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

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

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or

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ACTA
ORTHOPAEDICA ET TRAUMATOLOGICA HELLENICA

CONTENTS

ACTA
ORTHOPAEDICA ET TRAUMATOLOGICA HELLENICA

LETTER FROM THE GUEST EDITOR

Metabolic Bone Diseases cover more than one third of Orthopaedic Pathology. In Greece, the education and training of Orthopaedic Surgeons in Metabolic Bone Diseases is advanced due to the existence of relative Scientific Societies, Journals, Laboratories dedicated to this special field, as we will refer in detail in the next Introductive – historical article.

My distinguished friend, Professor Nikos Papaioannou, Chief Editor of the Journal, kindly asked me to organize the publication of two consecutive special issues dedicated to Metabolic Bone Diseases. Most of the publications are reviews and the authors present the latest developments on topics related to Metabolic Bone Disorders.

I hope that the readers will find these issues quite interesting wishing that we covered most of the hot and current topics of Bone Metabolism Diseases.

George Kapetanos

Emeritus Professor of Orthopaedics

The Orthopaedic Surgeon and the Diseases of Skeletal Metabolism

George Kapetanos
Emeritus Professor of Orthopaedics

ABSTRACT

Fragility fractures, namely fractures from low-energy mechanisms that would not produce fracture in a healthy bone, are most commonly caused by osteoporosis, and constitute a major financial burden worldwide. The effectiveness of systems for the prevention of fragility fractures, also known as fracture liaison services (FLS) has been investigated by numerous programs. The FLS is a coordinated care paradigm where several providers work together to help the patient manage their osteoporosis following a fragility fracture in order to help prevent subsequent fractures. FLS offers a thorough method for not only identifying individuals who are at risk for secondary fracture but also for putting into practice evidence-based therapies to stop further fractures. For the FLS to be successful, doctors, nurses, administration and national healthcare systems must work together toward the common objective of protecting patients aged 50 and older from fragility fractures. This review article discusses the current FLS programs, their pros and cons, and emphasizes on the Greek FLS model.

KEYWORDS: Osteoporosis; Fragility fractures; Fracture liaison services

Although the medical and financial consequences of Bone Metabolic Diseases and their main representative, Osteoporosis, are serious, the knowledge and the education of doctors all over the world is not proper, nor adequate. Fortunately, in Greece, doctors' education on this subject is better compared to other countries. That is because in our country we have three scientific societies (HSSBM, HELIOS, FFN) with numerous activities, such as teaching, research, etc, nationally and internationally. We also have five relating journals and a great central laboratory in Athens and some other smaller in university departments.

As Orthopaedic Surgeons, we have to be updated with the increasing knowledge concerning the Metabolic Bone Diseases and to be aware of all the new developments around this wonderful tissue, the Bone. That is our main subject in every day clinical practice and the Metabolic Diseases are actually all the "Pathology" of our specialty, all the "cold" Orthopaedics which covers more than 70%of our everyday practice.

Continuous Medical Education (CME)

In our days every doctor accepts daily a "hurricane" of medical knowledge. In fact, general medical knowledge is doubled today every two months! That is due to 28000 medical journals with 25 million new

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

scientific papers which are published every year, to thousands of scientific meetings worldwide and to the continuous clinical and research efforts from general medical stuff. Two other factors for Medical knowledge are that after two years the doctors lose 50% of their medical knowledge as well as that this knowledge changes every day. (1) So, continuous Medical Education (CME) is absolutely necessary for all the new and older doctors through their lifetime.

Bone metabolic diseases and their main representative Osteoporosis are among the fast-growing topics and also many things have changed over the time in this subject. For example, it is not long ago when Estrogens, Calcitonin, Strontium, Parathormone, Fluorate and other drugs were among our basic weapons in the osteoporosis treatment and today have been withdrawn. (2,3,4)

It is well known that despite the size and the serious medical and financial consequences of osteoporosis, the knowledge and education of doctors for this disease is not all over the world the proper and adequate one. (4,5) One first explanation for this may be that physicians of many different specialties are implicated with osteoporosis and many of them find other topics more "attractive", like Orthopaedics--- operations, Rheumatologists-----rheumatic diseases, Endocrinologists-----hormonal disturbances and Diabetes. In a big international survey (2000) with the participation of National Societies of the UK, France, Germany, Italy, Spain and New Zealand a questionnaire was sent to all Orthopaedics asking for anonymous answers. The analysis of the results was performing in Sweden, and found that Orthopaedic Surgeons rarely send their patients for further treatment for osteoporosis after hip fracture and also that 50% of Orthopaedic Surgeons have no or insufficient education in osteoporosis. (4,5)

