is regulated by several factors through specific signaling pathways including endogenous inhibitors, transcriptional factors, promoters, growth factors, receptors, proteases, hormones, and others **(Figure 2)**.

Selective Inhibitors of MMP-13

Since MMP-13 role in OA is significant, many researchers have developed therapies to treat OA by targeting its expression and inhibiting its synthesis and/or activity leading to remarkable reduction of the side-effects that observed after MMPs non-selective inhibitors application. Two main MMP-13 selective inhibitors have been developed: biologically synthesized inhibitors and chemically synthesized inhibitors. The chemically synthetic inhibitors can be divided into two further sub-groups: the Zinc and Non-Zinc Binding inhibitors.[28] MMP-13 zinc-binding inhibitors generally contain not only a zinc-binding group (ZBG) to bind with the catalytic $Zn^{2+,}$ but also a P10 subsite sequence fragment that can be accommodated in the S10 subsite of the enzyme active site. A category of N-O-Isopropyl sulfonamido-based hydroxamates, in which different aryl substituents on the sulfonamidic portion were examined and have been evaluated as MMP-13 inhibitors for potential therapeutic agents of OA.[28] Additionally, series of carboxylic acid and pyrimidine-2-carboxamide-4-one-based inhibitors of MMP-13 were also designed for the treatment of OA without inhibiting the related MMP-1 or TNF-α converting enzyme (TACE).[28] Another category of MMP-13 inhibitors was developed not to bind to the catalytic zinc ion, but to deposit themselves deeper in the S10 pocket, engaged to the specificity loop combined the increased potency with highly selectivity profiles. An advantage of non-zinc-binding MMP inhibitors is a potential decrease in non-specific, off-target metalloenzyme inhibition.[28]

It has been displayed that fully selective MMP-13 inhibitors reduced the collagen degradation in human OA cartilage explants. Interestingly, the total amount of collagen degradation and the inhibition differed with the individual cartilage. This report could be the result of the different degrees of OA cartilage damage.[29] Many studies demonstrated increased levels of IL-1a and oncostatin M (OSM) in OA joints accompanied by synergistic upregulation of aggrecanases and collagenases.[28] The application of selective MMP-13 inhibitors not only demonstrated efficacy in the inhibition of collagen and proteoglycan degradation in this system but also showed fully blocked collagen degradation in bovine articular cartilage explants.[29] However, the IL-1/OSM induced degradation of collagen in human OA cartilage was remarkably lower and slower due to very high sample variability. These discrepancies in the response of IL-1/OSM axis may be partially explained of the differences between cell density, age, health, or tissue permeability between the samples. Notably, selective inhibitors of MMP-13 reduced the collagen degradation up to 80% but complete inhibition was never achieved. Moreover, higher concentrations of selective MMP-13 inhibitors were necessary to minimalize the collagen breakdown in human OA cartilage.[29] Finally, recent reports from *in vitro* and *in vivo* studies showed that selective MMP-13 inhibitors can provide protection of cartilage in OA patients preventing further joint damage and possibly facilitate cartilage recovery and degeneration through balanced synthesis and breakdown homeostasis.[30-31]

Conclusions

MMP-13 plays a pivotal role in cartilage destruction during OA progression. The elucidation of the pathophysiological processes and the understanding of the mechanisms of MMP-13 regulation in OA and the development of MMP-13 selective inhibitors may provide a potential target therapeutic option for OA cartilage prevention and regeneration.

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Review

Intrarticular injections: when and with what substances?

Konstantinos Saropoulos[1], Pavlos Christogeorgos[2], Antonios Angoules[1], Konstantina Kourou[1], Athanasios Badekas[1], Leon Oikonomou[3]

[1]*Henry Dunant Hospital Center, Athens, Greece*
[2]*Mediterraneo Hospital*
[3]*General Hospital of Athens G. Gennimatas*

Abstract

Intra-articular injections are frequently used as treatment option in primary care clinics for the management of pain in patients with arthritis. However, it is unclear the optimal effect of intra-articular injections for the various types of arthritis. Therefore, we performed this review article to present the available intra-articular injections for arthritis and to discuss their short and long term effect in these patients.

Keywords

Intra-articular injections; arthritis; osteoarthritis; cortisone; hyaluronic acid.

Intra-articular injections are frequently utilized as treatment option in primary care clinics for arthritis and particularly osteoarthritis (OA) of the knee. Over the past three decades, treatments which have been developed for OA aim to reduce inflammation and pain, enhance functionality, prevent joint damage, and slowdown the disease progression. In cases when symptomatic treatment of OA with pharmacologic and nonpharmacologic agents is ineffective in managing pain and dysfunction, we proceed to surgical joint replacement. Until that point, provided early diagnosis and therapeutic intervention have already taken place, we can make an effort to alleviate symptoms and improve the overall quality

Corresponding author

Konstantinos Saropoulos
konsaropoulos@gmail.com

of life for patients.

Depending on patient's medical history, clinical examination and laboratory tests, recommendations may include weight and strain control, exercise as well as the use of analgetics, such as paracetamol, mild opioids and particularly non-steroidal anti-inflammatory drugs (NSAIDs), locally or systemically. In addition, medications for chronic pain are recommended, such as duloxetine and pregabalin. In cases where the disease progresses, intra-articular corticosteroids can be administered. However, it should be noted that corticosteroids are not recommended as a long-term treatment strategy, as their benefits are short-lived and they may have negative effects in patients with comorbidities, like hypertension and diabetes mellitus. Over the last decades, alternative treatments have also been used such as injections of hyaluronic acid, autologous platelet-rich plasma, and stem cells in order to relieve symptoms and delay the need for total arthroplasty.

In the treatment of acute inflammatory, crystal or autoimmune, arthritis and OA flare-ups, intra-articular cortisone injections (betamethasone, triamcinolone, dexamethasone) are beneficial in pain control. However, although concerns have existed regarding their potential to accelerate joint wear over time, there is a theoretical possibility that these injections could slow down the rate of cartilage loss and other structural manifestations of osteoarthritis, because suppressing inflammation could moderate its catabolic effects and minimize joint damage.

Administering injection of cortisone into a joint with synovitis, with the option to repeat the procedure after 4-6 weeks (within a limit of 3-4 per year) does not appear to harm the articular cartilage. In fact, it reduces the inflammation for a duration of at least 2- 4 weeks up to 2-3 months. Therefore it helps to restrict the potential damage that can be caused by its extension, while also allowing other treatments to take effect, such as non-pharmacological interventions like physical therapy.[7]

Hyaluronic acid (HA), a structural molecule of articular cartilage, is the main component of synovial fluid and serves multiple functions such as a lubrication, shock absorption and modification of the inflammatory response. Also, it protects the articular cartilage and maintains joint functionality. However, as individuals age or due to various external factors, the production and molecular weight of HA decrease. Consequently, the joint is not adequately protected, leading to degenerative changes and development of OA. The administration of HA intra-articular (known as viscosupplementation) can be considered as a replacement therapy. It mechanically and biologically supports the joint, providing long-lasting effects by stimulating the secretory cells of the synovial membrane to produce new HA beyond the drug's normal half-life.[2]

The potential benefits include mild inflammation control, improved lubrication, enhanced biomechanics, promotion of cell proliferation, differentiation, migration, and increased protein biosynthesis and secretion[6]. The utilization of HA injections is prevalent in the treatment of OA, especially of the knees, expecting improvement in pain relief and enhanced mobility over the next 1-6 months, particularly when repeated injections are administered on a 2-5 weekly basis. Despite the significant market demand for these injections, their effectiveness is still in question. As a result, many scientific companies opt not to include them in their recommendations.

There is a variety of HA products that differ in formulation, molecular weight, rheological characteristics and concentration. Certain formulations are considered more suitable for specific joints and patient populations, e.g. athletes[1]. As a result, HAs have been developed, with high and low molecular weight, synergistic complexes, such as HA plus chondroitin and other structural components of the joint, that more closely resemble the normal composition of synovial fluid. However, currently there is lack of clinical evidence to support their widely application in our daily practice. HAs of high molecular weight (one shot) are recommended at less frequent intervals but have not demonstrated long-term superior clinical benefit than those with 1,000,000 D. However, they may be more convenient for the patients. Sometimes HAs, particularly those with higher molecular weight, can cause temporary synovitis with pain and stiffness that lasts a few days.

Further research is necessary to acquire a compre-

hensive understanding of the factors that contribute to the repair of musculoskeletal tissue, despite the increasing number of new HA derivatives for the treatment of orthopedic conditions. Regarding symptomatic OA, intra-articular injection of polyacrylamide hydrogel has also been explored as a treatment, yielding positive clinical results[5].

The treatment with autologous plasma rich in platelets (PRP) falls under the category of Orthobiologics that help the body deal with its own injuries and repair itself[4]. It is a fact that platelets are blood cells that participate in blood clotting. PRP is essentially a concentrate of cells, growth factors and inflammatory mediators. This concentrate possess anabolic and anti-inflammatory properties, providing the ability to repair damaged soft tissues and articular cartilage, promote healing, prevent degeneration, reduce pain and accelerate functional recovery. Additionally, PRP stimulates the differentiation of stem cells into the specific tissue type affected by the disease and can also act as a scaffold by utilizing the ability of fibrinogen to form meshes and fill in damaged areas, contributing to normal regeneration and healing. Its analgesic effect is achieved by controlling both the inflammatory reaction and the activation of receptor 4 in nociceptor neurons by proteases. It is utilized in the treatment of acute and chronic musculoskeletal conditions, providing relief from acute and chronic pain and improving functionality in soft tissue diseases such as muscle strains, ligament injuries, tendinopathy, skin lesions and periodontal diseases. Additionally, PRP is beneficial in repair of articular cartilage damage, prevents degeneration and minimizes pain, and is used to address cartilage deficits and early-stage OA.[9]

Platelets continue to produce and secrete growth factors for approximately the initial 7 days. After this period their role is continued by macrophages. That is the reason why the procedure can be repeated after a week, whereas depending on the severity of the condition, 1-5 injections can be administered. The selection of one of the 4 concentrations depends on the specific condition and whether leukocytes and fibrin are included (P-PRP, L-PRP, P-PRF; L-PRF). In OA the recommended administration includes 3 injections. Typically, the second is administered within a week after the first and the third 2-3 weeks later. In case of damages, such as e.g. defects of skin, gums, or other mucous membranes, a gel form can be placed, immediately after centrifugation, without the use of special anticoagulant or after being placed on a special scaffold.

As the use of PRP expands, more scientific challenges will arise. Since our aim is to maximize its effectiveness, our therapeutic strategy ought to be based as much as possible on the pathophysiological condition of the particular disease we are dealing with each time. For example, the role of white blood cells in the concentrate is significant because their participation has the ability to delay healing, e.g in tendon cells, as it causes catabolic and inflammatory effects. On the other hand, if PRP without white blood cells is utilized in acute injuries, due to its strong anabolic effect, it can cause a larger scar, which is something we want to avoid. In recent injuries, the use of L-PRP (leukocyte) and in subacute P-PRP (pure) appears to be more beneficial.

Similarly, comprehensive understanding of the role of each growth factor (GF) is necessary in order to make our treatment more targeted so that the most beneficial components of PRP would be used in the right place and at the right time. Some GFs may be beneficial in certain applications and harmful in others. For example, TGF-β can promote the process of fibrosis, can be useful in the healing of ligaments and tendons, but can hinder the healing of muscle sprain. Vascular endothelial growth factor (VEGF) aids vasculogenesis and muscle regeneration, but may be detrimental to articular cartilage healing. Moreover, cytokines may act through conflicting pathophysiological pathways. Therefore, it is important to accurately assess the evolving microenvironment of the particular condition at the crucial point in order to achieve effective treatment.

The main recommendations for intra-articular PRP injections which were presented by the European League against Rheumatism (EULAR) are the following: an effective treatment regarding early or moderately symptomatic OA includes PRP injections. However, they also may be beneficial in severe OA. They are suggested as second option in case the usual symptomatic treatment does not have

the desired results. They should not be applied during OA flare -ups with significant fluid build-up. Treatment may include 1 to 3 consecutive injections. P-PRP (leukocyte poor) should be preferred and should not be mixed with injectable anesthetic or corticosteroid.

In recent years, the role of stem cells (MSCs: Mesenchymal Stem Cells) has become more significant, particularly in regenerative medicine and the treatment of OA, especially of the knee and hip. The fact that they are present throughout the whole body is indicative of their significant role in tissue repair and regeneration[8]. Their ability to migrate to injured areas, to inhibit pro-inflammatory pathophysiological pathways, to promote tissue repair through the release of anabolic cytokines in combination with their direct differentiation into specialized cartilage and bone cells, enhance their immunomodulatory and anti-inflammatory properties and consequently their potential in treatment of OA.[10]

It is an easy procedure to collect stem cells from various tissues such as bone marrow, adipose tissue, synovial membrane and amniotic fluid and directly inject them into the lesion area without the need for the patient to be hospitalized.

Local anesthetics should be administered intra-articular sparingly, because there is a possibility to cause chondrolysis, particularly when co-administered with steroids.[3] In daily clinical practice, injections into superficial and large joints such as the knee, shoulder and ankle are performed through specific access points. On the other hand, in cases of deep ones such as the hip and facet joints of the spine, ultrasound guidance or other imaging method may be utilized. The injection in small joints is sometimes not easy, especially in cases of obvious degenerative changes. Injections with local anesthetic, combined or not with steroid, can also be administered peri-articularly in serous bursae, tendon sheaths and ganglion cysts in order to relieve inflammation and pain, as well as other soft tissues such as in the trigger points of muscle aponeurosis and around nerves. Dry needling, meaning injection without medication, has also appeared beneficial regarding tendon healing and trigger point release. In addition, trials have been conducted regarding co-administration of steroid and HA, as well as HA and PRP.

In conclusion, in a chronic disease such as OA, the appropriate treatment option is critical for each individual patient. Current literature in combination with our experience indicate that intra-articular injections are safe, with minimal side effects, such as arthralgia and edema, and in even more rare occasions infection, and have positive results in terms of patient satisfaction.

Intra-articular administration of corticoids has short-term results, but is considered the best option in treating OA flare-up with hydrarthrosis that persists despite the use of NSAIDs. In this particular case, the result can be evident due to the remission of inflammation and hydrarthosis. Regarding the effectiveness of the other injections, because of the fact that we rely mainly on the patients' reports, we cannot be certain whether this result is due to the modification of the disease or the placebo effect. However, PRP and stem cells seem to work better in patients under 60 with mild OA. In cases of older patients or those with more advanced OA who do not wish to undergo surgery, a better option seems to be the administration of HA or a combination. Especially in knee OA and other supporting joints, PRP and stem cells are preferred in patients with a body mass index <30, while HA administration is more common in overweight patients or those with axial disorders.

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AOTH

Case report

Orthopaedic manifestations of Beckwith-Wiedemann syndrome: a case report

Evdokia Ttooulou[1], Dikaia Orfanou[2], Egor Kostin[3], Ioannis Orfanos[1*]

[1]*Department of Orthopaedic Surgery, Nicosia General Hospital, Cyprus*
[2]*Agios Athanasios - Agros Health Center, Corfu, Greece*
[3]*Medical Student, University of Cyprus*

Abstract

Beckwith-Wiedemann syndrome (BWS) is a genetic/epigenetic disorder with overgrowth and cancer predisposition, presenting with symptoms like macroglossia, abdominal wall defects, and limb length discrepancy (LLD). This case report details a 4-year-old female with BWS and a 3 cm LLD, treated with epiphysiodesis using eight-plates in her left femur and tibia. After two years, the plates were removed, achieving equal limb length. The report highlights effective surgical intervention for moderate LLD in BWS, emphasizing the importance of early diagnosis and comprehensive orthopedic management, applying general LLD treatment principles to patients with Beckwith-Wiedemann syndrome.

Keywords

Beckwith-Wiedemann Syndrome; musculoskeletal disease; hemihyperplasia

Introduction

Beckwith-Wiedemann syndrome is a growth disorder that can affect several parts of the body. Children with BWSp presenting with macrosomia are taller and/or larger than average even though the growth rate slows down after the age of eight. Less often the overgrowth disorder affects half of the body (hemihyperplasia).[1-5]

Case Presentation

A 4-year-old female with a known BWS (abnormal methylation of maternal DMR2 at 11p15) was re-

Corresponding author

Evdokia Ttoulou
evdokua@hotmail.com

ferred by a paediatrician for lateralized overgrowth. Other symptoms included diastasis recti, macroglossia, facial naevus flammeus, exophthalmos and left hemihyperplasia extending to the upper and lower extremities. Full leg x-rays were obtained to assess radiographic evaluation of the leg length discrepancy or any deformity of the legs that could affect the surgical management of the patient. Clinical evaluation showed 0,9cm length difference of the upper extremities and 3cm leg length discrepancy (Figure 1). We performed epiphysiodesis of the knee using eight-plates medially and laterally of distal femur and proximal tibia (Figure 2). At three months post-op, the patient reported no problem continuing regular daily activities and a new radiographic evaluation was obtained. The difference between the legs decreased to 2,6cm. The patient was tactically followed up in outpatient clinic and the limb's length was monitored (Figure 3). After two years of treatment the same leg length was achieved (Figure 4) and eight-plates were removed. Because of the possibility of Rebound phenomenon (reoccurrence of LDD), patient will be monitored in outpatient clinic until complete skeletal maturity.

Discussion

Beckwith-Wiedemann syndrome is caused by genetic or epigenetic defects around the

11p15.5 region that contains growth regulator genes. It affects 1 per 10,340 live births, with increased incidence of 1 every 4000 children conceived with assisted reproductive technologies (ARTs). Diagnosis is usually made in the neonatal period or early childhood[1]. Cardinal and suggestive features are used to make a clinical diagnosis or to refer a patient for genetic testing (Table 1).[8] Macrosomia (defined as height and/or weight >2SDS) is present in half of the BWS patients, and even though overgrowth is noted to slow down in late childhood, the final adult height tends to be greater than the parental target height. Growth charts are strongly indicated.[1,4,5] Lateralized overgrowth occurs in only 13% of BWS patients and it might include the upper and/or lower extremity. Cases of lateralized overgrowth with painful scoliosis have been reported. Along with the growth charts, an annual clinical evaluation for leg length discrepancy is strongly indicated and when present, should be referred for Orthopaedic evaluation. LLD ≤2cm can be corrected with shoe lifts, internal (1cm) or external (2cm).[6,7] LLD 2-5cm is indicative for surgical correction, reversible epiphysiodesis of the longer limp is usually the way to go in BWSp, as they tend to reach tall statures.[9,10] With closed growth plates femoral or tibial shortenings with IM nailing are the other options. LLD 5-20cm requires limp lengthening techniques with osteotomies and gradual distraction with external fixation or magnetic IM nail, although these techniques should only be considered for specific cases. Surgical correction of asymmetric overgrowth of the upper limbs is generally not indicated. Joint laxity has been reported to be around 70% in BWS patients in a study, but advanced bone age is only present in 3%.[5-9] In case of the reported patient, epiphysiodesis was proved an effective management of LLD, as during the period of treatment she had no complications and could continue doing her regular daily activities.

Conclusion

The broader implications of this report lie in its contribution to the evolving field of orthopedics, providing valuable insights into effective surgical interventions for moderate LLD in the context of BWS. As the understanding of genetic and epigenetic factors in BWS grows, the importance of early diagnosis and comprehensive management strategies becomes increasingly evident. This article serves as a practical guide for clinicians, offering evidence of the efficacy and tolerability of epiphysiodesis in addressing LLD in BWS patients. Epiphysiodesis of the femur and/or tibia is usually indicated for predicted LLD >2cm, preferably reversible epiphysiodesis with eight-plates is preferable. Limp lengthening should only be considered in specific cases.

Clinical message

Correction of LLD in Beckwith-Wiedemann syndrome follows the general rules of treatment of any limb length discrepancy.

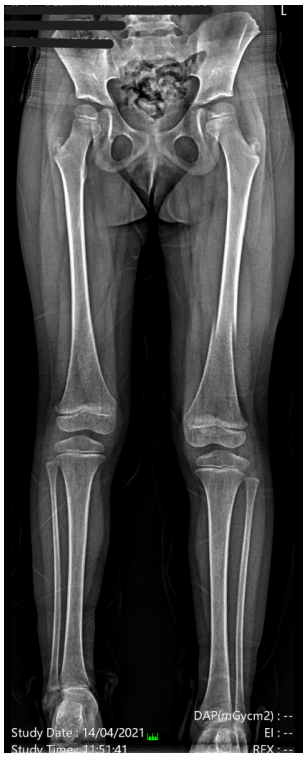

Figure 1. *Preoperative AP full-length leg radiograph*

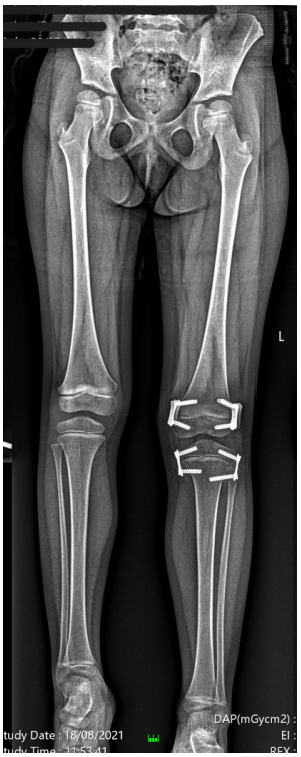

Figure 2. *Postoperative AP full-length leg radiograph*

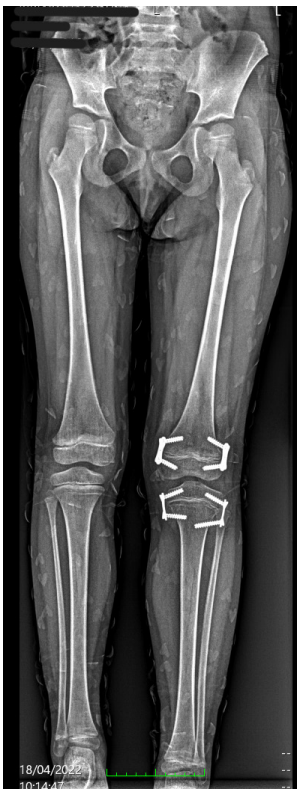

Figure 3. *1 year Postoperative AP full-length leg radiograph*

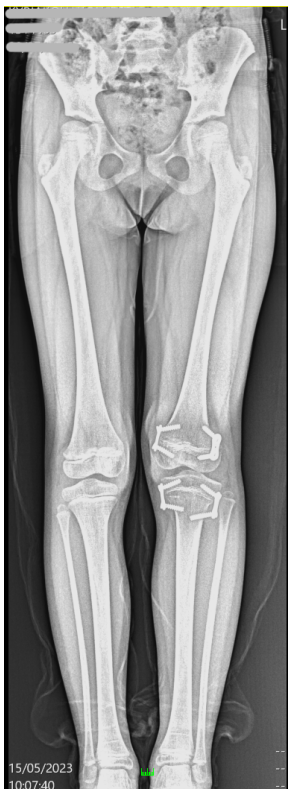

Figure 4. *2 years Postoperative AP full-length leg radiograph*

Table 1. Clinical features of Beckwith–Wiedemann Spectrum	
Cardinal features (2 points per feature)	**Suggestive features (1 point per feature)**
Macroglossia	Birth weight >2 SDS above the mean
Exomphalos	Facial naevus simplex
Lateralised overgrowth	Polyhydramnios and/or Placentomegal
Multifocal and/or bilateral Wilms tumour or nephroblastomatosis	Ear creases and/or pit
Hyperinsulinism (lasting beyond one week and requiring escalated treatment)	Transient hypoglycaemia (lasting less than a week
Pathology findings:adrenal cortex cytomegaly, placental mesenchymal dysplasia orpancreatic adenomatosis	Typical BWSp tumours (neuroblastoma, rhabdomyosarcoma, unilateral Wilms tumour, hepatoblastoma, adrenocortical carcinoma or phaeochromocytoma
-	Nephromegaly and/or Hepatomegal
-	Umbilical hernia and/or diastasis rect