Educating Physicians in Metabolic Bone Disorders

In Greece, I would dare say that doctors' education on osteoporosis and other bone metabolic diseases is fairly good compared to the majority of other countries.(6,7,8) A great percentage of doctors of the three main specialties involved in bone metabolic diseases (Orthopeadics, Endocrinologists, Rheumatologists) know and are interested in metabolic bone diseases and mainly osteoporosis.(8,9,10) Although until now no serious care and planning from the State exists, concerning the continuous education, osteoporosis and Metabolic bone diseases have gained the interest of great groups of doctors in Greece in the beginning of the 80's with the activity of some individuals as well as pharmaceutical companies. So today in our country we have societies, journals, books and research laboratories concerning the education of metabolic bone diseases. In detail three scientific societies exist. In 1986 the "Hellenic Society for the study of bone metabolism" (HSSBM) was founded which is a member of IOF. It has almost 700 members and has organized more than 80 National, International and Local meetings, as well as numerous protocols and guidelines. In 1996 the "Hellenic Osteoporosis Foundation" (HELIOS) was founded with almost 900 members, 150 scientific meetings, scholarships, monographies, clinical studies and guidelines. HELIOS is also a member of IOF. Recently the "Fragility Fracture Network" was founded, member of the International Network with increased similar activity. In our country five related scientific journals are also circulating, namely "Ostoun" (1990), "Musculoskeletal and Neuronal Interactions" (2000)," Skeletal Health" (2002), "Journal of Frailty, Sarcopenia and Falls (JFSF,2019), and "Journal of Research and Practice on Musculoskeletal system" (JRPMS,2020). In 1974 a great Laboratory research center in "KAT" Accident hospital was established. This belongs to the Medical School of Athens University. Its founder and first Director for many years was prof. Lyritis and after him the profs. N.Pap ioannou, I. Dontas and E. Chronopoulos. This center has had a lot of activities like lessons, scientific protocols, Masters, PhDs and from 2007 a postgraduate program for Metabolic Bone Diseases, with more than 600 students. Finally for educating physicians in Osteoporosis there are more than 30 books in our country about bone metabolism. The vast majority of them by professor G. Lyritis and some by professors A. Avramides, G. Kapetanos and others.

Orthopaedic Surgeon and Osteoporosis

As we have mentioned before, according to an international survey (2000), 50% of Orthopedic Surgeons have no or insufficient knowledge of bone metabolism and osteoporosis. (4,5). So, the first question arises. Are we orthopaedics or surgeons? Obviously, both.