Table 1 Clinical features of Beckwith–Wiedemann Spectrum[8]

An essential diagnostic tool for classical Beckwith-Wiedemann syndrome (BWS) is the standard deviation score, or SDS. For a clinical diagnosis, a score of ≥4 is required; however, molecular confirmation of an 11p15 anomaly is not required. For patients with a score of ≥2, including those with a traditional BWS score of ≥4, genetic testing is advised in order to further explore and validate the diagnosis of BWS. Individuals who have a score below two are not eligible for genetic testing. For patients with a score of ≥2, it is recommended to investigate alternate diagnosis options or refer them to a BWS expert for additional assessment if genetic testing produces negative results[8]

Competing interests

The author(s) declare that they have no competing interests.

Consent

We hereby confirm that written informed consent has been obtained from the patient's guardian for the publication of this case report. All identifying information has been omitted or altered to protect the patient's privacy.

Authors' Contributions

In the collaborative effort of this study, IO, DO, ET, EK all played integral roles encompassing the conceptualization and design of the research, the meticulous acquisition, comprehensive analysis, and insightful interpretation of the acquired data. IO assumed the responsibilities of drafting the manuscript, conducting the clinical examination of the patient and performing the surgery. IO also conducted the necessary diagnostic tests as part of this process. DO and EK, in addition to reviewing the manuscript critically for substantial intellectual input, actively participated in its drafting, further enhancing its intellectual content. ET's proficiency was evident in her assistance during surgery and in the patient's postoperative evaluation. The collaborative writing process involved all four authors, IO, DO, ET and EK who collectively lent their insights to the manuscript, ensuring its quality and significance. With unanimous approval, IO, DO, ET and EK all endorsed the final manuscript. They have embraced full accountability for the research, taking the responsibility to thoroughly investigate and resolve any queries regarding its accuracy or integrity.

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Review

The multiplane initial skeletal remodeling during scoliogenesis

Theodoros B. Grivas[1*], Elias Vasiliadis[2], Galateia Katzouraki[3], Dimitrios Lykouris[4], Nikolaos Sekouris[5], Christina Mazioti[6], Aristea Mamzeri[7], Despina Papagianni[8], Elissavet Mparka[9], Eleni Kataraxia[10]

[1]*Department of Orthopaedics & Traumatology, "Tzaneio" General Hospital of Piraeus, 185 36 Piraeus, Greece*
[2]*Third Department of Orthopaedics, National and Kapodistrian University of Ath-ens, School of Medicine, KAT Hospital, 14561 Athens, Greece*
[3]*Consultant Spine Surgeon, Spinal Department of Hygeia Hospital. 4 Erythrou Stavrou, Maroussi 151 23, Greece*
[4]*Orthopaedic Surgeon, Metropolitan Hospital, Ethnarchou Makariou 9 & El. Venizelou 1, 185 47 Neo Faliro, Pitaeus Greece*
[5]*First Department of Orthopedics, P. & A. Kyriakou Children's Hospital, 23 Levadeias, Ath¬ens 115 27, Greece*
[6]*Health Visitor, "Tzaneio" General Hospital of Piraeus, 185 36 Piraeus, Greece*
[7]*Health Visitor, TOMY Attica Square, 104 45 Athens, Greece*
[8]*School Nurse – Health Visitor, Special Primary School of Rafina, 190 09 Rafina, Greece*
[9]*Health Visitor, Health Center of Spata, Attica*
[10]*Health Visitor, 1st TOMY Agiou Dimitriou, Athens, Greece*

Abstract

In this opinion paper a concise introduction, describes the variety of published 2D and 3D related studies enabling deeper insight on the initial skeletal patho-remodeling during scoliogenesis. The changes in the spinal column and thorax are quoted for adolescent, childhood and infantile idiopathic scoliosis (AIS, CIS and IIS). In spinal column the changes analyzed in frontal, transverse and sagittal plane, and is commented where is initially the spine deformed while developing the idiopathic scoliosis (IS) that is vertebra vs intervertebral discs (IVD). Next the initial changes at the rib cage (RC) and the impact of these changes on spine deformity are mentioned as well as the impact on RC of the spinal operations for correction

Corresponding author

Theodoros B. Grivas
tgri69@otenet.gr; grivastb@gmail.com

of AIS. Finally, the concept of the progression of IS due to the diurnal variation "accordion"-like phenomenon of wedged IVDs is quoted and suggested as the 3D model of initial spinal changes of IS.

Keywords

Idiopathic scoliosis; rib index; double rib couture sign; segmental rib index; rib cage; thorax; diurnal variation; rib vertebra angle; thoracic ratios.

Introduction

Knowledge of normality is necessary for the study of abnormality. One way to study the normality, is the analysis of data which are collected not only from the Paediatric and Scoliosis Clinics of the outpatient departments of the hospitals but also from the implementation of school scoliosis screening programs (SSSP). The SSSP beyond its original aim, which is prevention in terms of selecting and referring the scoliotic and asymmetric children, provides the opportunity for collection of various cross-sectional data of normal children in the general population (height, weight, menarche, handedness etc.) except of the similar data of asymmetric/ scoliotic children and adolescents. Then comparison of normals to asymmetric/scoliotics can be done. SSSP serves also the epidemiology and natural history of idiopathic scoliosis (IS). Moreover and most interestingly, SSSP is a "human evidence- based" "clinical research" tool of IS scoliogeny based on the study of humans not animals and on the established concept that the "morphology" expresses-reflects and deciphers-decodes the physiology and pathology.

At the initial stages of IS development and progression, deformity is not easily diagnosed since the signs are subtle. The structural skeletal changes on the thorax and spine are initiated also gradually and the patho-remodeling happens more rapidly later during the rapid growth period of these children.

The aim of this opinion paper is to describe the sequential changes happening in the bones of thorax in spinal column and the truncal deformity in initiating and mild IS and not at developed and progressed deformity. These initial changes are described in the published radiological and clinical literature.

First it would be necessary to have a look at the definitions of the severity of scoliosis. Mild idiopathic scoliosis is characterized by a Cobb angle either of more than 10 and less than 30 degree[1] or of more than 10 but less than 25 degrees[2] or of more than 10 but less than 20 degrees.[3] Moderate IS is characterized by a Cobb angle of 25–40 degrees, which is indicated for non-operative treatment[4, 5] or a Cobb angle greater than 21 to 35 degrees.[3] We consider as mild curves those with a Cobb angle of greater than 10 but less than 20 degrees and as moderate those with a Cobb angle of greater than 21 to 35–40 degrees. The above published definitions are listed as we consider that "at initiating and mild scoliosis, the patho-biomechanics are dissimilar from the biomechanics when the curve is severe". Furthermore, it appears that at initiating and mild IS, genetics, epigenetics, and biology have the dominant / protagonistic aetiological role, having non or minimal structural skeletal changes; however, it should not have overlooked the non-protagonistic role of patho-biomechanics, which later become dominant for progressive IS, when the skeletal deformities are well established.

At present, more frequently three-dimensional analysis is used as a procedure to study the morphology of IS curvature and rib cage, as any study based exclusively on coronal, sagittal or transverse plane has its limitations. However, the most important and frequently used radiological parameters are designed and measured on postero-anterior (P-A) and lateral radiographs (i.e. Cobb, Mehta RVAs, Perdriolle angles). Lateral radiographs are not systematically made for children with IS in most hos-

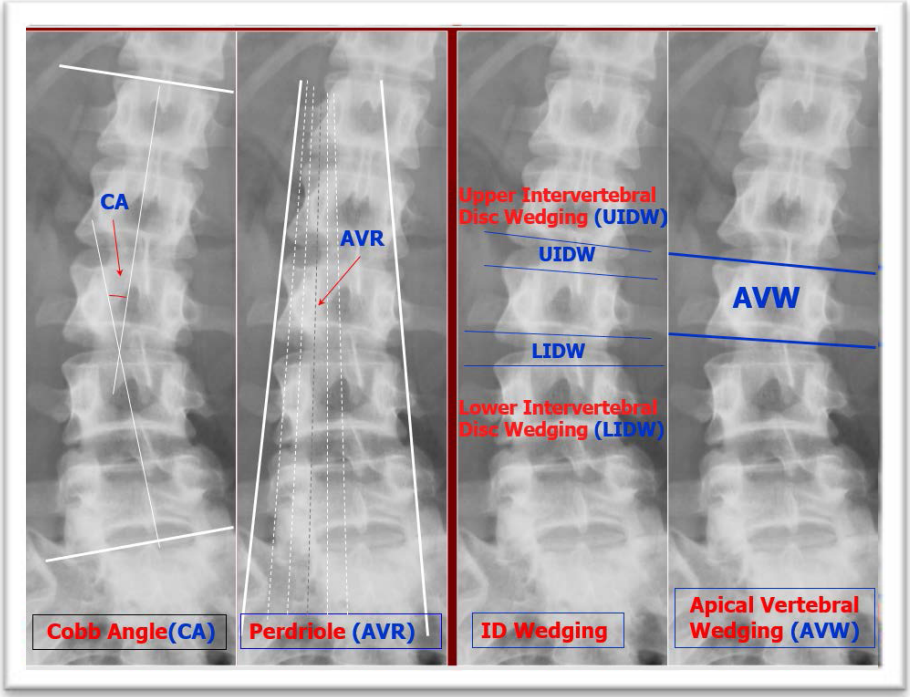


Figure 1: *The readings on the PA radiographs Cobb angle (CA), apical vertebral rotation (AVR), apical vertebral wedging (AVW) and the adjacent to the apical vertebra Upper (UIVDW) and Lower (LIVDW) Inter-Vertebral Discs Wedging.*[5]

pitals and the useful parameters for longitudinal or retrospective studies are taken almost exclusively from frontal plane radiographs. Currently the new technology of GAN-based deep learning framework can generate synthetic sagittal radiographs from coronal views to cure the limitation of missing lateral radiographs and to reduce radiation exposure in monitoring AIS. However, while these synthetic images appear visually consistent with real ones their quality remains insufficient for accurate clinical assessment, as the authors note.[6]

Imaging available for retrospective studies primarily consists of frontal plane radiographs. Plain chest and spinal films, which are readily accessible in medical archives, can effectively provide the necessary parameters for studying the onset, development, and progression of scoliotic thoracic and spinal deformities, without requiring additional special radiographs or extra radiation exposure. By utilizing the initial films of IS patients, the 2D parameters can support both cross-sectional and longitudinal studies on the development of these children or those with truncal asymmetry at risk of developing scoliosis.[6] Furthermore, these films can be used for both prospective and retrospective studies on non-operative and operative treatments of IS, as long as radiographic procedures are standardized. Such studies are also valuable for examining post-operative thoracic and spinal column morphology, allowing us to assess the impact of surgery on remaining growth potential and the progression of thoracic and spinal deformities.[7] It is important to note that the models currently used for predicting the progression of IS curves in cross-sectional and longitudinal studies also rely on parameters from 2D radiographs. This is because the foundational data for IS assessment, which forms the basis of these models, was primarily derived from 2D imaging methods in most centers, rather than 3D. While 3D analysis is increasingly used to study the morphology of scoliotic children, studies based solely on the coronal or sagittal planes have inherent limitations.[8-10]

Dansereau el al. 1987 proposed a 3D rib cage as-

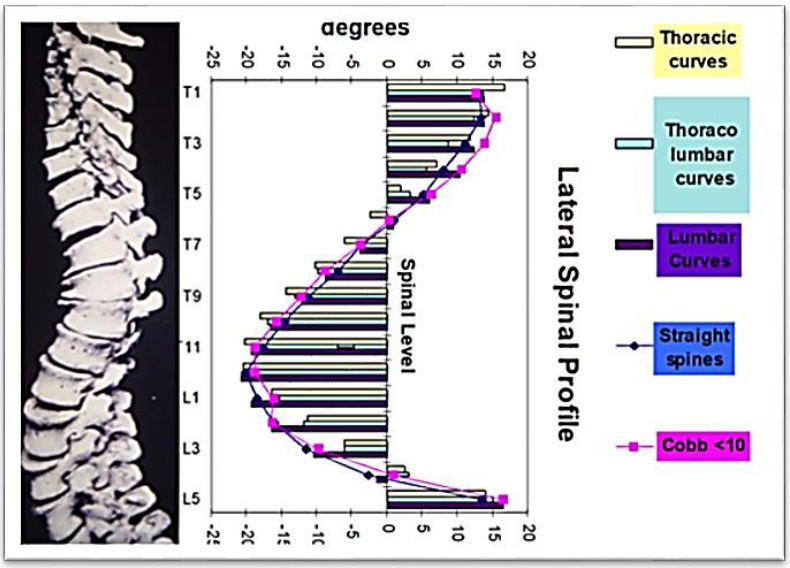


Figure 2. *The Lateral Spinal Profile for the various groups of children, boys and girls. Yellow bars = thoracic curves, azure bars = Thoracolumbar curves, mauve bars = lumbar curves, line with blue diamonds = straight spines, line with red rectangles = curves with Cobb < 10 degrees.*[35]

sessment, which certainly offers interesting possibilities but requires special equipment.[7-9] However, 3D reconstruction from CT scans is not routinely performed due to exposure to ionizing radiation.[10, 11]

In recent years, there has been a rise in transdisciplinary studies using machine learning on clinical data to develop in-house programs for predicting curve progression, which involves specialized terminology that may be not only challenging to digest yet difficult to assess. It is also interesting to note that these currently developed models of the prediction of progression of IS curves use as predicting parameters resulted from 2D radiography.[12-16]

Initial changes in the spinal column in IS

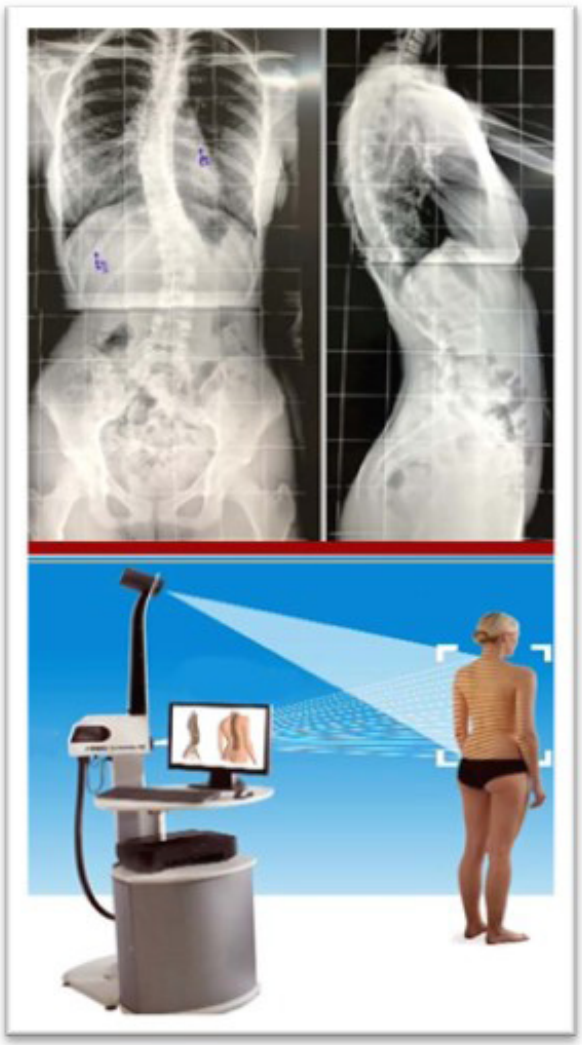
Initial changes in the spinal column: In frontal plane

The frontal plane morphology of the spine during the initial development of IS, has been reported.[5] In standing P-A radiographs of 92 children suffering mild scoliotic IS the following readings were obtained: Cobb angle (CA), apical vertebral rotation (AVR), apical vertebral wedging (AVW) and the adjacent to the apical vertebra Upper (UIVDW) and Lower (LIVDW) Inter-Vertebral Discs Wedging (Fig. 1). The mean thoracic CA was 13,4°, lumbar CA 13,8°, thoracic AVR 5,3°, lumbar AVR 4,7°, thoracic AVW 1,4°, lumbar AVW 1,5°, thoracic UIVDW 1.6°, thoracic LTVDW 1°, lumbar UIVDW 1,3° and lumbar LIVDW 2°. It was shown that in mild IS curves, when the deformity is initiating, the IVD is found wedged, but not the vertebral body. The spine is deformed first at the level of the IVD, due to the increased plasticity of the IVD, in the way of either torsion or wedging as an expression of other initiating factors that may start the deformity.[5]

In their 2009 study, Will et al. aimed to assess the relative contributions of vertebral and disc wedging to the increase in Cobb angle in IS by examining 18 girls across three phases of adolescent skeletal growth and maturation.[17] Their findings, consistent with Grivas et al.'s 2006 study, concluded that AIS first increases due to IVD wedging during the rapid growth spurt, followed by a gradual progression of vertebral wedging at a later stage.[5]

Initial changes in the spinal column: In sagittal plane

The lateral spinal profile (LSP) and its significance



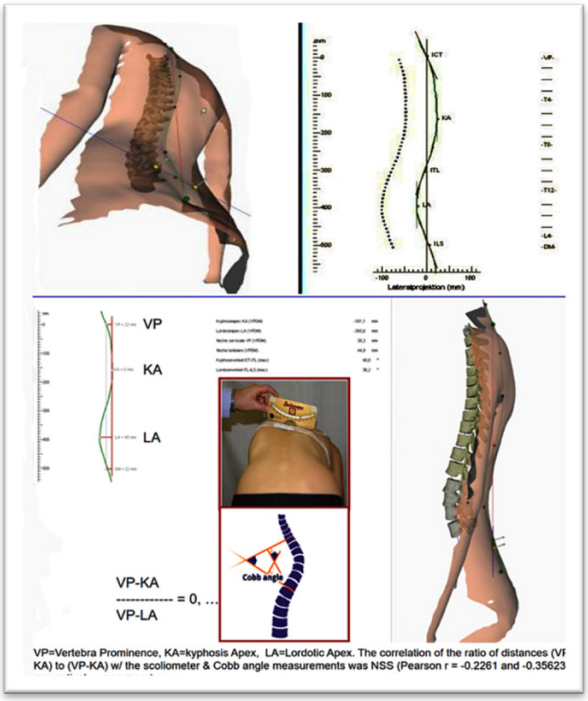


***Figure 3**. Study of the sagittal profile of the spine in IS using radiography and surface topography.*[42]

in IS scoliogenesis is a topic that was discussed by research for many years.[18-38] The LSP was often regarded as a primary cause of IS because the kyphotic thoracic apex in IS is positioned higher in the thoracic vertebrae, causing more vertebrae to tilt posteriorly. This creates conditions of increased rotational instability, leading to a higher susceptibility for the development of IS.[28] The role of the configuration of the sagittal profile in the initial stages of development in IS was reported by Grivas et al.[35] This study assessed the lateral spinal profile (LSP) in school-screening referrals with and without late-onset idiopathic scoliosis (IS) of small curves (10°-20° Cobb angle) in 133 children—47 boys and 86 girls, with mean ages of 13.28 and 13.39 years, respectively. The Axial Trunk Rotation (ATR), Cobb angle, and segmental spinal profile from T1-L5 were evaluated. Intervertebral LSP (ILSP), which is the difference between two consecutive spinal levels of LSP, was also calculated. Five groups were established: 1) straight spines, 2) spinal curvatures with Cobb angles less than 10°, and 3) scoliotic children with a) thoracic, b) thoracolumbar, and c) lumbar curves of 10°-20° (Fig.2).

The results indicated that scoliotic children had slightly less kyphotic segmental angulation and almost normal lordotic angulation compared to normal children. LSP correlations with the Cobb angle showed: a) a positive correlation at T6, T7, T8, and T9 in thoracic curves of scoliotic boys, and b) a negative correlation at T3, T4, and T5 in lumbar curves of scoliotic girls. The observed LSP differences were primarily located in the lumbar spine, suggesting that factors affecting the lumbar spine in the sagittal plane contribute to the development of AIS in boys. The slight hypokyphosis of the thoracic spine and the minimal differences observed in the small curves when compared to non-scoliotic individuals support the idea that reduced kyphosis may facil-