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

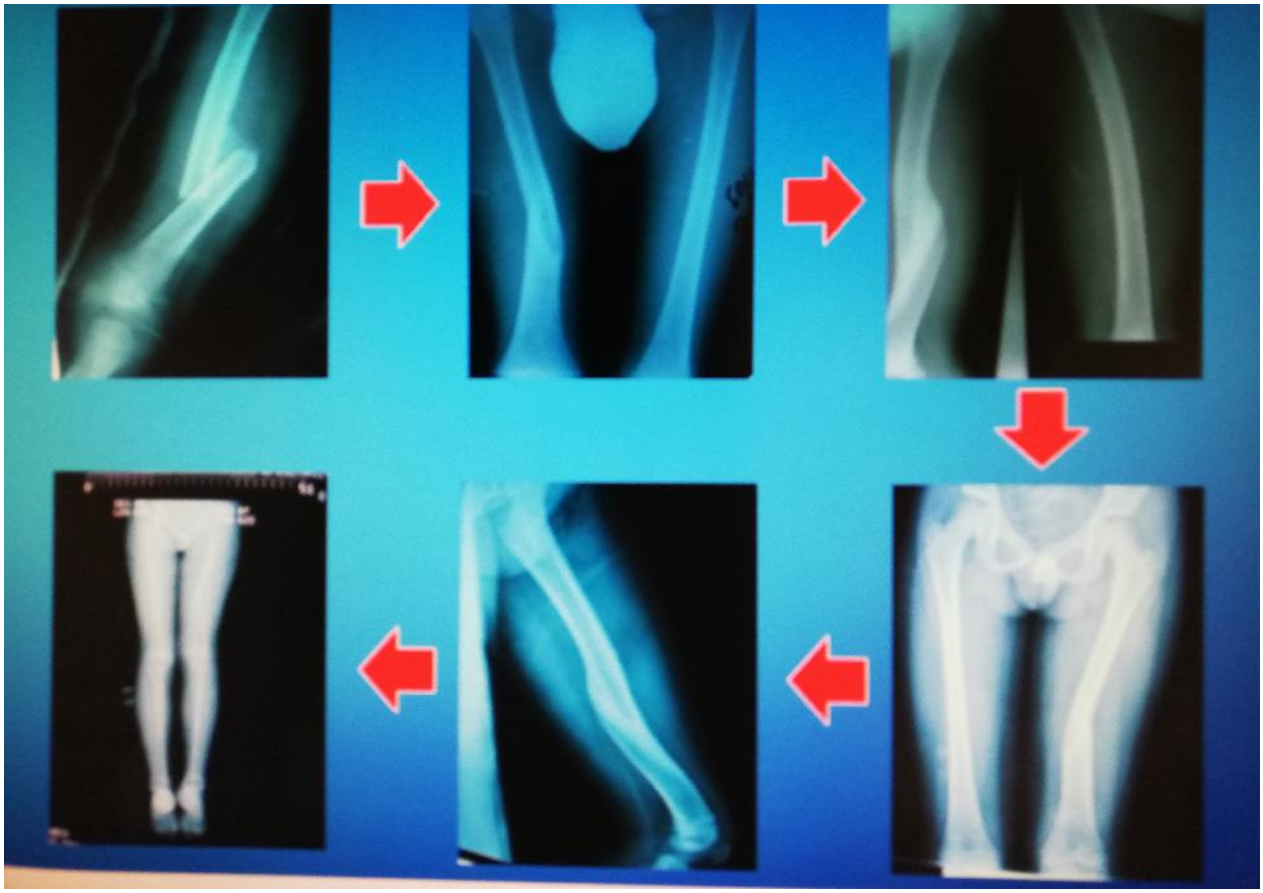

Fig. 1 *Self-remodeling of a femoral fracture one year after the fracture.*

And also" Are we orthopaedic surgeons or surgeons' orthopaedics?" I believe the first as "plastic surgeons and neurosurgeons", and not as "surgeons of abdomen etc." The second question is who knows who keeps in his hand the bone, in every day clinical practice like orthopaedics? Nevertheless, we have to admit that "BONE" is not a simple material, a primitive tissue but it has wonderful and unique properties in comparison to other tissues, even with the so-called "kind" tissues.

These unique properties are; 1. The Regeneration. Every 10 years the whole skeleton is replaced. 2.The wonderful healing possibility Often after some years we cannot recognize the fracture.3. The self-remodeling and correction of minor deformities (Fig. 1) and 4. The long-even eternal- survival. The BONE counts the human and physical history and life.

From the above is obvious that pathophysiology of the bone is a very complicated issue which approaches and involves many specialties like endocrinology, rheumatology, orthopaedic, general medicine and others.

We have to point-out that in fact "metabolic bone diseases" cover more than 80% of every day clinical practice of Orthopaedics. Osteoporosis, osteoarthritis, healing of the fractures, Paget, rachitis-osteomalacia, tumors, rare metabolic syndromes are included to the metabolic bone diseases.

Why therefore a minority of Orhopaedics is not interested in bone metabolism? Is that topic very difficult? Is "surgery" more attractive and profitable? But after these all, have we the right to leave this attractive and promising topic of our specialty to the endocrinologists and rheumatologists only? Have we the right to deny the orthopaedic pathology and to keep only the title of "bone surgeons"?

It is well known that despite the size and serious medical and financial consequences of osteoporo-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

sis and the wonderful world of bone metabolics, the knowledge and education of doctors for this topic is not all over the world the proper and adequate one. After all the above it is obvious how important for our specialty is to keep in touch and to stay close to this subject and to stop being only good: technicians" for the bone surgery.(10,12)

What do we have to do?

1. To open and enlarge the topic by including Osteoarthritis, Bone Tumors, and the healing of the fractures.
2. To establish in all University Orthopaedic departments as well as in the big regional hospitals' outpatients' departments and laboratories for bone metabolism.
3. To increase the activity of our societies, for education of the young doctors on these topics.
4. To persuade the authorities for the financial consequences of metabolic bone diseases (i.e. osteoporosis and osteoarthritis).Recently the Government announced the introduction of an optional a six months period training on metabolic diseases for the specialty in orthopaedics, that is of course a very important step.
5. To persuade the media to give the people the proper information.
6. Some other subjects should have better study and planning like: pre-certificate education of the students with proper books for them, the preparation of trainers, the legistration of doctors' and scientific centres certification, the promote and encouraging of the clinical research and participation in local, national and international meetings relative to the topic, etc.

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REVIEW

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Fracture Liaison Services (FLS): a Review

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ABSTRACT

Fragility fractures, namely fractures from low-energy mechanisms that would not produce fracture in a healthy bone, are most commonly caused by osteoporosis, and constitute a major financial burden worldwide. The effectiveness of systems for the prevention of fragility fractures, also known as fracture liaison services (FLS) has been investigated by numerous programs. The FLS is a coordinated care paradigm where several providers work together to help the patient manage their osteoporosis following a fragility fracture in order to help prevent subsequent fractures. FLS offers a thorough method for not only identifying individuals who are at risk for secondary fracture but also for putting into practice evidence-based therapies to stop further fractures. For the FLS to be successful, doctors, nurses, administration and national healthcare systems must work together toward the common objective of protecting patients aged 50 and older from fragility fractures. This review article discusses the current FLS programs, their pros and cons, and emphasizes on the Greek FLS model.

KEYWORDS: Osteoporosis; Fragility fractures; Fracture liaison services

Introduction

Fragility fractures, namely fractures from low-energy mechanisms that would not produce fracture in a healthy bone, are most commonly caused by osteoporosis. Nearly 9 million of these fractures occur each year due to osteoporosis worldwide (1). Fragility fracture rates will probably continue to rise as osteoporosis prevalence rises with aging and our population gets older, resulting in a lower quality of life and increased mortality; 24% of hip fracture patients who are fifty years of age or older pass away within a year of the fracture (2). Additionally, fragility fractures have significant economic expenses in addition to their immediate impact on the patient. The cost of osteoporosis-related fractures in the US in 2005 was estimated at $19 billion. These expenses are expected to increase to almost $25.3 billion by 2025 (2,3). A patient's risk of subsequent fracture increases by approximately two foldafter suffering a vertebral fracture, and by three fold after suffering a subsequent hip fracture (4). Due

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

to the severity of these effects, prevention of a secondary fracture is considered of great importance, both from a patient-care and social perspective.

The effectiveness of systems for the prevention of secondary fractures, also known as fracture liaison services (FLS) has been investigated by numerous programs (5–17). The FLS is a coordinated care paradigm where several providers work together to help the patient manage their osteoporosis following a fragility fracture in order to help prevent subsequent fractures. This review article discusses the current FLS programs, their pros and cons, and emphasizes on the Greek FLS model.

Prediction of secondary fractures

A bone mineral density (BMD) T-score of –2.5 or lower was the operational definition of osteoporosis provided by the World Health Organization in 1994 (18), and this criterion has since been adopted as the diagnostic standard. Although there is a 1.5–2.5 fold increase in fracture risk with each standard deviation decrease in BMD, the sensitivity of BMD alone to identify people at risk for a fracture is <50% (19,20), and many patients experience fractures with a T score > –2.5. For this reason, techniques for predicting fractures have been created to help identify people who are "at risk." The Fracture Risk Assessment Tool (FRAX) was created by conducting a thorough meta-analysis of the primary data from nine geographically dispersed cohort studies. It was then verified in an additional eleven cohorts, and it was published in 2008 (21).

Age, sex, weight, height, previous fracture, parent's hip fracture, current smoking, use of glucocorticoids, rheumatoid arthritis, secondary causes of osteoporosis, alcohol use, and BMD (although this can be disregarded in resource-constrained situations where BMD assessment is not possible) are the parameters used in FRAX. The results include the 10-year likelihood of a major osteoporotic fracture (clinical spine, proximal humerus, distal forearm, or hip fracture), as well as the 10-year likelihood of hip fracture. Globally, fracture incidence varies by geography, and FRAX is calibrated to offer nation-specific models (22).