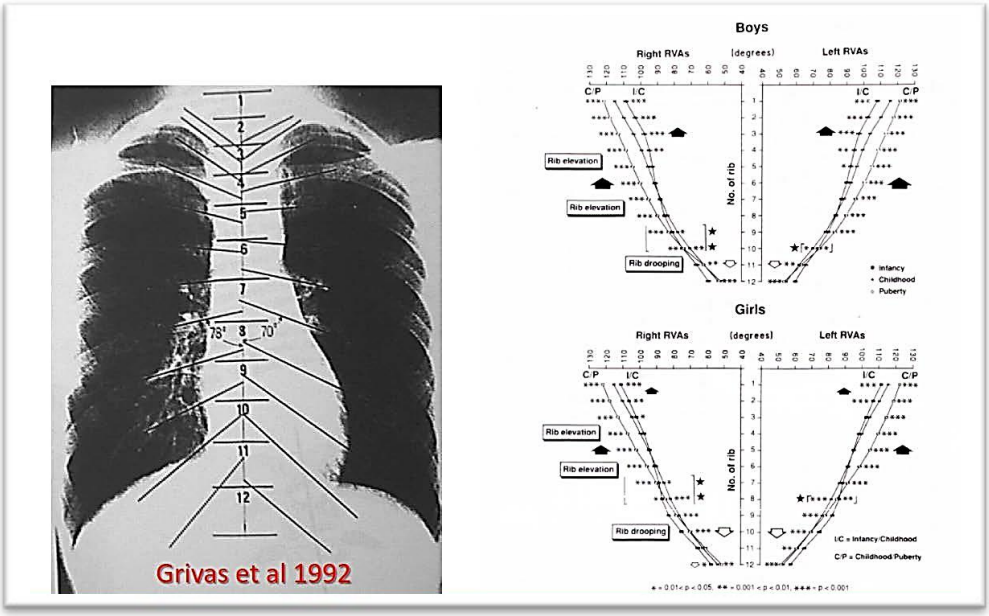


***Figure 4**: Segmental Rib-vertebra angles (RVAs),in infant childhood and adolescent boys and Girls.*[45]

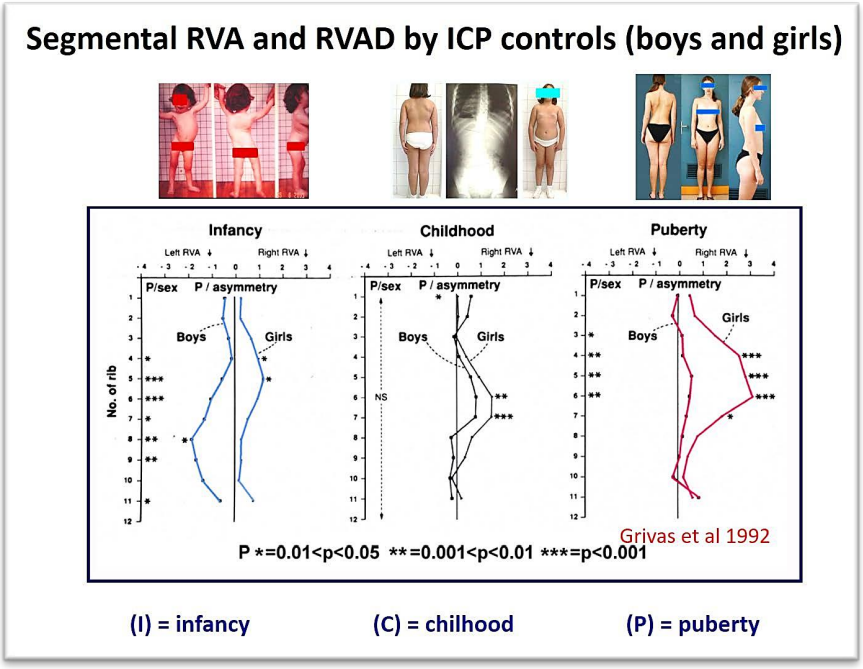


***Figure 5**: Segmental RVAD in Boys and girls by Infancy Childhood and Puberty (ICP) model.*[45]

itate axial rotation, acting as a permissive factor rather than an etiological one in the development of IS. In other words, a straight (non-curved) beam is more easily rotated than a curved one.[35]

The view that the reduced kyphosis, by facilitating axial rotation, could be viewed as being permissive, rather than as aetiological, in the pathogenesis of IS was confirmed in other research studies.[39-41] The sagittal profile of the spine in IS was evaluated using surface topography and radiography. The study included 45 children, 4 boys and 41 girls, with an average age of 12.5 years (range 7.5–16.4 years),

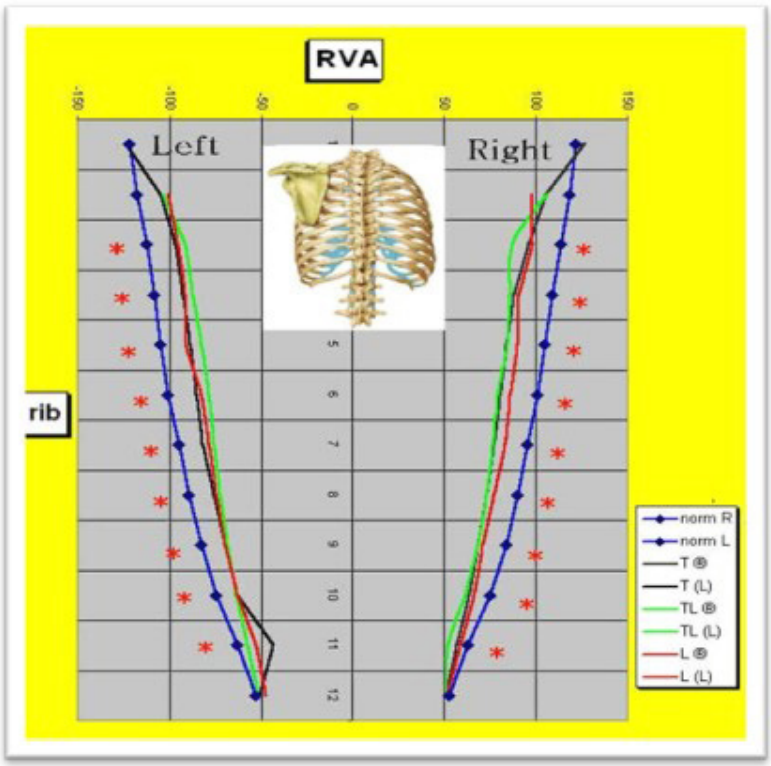


Figure 6: *Radiological evaluation of the deformation of the Thoracic Cage in AIS.*[49]

who were referred to the scoliosis clinic from the SSS. The children were divided into two groups: Group A consisted of 17 children with IS (15 girls and 2 boys), all of whom had a scoliometric trunk asymmetry of 5 degrees or greater. Group B, the control group, included 26 children (15 girls and 11 boys) with an Axial Trunk Rotation (ATR) of less than 2 degrees. The children's height and weight were measured, and the Prujis scoliometer was used during the standing Adam test in the thoracic (T), thoraco-lumbar (TL), and lumbar (L) regions. The Cobb angle was assessed using postero-anterior radiographs in Group A. A posterior truncal surface topogram was also taken using the "Formetric 4" apparatus, and the distance from the vertebral prominence (VP) to the apex of the kyphosis (KA), as well as from VP to the apex of the lumbar lordosis (LA), was calculated. The ratio of the distances (VP-KA) to (VP-LA) was also computed. The averages of these parameters were analyzed, and the correlation between the ratio of distances (VP-KA) to (VP-LA) and the scoliometer and Cobb angle measurements were assessed (Pearson correlation coefficient, r) within both groups and between them (Fig.3).

In Group A (IS), the average height was 1.55 m (range 1.37–1.71) and the average weight was 47.76 kg (range 33–65). The children with IS had right-sided (Rt) thoracic (T) or thoracolumbar (TL) curves. The mean Cobb angle for thoracic curves was 24 degrees, and for lumbar curves, it was 26 degrees. In the same group, the kyphotic apex (KA (VPDM)) distance was −125.82 mm (range −26 to −184), and the lordotic apex (LA (VPDM)) distance was −321.65 mm (range −237 to −417). The correlation between the ratio of distances (KA (VPDM) / (LA (VPDM)) and the Major Curve Cobb angle as well as the scoliometer findings were not statistically significant (Pearson r = 0.077, −0.211, p = 0.768, 0.416, respectively). Similarly, in the control group, the ratio of distances (KA (VPDM)) / (LA (VPDM)) was not significantly correlated with scoliometer results (Pearson r = −0.016, p = 0.939). The findings of this and the former mentioned study[35] do not con-

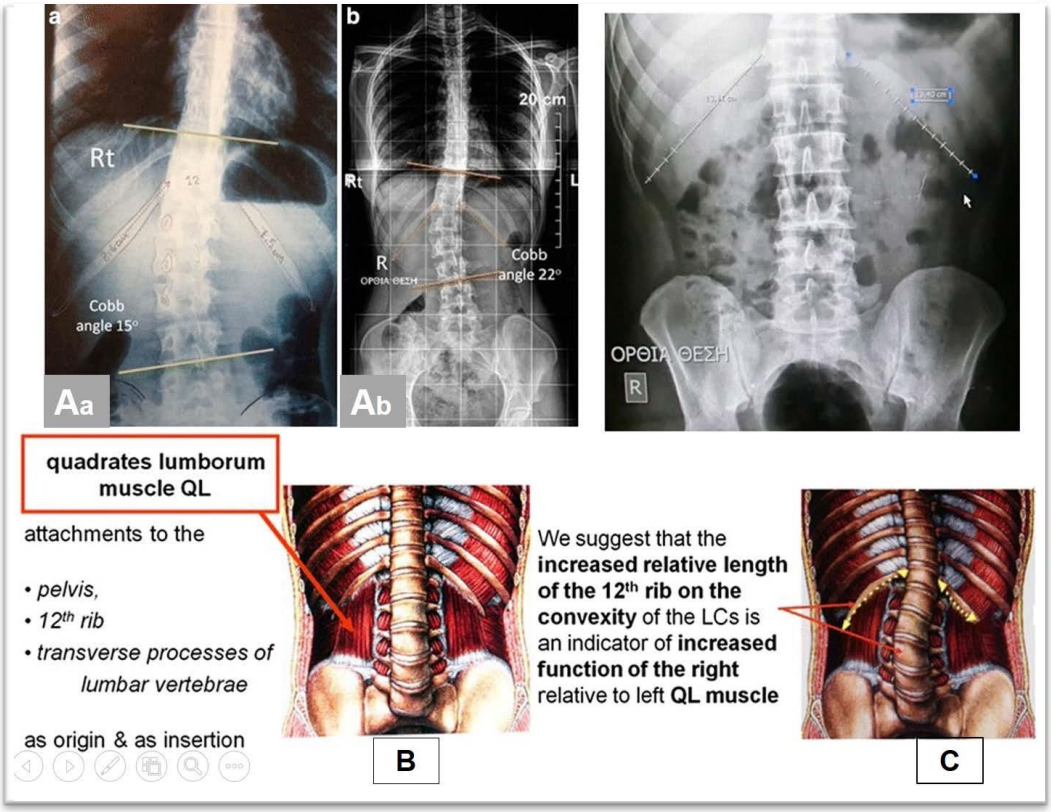


***Figure 7**: A)a, Cobb angle Rt lumbar IS curve with a longer Rt 12th rib, likewise in b, a 22 of Cobb angle Rt lumbar IS with a Rt 12th rib longer B) QL attachments, C) the suggested hypothesis for Rt lumbar IS curves.*[54]

firm this hypothesis, that lateral profile of the spine is a primary aetiological factor for IS, since the correlation of the (VP-KA) to (VP-KA) ratio with the truncal asymmetry, assessed with the scoliometer and Cobb angle measurements, is not statistically significant, in both groups A and B. In addition, the aforementioned ratio did not differ significantly between the two groups in other studied samples.[39-41]

As mentioned earlier, it seems that the patho-biomechanics in the early stages and mild forms of IS may differ from those in more severe curves. The studies referenced above offer insight into whether there is an inherent disorder in vertebral body growth in mild to moderate IS. It was observed that the sagittal profile of these IS curves does not differ significantly from the profile of normal peers.[35] In other words, the growth potential in the sagittal plane (lateral spinal profile) for mild to moderate IS is similar to that of peers with normal spines, affecting both the vertebral bodies and intervertebral discs (IVDs). These two studies suggest that hypokyphosis is not a primary cause of the onset or progression of mild to moderate scoliotic curves, contrary to what has been reported elsewhere.[28] Moreover our view is consistent with views previously published.[43]