Thresholds for therapeutic intervention can be determined using these percentage risks. Over 80 guidelines from around the world include FRAX (22). In general, patients who are at risk for primary and secondary fractures can be identified with the help of population screening techniques, BMD measurements (if available), and fracture prediction algorithms such as FRAX. Nevertheless, using an FLS is another way to spot and assist those who are "at risk" for fractures.

Prevention of secondary fractures – FLS programs

FLS is a specialized program created to recognize, investigate, and facilitate the initiation of the right treatment for individuals who have poor bone health and are at high risk for secondary fractures. When a patient suffers a fragility fracture, he/she is considered as having poor bone quality and thus susceptible to more fractures. The FLS model of care automatically enlists those patients for the medically necessary assessment of their risk for a secondary fracture, offers treatment recommendations, and may initiate treatment as needed. The FLS model results in higher rates of diagnosis and therapy and less attrition in the post-fracture phase of care as compared to other osteoporosis management methods, such as referral letters to primary care physicians or endocrinologists following fracture.

Prior to the implementation of secondary fracture prevention initiatives, 2% to 25% of people worldwide received evidence-based osteoporosis treatment following a known fragility fracture (23). These figures suggest that doctors are not greatly involved in their patients' secondary fracture prevention. With a marked growth in the use of post-fracture care, national healthcare systems and regional centers in many nations have begun to build their own FLS-type systems (5–13,24,25). Additionally, as a result of these programs' longevity, numerous studies have demonstrated an increase in the number of treatments started and a lengthened period of treatment adherence (7,9,10). Additional analysis revealed that these programs over time reduced the incidence of secondary fractures and even mortality (10,14,15,25–27).

FLS has also been demonstrated to be a cost-effective approach in numerous studies (6,15,16,28–33).

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Particularly, cost savings are driven not just by lower osteoporosis management costs but also by a rise in quality-adjusted life years and a decline in fracture rates.

FLS implementation

A clear road map is essential to guarantee that everyone involved in the FLS implementation has the same understanding of the program's goals and objectives,. An FLS coordinator or practitioner, a nurse navigator, and a leading physician can be the founding members of the FLS program while the team can be expanded as necessary in the future. According to previous research less success has been reported with an FLS core made up of primary care physicians, rheumatologists, or endocrinologists (34,35), rather than with orthopaedic surgeons and this is mainly due to: when treating a fracture, the orthopaedic surgeon is already familiar with the patient and family, and he or she is the one who establishes a connection between the fracture and osteoporosis; patients frequently wait until fracture healing before visiting their primary care physician, which creates the misconception that no further treatment is necessary.

The FLS program coordinator is oftena nurse practitioner or physician assistant with a focus on secondary fracture prevention (5,26,36,37). This provider needs to be proficient in many different areas such as being able to involve patients and their families in their care, have a thorough understanding of the most recent treatment algorithms and osteoporosis standards, while being capable to establish connections with other specialties and services within the institution. In order to ensure that patients keep their appointments and receive care as needed, this practitioner should collaborate closely with the leading physician and is frequently housed in the same office. To allow for simultaneous care from both physicians, this practitioner could also practice separately. Depending on the advanced practice practitioner's license, the FLS coordinator may also run a clinic independently from the leading physician. The FLS coordinator should regularly update practice patterns based on national recommendations and stay up to speed with national quality metrics (37).

To ensure that all eligible patients are engaged in the FLS program and to promote communication within the care team, the FLS coordinator needs nursing support (37,38). A "nurse navigator" is necessary in this position to help with osteoporosis education, medicine administration and training, and prescription insurance verifications. Additionally, a nurse navigator is used to find patients who should be referred to FLS by looking at inpatient censuses, emergency room discharges, and outpatient referral trends. The navigator may serve as the FLS program's first point of contact, arranging outpatient referrals and scheduling with the FLS while also offering instructional sessions for inpatients that may include handouts or films. To ensure that all patients who may potentially benefit from the FLS are enrolled, the nurse navigator should build cooperative partnerships with services other than orthopaedic surgery. Other services in the FLS coordination include the departments of radiology, neurosurgery, general practice, women's health, hospital medicine, and so forth because these specialties can also recognize and treat individuals with fragility fractures who do not need orthopaedic care (26). Patients may also be identified as FLS candidates using the electronic health record based on diagnostic or procedural coding.