Initial changes in the spinal column: In transverse plane

In mild curves, the rotation of the apical vertebrae is minimal, this morphology plays a crucial role in obtaining an accurate sagittal profile. Since the sagittal profile in these cases is only minimally affected, it leads to more reliable measurements, which is essential for our assessment.[5, 44]

Initial changes in the thoracic cage, Impact of the thoracic on the spine deformity

Initial changes in the thoracic cage in Adolescent Idiopathic Scoliosis

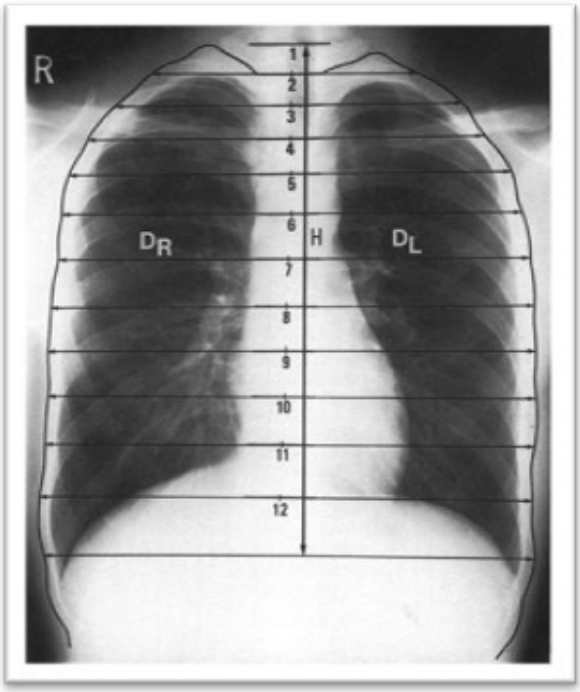
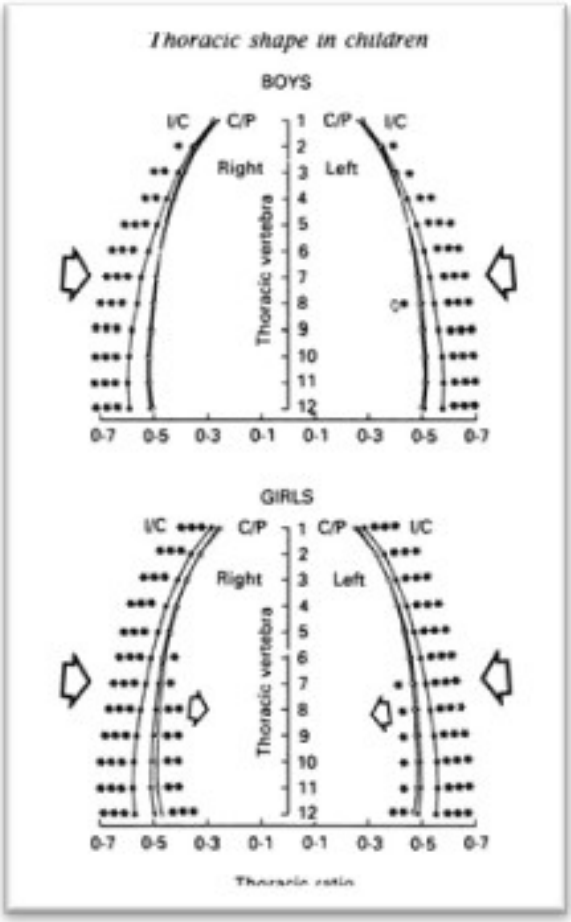


Figure 8: *Segmental thoracic ratios (TRs): way of measurement and values for boys and girls in infancy, puberty and adolescents.*[60]



The study of the segmental (T1-12) RVAs and segmental rib-vertebra angle differences (RVADs), was reported as a new method (Fig 4, Fig, 5). The Infancy Childhood and Puberty (ICP) model of growth was used for analysis of these data.[46] It was hypothesized that RVAs are influenced by the central nervous system (CNS) mediated trunk muscle activity, and RVADs pattern reflects the common age, sex, and laterality patterns of IS. Extremes of such asymmetries may be an aetiological factor for both IIS and AIS. Segmental analysis of RVAs in AIS RC (Fig. 5), reveals crossed RVA asymmetry with aetiological implications.[45, 47]

The findings from these cross-sectional studies highlight the changes in the RC's structure by age and gender during growth. It is proposed that the funnel-shaped RC of neonates gradually transforms into a barrel-shaped structure as they grow, which, from an evolutionary perspective, may represent an adaptation of the RC to the human bipedal gait.[48, 49] The above led to a novel multifactorial theory for the pathogenesis of IS.[43]

A comparison of the RVAs between scoliotic and nonscoliotic children, involving 47 children with T, TL and L curves ranging from 10-20 degrees of Cobb angle and an average age of 12.4 years, and 60 age-matched non-scoliotic children, revealed that the RC of the late onset scoliosis (LOS) children had significantly lower RVAs ($p<0.01$) at nearly all thoracic levels.[49] It was reported that RVAs is an expression of the opposing muscle forces, that act on each rib, and that RVA asymmetries are aetiological for IS by weakening the spinal rotation defending system.[43] This study showed that scoliotic children with mild curves have underdeveloped RC compared to normal (Fig. 6). The differences are most pronounced in scoliotic children with thoracic curves. It has been suggested that the variations in RVAs between the right and left sides in this group reflect asymmetric muscle forces acting on the RC. We concluded that these asymmetric muscle forces

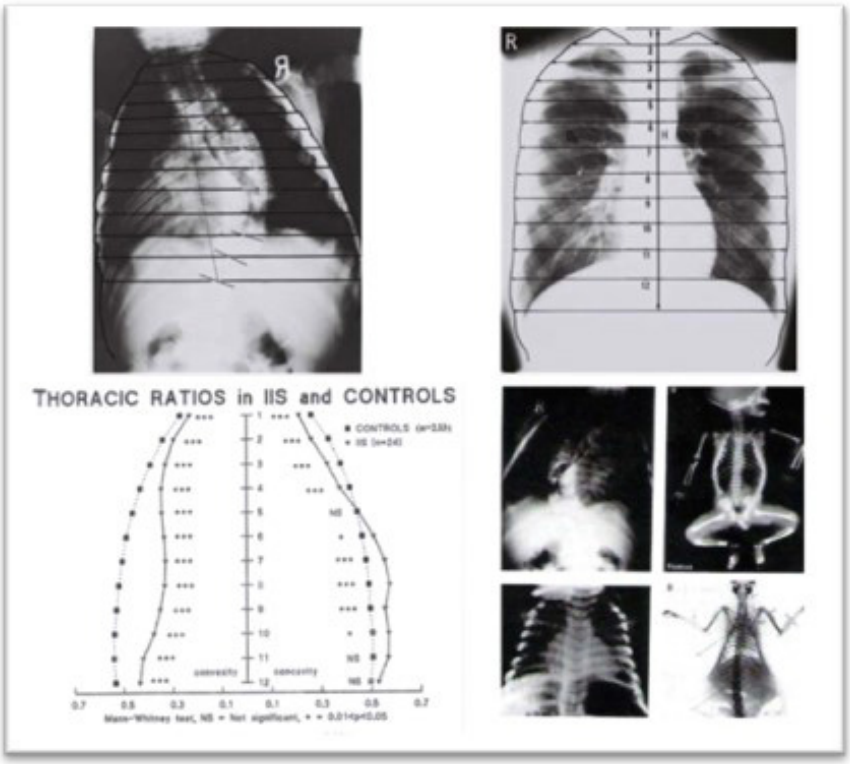


***Figure 9**: The rib-cage deformity in infantile idiopathic scoliosis-the funnel-shaped upper chest.*[60]

contribute to the pathogenesis of IS by deforming the RC prior to affecting the spine.[49]

One characteristic of the deformation of thorax in IS is the drooping of RVAs. Measurement of the drooping value in convex RVA is equally important as that of initial convex RVA or RVAD in the literature.[50]

Interesting, Sevastik et al 1997, studying the RVAs in IS, concluded that the typical pattern of the RVAs on the concave and convex sides seems to be independent of the underlying cause of the spinal curvature.[51]

Canavese et al. (2011) reported that in their study of AP digital radiographs of 44 female patients with right convex idiopathic scoliosis and 14 normal females, the RVAD and RVARa values in the scoliotic segment were higher in patients with untreated scoliosis greater than 30° compared to those with untreated deformities of less than 30° or normal subjects. A significant difference was observed between the groups for the RVA, RVAD, and RVARa variables. They also recommended that measurements of RVA, RVAD, and RVARa should be conducted not only at or near the apex of a thoracic spinal deformity but should also encompass the entire thoracic spine.[52] Foley et al (2012) commented that RVAD 3D provides additional information to Mehta's RVAD on the torsional nature of the deformity.[53]

Initial changes in the thoracic cage in lumbar AIS

Grivas et al. (2016 in their study of idiopathic and normal lateral lumbar curves (LLC), discussed the presence of asymmetry in the length of the 12th rib associated with these curves.[54] They proposed a pathomechanical role for the quadratus lumborum (QL), based on the novel finding of bilateral length asymmetry of the 12th rib in relation to IS and minor non-scoliotic LLC (Fig. 7). To the 12th ribs are attached numerous small muscles, including the diaphragm, QL, internal and external intercostals, serratus posterior inferior, short and long rib elevators, external oblique abdominal, internal oblique abdominal, transversus abdominis, iliocostalis and

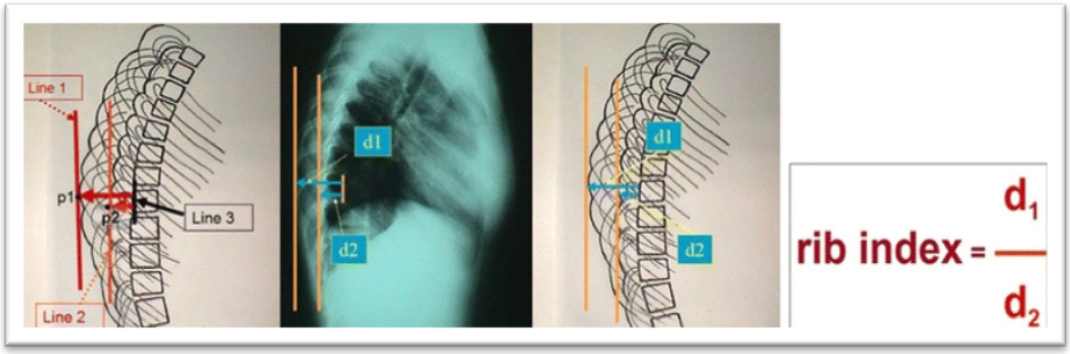


***Figure 10**. The way the RI is assessed on the standing lateral spinal radiographs.*[64]

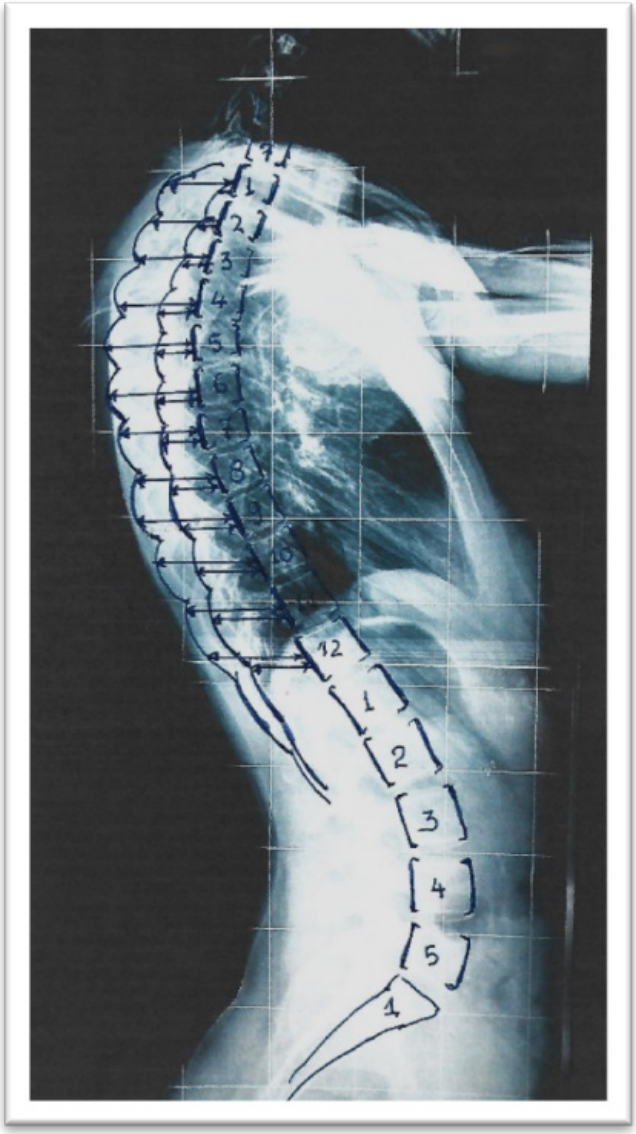


***Figure 11:** The way the segmental RI (SRI) is assessed on the standing lateral spinal radiographs.*[65]

longissimus thoracis. The largest of these muscles is the QL, which attaches to the pelvis, 12th ribs, and the transverse processes of the lumbar vertebrae, likely exerting the greatest forces on the 12th ribs. Two theories were proposed: a) the relatively increased activity of the right QL muscle causes the LLC curves, and b) the QL muscle counteracts the lumbar curvature as part of the body's attempt to compensate for the curvature.[55] Grivas et al. (2016) suggested that one mechanism behind the relatively increased length of the right 12th rib is mechanotransduction,[54] in line with Wolff's and Pauwels' laws (Fig. 7).[55-58]

Based on the research outlined above, the implication is that the rib cage, particularly the asymmetry of the 12 pairs of ribs, precedes and plays a role in the pathogenesis of IS, contributing to the development of lumbar spinal deformity.

Initial changes in the thoracic cage in Infantile idiopathic scoliosis - Segmental thoracic ratios (TR) and Segmental TR differences (TRs)

Segmental thoracic ratios (TRs) were measured at each segment (T1-T12) in chest radiographs of 412 children, aged 0-17 years, who visited the hospital with minimal disorders or diseases (193 boys, 219 girls). A new method for measuring TRs was employed, which calculates the width of the left hemithorax, right hemithorax, and the total thorax relative to the T1-T12 distance.[59] The data were analysed in 3 age groups--infancy, childhood and puberty, after the classification of Karlberg (1989).[46] The study's analysis revealed several key findings. In the coronal plane, the chest broadens from T1 to

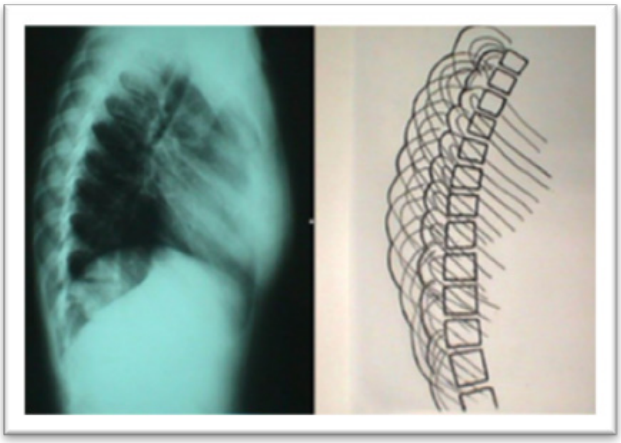


***Figure 12**. the contours of the two hemithoraces were always overlapping the one over the other, and this overlapping is the "double rib contour sign" (DRCS).[61-63]*

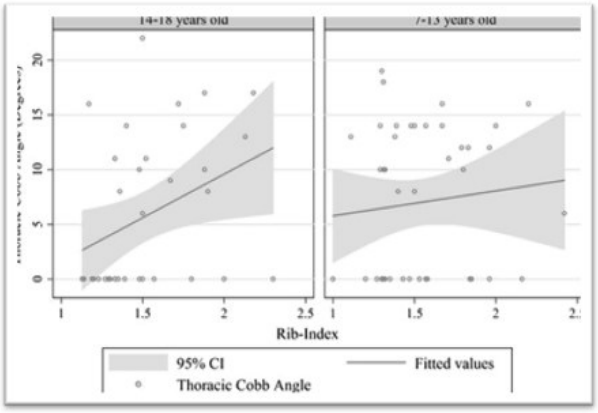


***Figure 13.** The linear relationship between thoracic Cobb angle and RI is graphically depicted. There is only linear association between thoracic Cobb Angle and rib-index in the age group of 14–18 years.[34] (Predicted Thoracic Cobb Angle = - 6.357 + 7.974 X (Rib-Index).[63, 72, 84]*

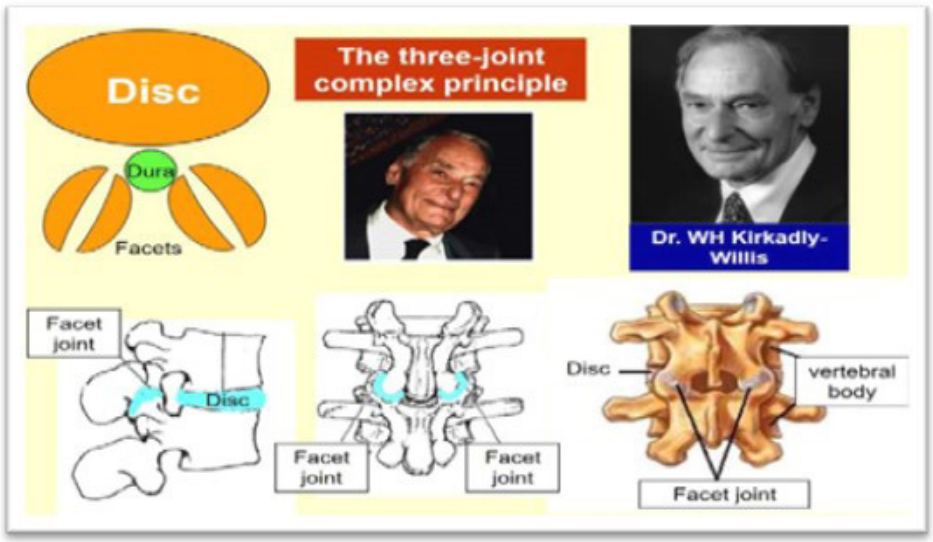


***Figure 14:** the three-joint complex of Dr WH Kirkadly-Willis.[98]*

about T10-11 between infancy and childhood, while relative to its length, the chest narrows from top to bottom, particularly in the lower chest. Between childhood and puberty, the chest narrows further in girls (but not in boys) in the lower half below T6. This relative narrowing of the chest during growth appears to result from several mechanisms: (1) elevation of the upper rib-vertebra angles (above 90 degrees); (2) drooping of the lower rib-vertebra angles (below 90 degrees); and (3) impaired linear rib growth in relation to thoracic spinal growth in the lower ribcage (T6-12) of girls between childhood and puberty (Fig. 8).[45]

The role of the rib cage in the development of progressive infantile idiopathic scoliosis (IIS) was investigated by Grivas et al. (2006) using segmental thoracic ratios from posteroanterior (PA) spinal radiographs of 24 patients with progressive IIS, with a mean age of 4.1 years. Thoracic ratios (TRs), including segmental convex and concave TRs, Cobb angle,

Figure 15: *The imbibed water (+ H2O) mainly in the apical IVD but also in the adjacent discs must be in a greater amount in the convex side than in the concave due to convex-wise asymmetrical distribution of glycosaminoglycans (GAGs) in NP collagen network type II. This results in: 1) asymmetrical pattern of water distribution, 2) Due to DV, asymmetrical convex-wise, concentrated cyclical loads to the IVD during the 24h, the convex side of the wedged IVD sustains greater amount of expansion than the concave side and as an eventual result the vertebra deforms.*[99]

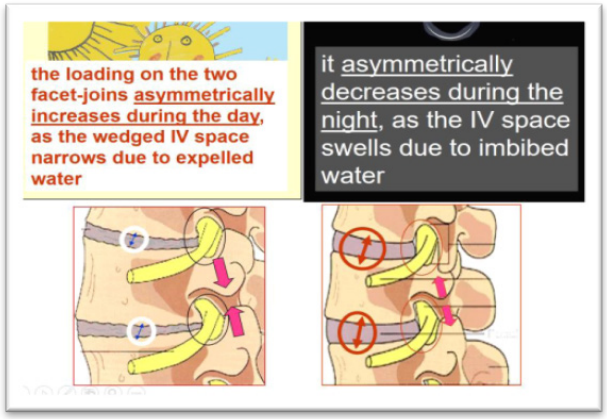


Figure 16: *The loading on the two facet-joins and IVDs is asymmetrical. The asymmetrical loading during the day occurs as the wedged IVD space narrows due to the expelled water, and decreases asymmetrically during the night as the IVD space swells due to the imbibed water. This results in asymmetrical growth of vertebral bodies and their posterior elements and also this is reflected in minor fluctuation of Cobb angle during the 24hour period, as was reported in Zetterberg et al 1983,*[101] *in the younger and more skeletally immature individuals.*[99]

segmental vertebral rotation, and vertebral tilt were measured (Fig. 9)[60].

Additionally, in a control group of 233 subjects with a mean age of 5.1 years, the segmental left and right TRs and the total width of the chest (left plus right TRs) were measured in PA chest radiographs. Statistical analysis, including Mann-Whitney, Spearman correlation, multiple linear regression, and ANOVA, was performed. The comparison showed that the scoliotic thorax is significantly narrower than that of the controls at all spinal levels. The upper chest in IIS is funnel-shaped, and vertebral rotation at T4 early in management significantly correlates with apical vertebral rotation at follow-up. The IIS thorax is narrower than that of the control group, with a funnel-shaped upper chest. Vertebral rotation at the upper limit of the thoracic curve in IIS is predictive, reflecting impaired rib control of spinal rotation, likely due to neuromuscular factors, which also contribute to the funnel-shaped chest (Fig. 9).[60]

Double Rib Contour Sign (DRCS) – Rib Index (RI) and Segmental Rib Index (SRI)

The "double rib contour sign" and the rib index (DRCS and RI), were introduced in 1999 (Fig 10) by the first author and lately the Segmental Rib Index at all levels from T1 to T12 (Fig 11).[61-66]

The significance of using these parameters lies in their contribution to scoliogenesis.[63, 65, 67]

Additionally, the rib index (RI) has been confirmed to a) serve as a strong surrogate for scoliometric readings in idiopathic scoliosis (IS),[68] and b) assist in the documentation of the thoracic deformity in the transverse plane,[61] the assessment of physiotherapy outcomes–(PSSEs),[70]

tracking the results of brace treatment,[71, 72] assessing pre- and post-operative thoracic deformity cor-

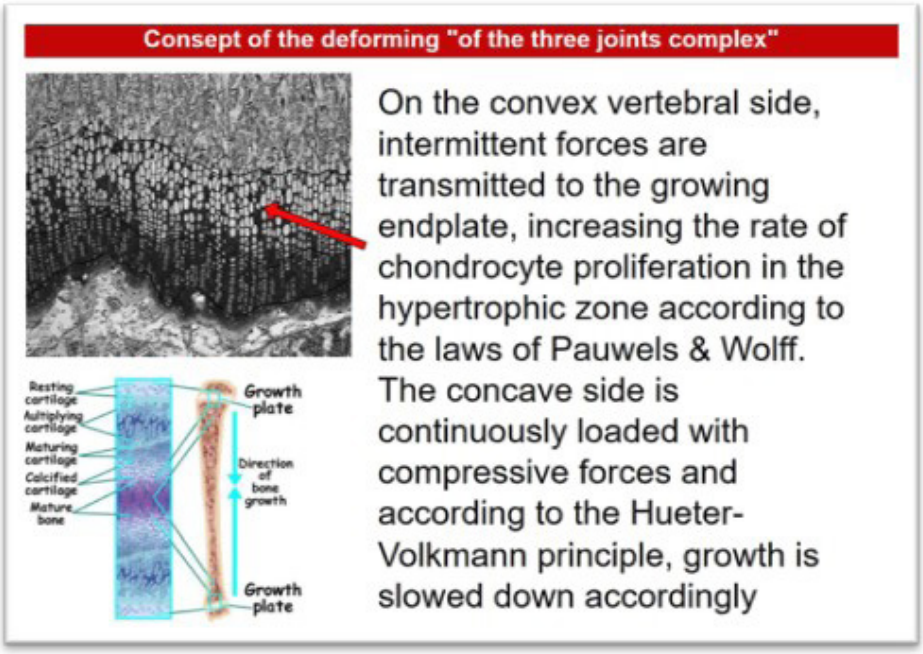


Figure 17: *Pauwels' law states that intermittent pressure within the normal range of stress and strain stimulates the growth plate of a healthy bone. Wolff's law states that bones in a healthy individual will adapt to the loads they receive. If the load is increased, the bone will progressively remodel to become stronger to withstand the load. Hueter-Volkmann principle "Continuous increased axial compression on the growth plate retards growth".*

rection with different types of instrumentation,[73-82] the use in prognosticating the accelerated deterioration in skeletally mature adolescent idiopathic scoliosis (AIS) curves of 40-50 degrees,[83] and helps in recognition of the proper rib level for thoracoplasty/costoplasty.[82]

During the clinical assessment of children with truncal asymmetry (ATR ≥ 5 degrees) referred from the SSS program, it was observed that in their lateral spinal radiographs, the contours of the two hemithoraces consistently overlapped, appearing asymmetrical. This observation was systematically noted in these asymmetric children, regardless of whether their spine was scoliotic or not. This overlapping was termed the "double rib contour sign" (DRCS) (Fig 12).

Consequently, the need for quantification of the degree of this overlapping, that is the asymmetry of this DRCS, in other words the thoracic deformity in terms of the hump, in the transverse plane, triggered the introduction of the RI (Fig 10).[63] The use of the RI helps prevent metric errors caused by variations in magnification on films showing the thorax. Furthermore, when plotting the RI against the Cobb angle, it was found that in girls under 13 years of age, there was no statistically significant correlation between their RI and Cobb angle. In other words, the spinal deformity was not related to the thoracic deformity assessed by the RI. It was also observed that in this age group, an RI of 2.5 corresponded to a Cobb angle of less than 10°. In older girls of age, the RI was statistically significant correlated with the Cobb angle (Fig. 13).[34] A 2.5 RI expresses a progressed thoracic deformity.[83]

The impact of growth on the correlation between spinal and rib cage deformities is evident. Growth significantly influences the relationship between thoracic and spinal deformities in girls with IS. Therefore, it must be considered when assessing spinal deformities from surface measurements. Based on the research outlined above, the implication is that rib cage deformity precedes spinal deformity in the pathogenesis of IS, particularly for thoracic and thoracolumbar curves. This perspective aligns with

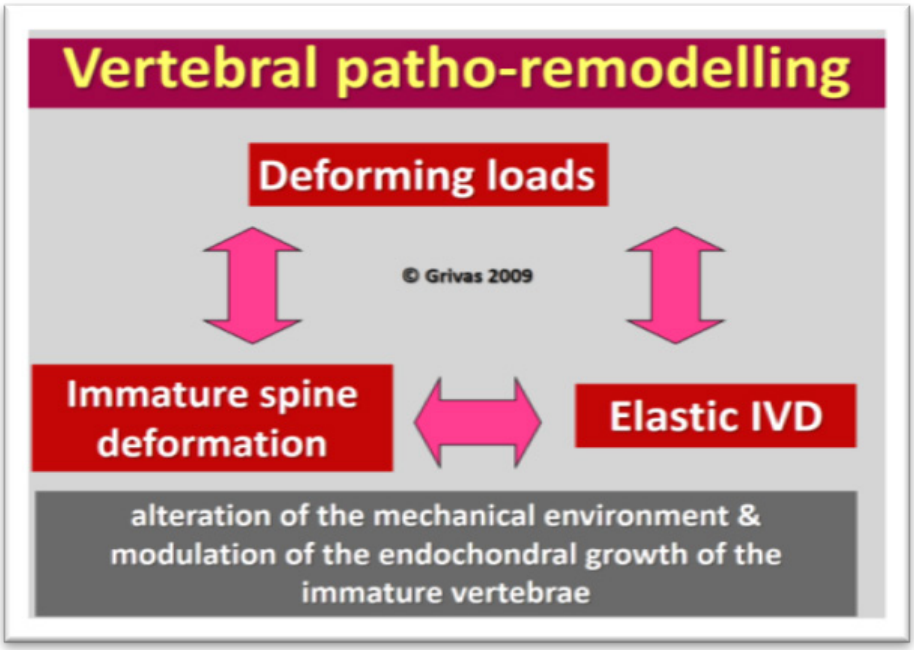


Figure 18: *The vicious cycle of patho-remodeling in apical and adjacent vertebrae in a IS curve, due to alteration of the mechanical environment and modulation of the endochondral growth of the immature vertebrae. (Modified from our citation.*[99]

previously reported views.[85-97]

The impact of the spinal operations on the thorax for correction of AIS

The rotation of the trunk and vertebral bodies, though interrelated, are analyzed as distinct parameters. It was shown that while surgery straightens the spine, the rib hump (RH) is corrected only to the extent of the spinal derotation achieved through the surgeon's instrumental adjustments. Additionally, not only is the hump incompletely corrected, but it also recurs and worsens during follow-up, particularly in skeletally immature scoliotic children who have undergone surgery. The only way to more effectively correct the RH is through costoplasty. The primary reason for this phenomenon is that RH deformity (RHD) is mainly caused by asymmetric rib development, rather than the rotation of the vertebrae in the thoracic spine. Surgery on the spine cannot address rib asymmetry or halt the mechanism that leads to their uneven growth. The findings from all the reviewed studies highlight the crucial role of RHD in scoliogenesis, as it precedes the development of the spinal deformity.[82]

The Progression of Idiopathic Scoliosis due to the Diurnal Variation "accordion"-like Phenomenon of Wedged Intervertebral Discs

In 1983, Dr. Kirkaldy-Willis described the intervertebral articulation as a "three-joint complex", including the disc anteriorly and the two facet joints posteriorly (Fig 14).[98]

Grivas (2021) proposed a concept for the progression of idiopathic scoliosis (IS) that emphasizes the role of diurnal variation in the asymmetric water distribution of the eccentric nucleus pulposus in the deformed scoliotic IVD, and how this affects the mechanical environment due to intermittent forces acting on the adjacent vertebral growth plates. These intermittent forces, driven by diurnal variation (DV), lead to asymmetrical vertebral growth and the progression of the IS deformity, a process referred to as the "accordion-like phenomenon." The supporting data for this concept draws on mechanobiology, the mechanotransduction process, as well as the fundamentals of spinal column

embryology and biology. It also connects to the normal and deformed intervertebral disc, the diurnal variation phenomenon, concepts of IS scoliogenesis, the three-joint complex, sleep phases, and muscular tone. This background information aims to clarify and make understandable the concept of "the diurnal variation accordion-like phenomenon of wedged intervertebral discs," which is proposed as a key 3D progression factor in IS (Fig 14, Fig 15).[84]

The asymmetrical anatomical growth changes not only in vertebral bodies but also in the posterior vertebral elements have been confirmed.[100]

The DV "accordion"-like Phenomenon of wedged IVDs is actually a 3D model of inducing skeletal patho-remodeling in the spine by means of a vicious cycle occurring in apical and adjacent vertebrae in a IS curve, due to alteration of the mechanical environment and modulation of the endochondral growth of the immature vertebrae, according to Pauwels', Wolff's and Hueter-Volkmann principle laws (Fig 17, Fig 18).[99]

This original concept could be highly beneficial for tailoring treatment for children with IS. Current treatment methods to address the progression of IS include PSSEs, bracing, or a combination of both.[102]

The greatest advantage for these children would be an unfused spine, as it was naturally designed. However, the high costs associated with traditional surgical treatments could be avoided if non-operative treatments are properly applied, based on prevention of the changes outlined in this concept.[5, 99, 103, 104]

It is crucial to emphasize the point made by Dr. TK Taylor in 1981, while the effectiveness of early detection and surgical techniques cannot be denied, orthopedic surgery must still be responsible for investigating the cause and pathogenesis of scoliotic curvature. Spinal fusion for scoliosis contradicts the core principle of orthopedic surgery— the preservation of musculoskeletal function— a principle that Trueta strongly upheld throughout his surgical career. Clearly, sacrificing spinal mobility should not be considered an acceptable final solution to the condition.[105]

In conclusion this opinion article presents the recent knowledge on the initial skeletal patho-remodeling during scoliogenesis based on the current pertinent literature.

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Conflicts of Interest:
The authors declare that they have no conflict of interest concerning this article

Abbreviations
AIS = Adolescent Idiopathic Scoliosis;
AL = apex lumbar lordosis
ATR = Angle of Trunk Rotation;
CIS = childhood idiopathic scoliosis
CNS = central nervous system
DRCS = Double Rib Contour Sign;
IS = Idiopathic Scoliosis
IIS = infantile idiopathic scoliosis
ICP = Infancy Childhood and Puberty model
ILSP = intervertebral values for LSP
KA = kyphosis apex
KA (VPDM)) = kyphosis apex mean distance
L = lumbar
LA (VPMD) = lordotic apex
LLC = lateral lumbar curves
LOS = late onset scoliosis
LSP = lateral spinal profile
MD = mean distance
MD = Mean distance
PA = posteroanterior
RI = Rib Index;
RC= rib cage
RVA = rib vertebra angle
RVAD = rib vertebra angle diference
SSS = School Scoliosis Screening;
SSSP = school scoliosis screening programs, (SSSP
SRS = Scoliosis Research Society
SRI = Segmental Rib Index
STR = Segmental thoracic ratios
TR - thoracic ratios
T = thoracic
TL = thoraco-lumbar
TA = Truncal Asymmetry.
VP = vertebra prominence
VPDM = vertebra prominence mean distance
QL = quadratus lumborum

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