It has been shown that preventing subsequent fractures lowers overall healthcare costs (23,39). It is recommended that the hospital administration pay for start-up costs as a part of a quality initiative associated with a musculoskeletal service line (40). A business plan can show cost savings from secondary fracture readmissions that are avoidable, and reportable metrics like readmission rates can support program implementation. To include volume predictions of office visits and related ancillary revenue directly related to the FLS service, the program is later integrated into the departmental or service line budget (such as bone densitometry, anabolic or antiresorptive medications, and laboratory studies). For better secondary fracture prevention and to show compliance with osteoporosis measures, data collection is crucial. There are typically two or three exam rooms in an office setting. To strengthen the care team for the disease condition and increase patient access and compliance, it is advised that the office location mirrors that of the leading - physician (40). Currently, billing is distinct from the overall duration of fracture care due to the FLS's

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

specialized knowledge in a fee-for-service paradigm; however, shifting to value-based healthcare systems will probably alter this practice.

To enhance the reporting of claims data and patient outcomes, segregating the FLS in the electronic health record seems to be efficient. Additionally, templates and order sets created specifically for osteoporosis aid in gathering information about patients' vulnerability to fragility fractures. To improve patient access and compliance, it is best to have laboratory and imaging services in the same place. Cost-effective ordering is also guaranteed when laboratory test orders are standardized and entered into the electronic health record using best-practice principles. Radiographs and bone densitometry should be included in imaging modalities. Insurance agencies frequently demand bone densitometry before beginning pharmacologic treatment, even when the patient has a known fragility fracture with poor bone quality (26).

Prior to the implementation of FLS (5), the leading physician, FLS coordinator, nurse navigator, referring providers, and administrative stakeholders must establish shared objectives to guarantee that everyone involved has the same vision. With a targeted FLS deployment for patients with low-energy hip fractures, a new program may be successful. The program can subsequently be expanded to encompass all low energy fractures in patients who are older than forty-nine years old after confirming the correctness of the referral procedure and data reporting. Data reporting is crucial and should cover the ratio of referrals to eligible patients, the rate of missed appointments, treatment compliance, and mortality and secondary fracture rates (41–46). This data can assist in reevaluating FLS resources and predicting the program's future requirements.

A specific FLS should work to address the problem of fragility fractures in their specific region; of course, there will be differences in the patient population's demographics and the healthcare facilities that are available. The resources needed to implement FLS are, however, actually quite meager. The only technological requirements are a DXA scanner and a computer, and in low-resource settings, paper copies of the FRAX® tool are available for use and treatment decisions can be made without bone mineral density information. While FLS is typically reserved for patients with less severe fractures or abnormal laboratory results, in some regions the orthopaedic team will initiate a single dose of zoledronate in patients with hip fractures and normal laboratory results with calcium and vitamin D supplementation.

Potential benefits

FLS offers a base to benefit from both recent and anticipated improvements in health-care reform (39). Organizations in the healthcare industry can benefit from FLS as they make the switch from volume to quality payment. The current system of reimbursement is fee-for-service driven and not often connected to the overall quality of care. Regardless of the standard of care delivered or the results for patients, providers are paid equally for treatments. Another paradigm may switch to renumeration based on quality-of-care standards and patient outcomes as the system transitions to value-based or quality-based payments. A health care system will need to implement quality-care initiatives and provide evidence of better patient outcomes in order to reap the rewards of these new incentives. The FLS model of care is an illustration of a strategy that can enhance results in the treatment of patients with fragility fractures and lower secondary fracture rates.

Potential pitfalls and solutions

Certain barriers occasionally prevent the initiation of FLS (47). One such situation involves insufficient funding to hire an FLS nurse specialist; one possible option is to hire (or re-deploy) a member of the secretarial staff to do the administrative responsibilities that are a part of the FLS nurse specialist function. Language can be a barrier to using international resources although the Best Practice Framework (BPF) document is currently available in 12 major languages. All FLS registering for the Capture the Fracture (CTF) program must complete it. Lack of prior FLS management expertise may cause a lack of trust and the suspension of an FLS initiative. Through the use of instructional resources and personal mentoring from skilled FLS providers, this can be solved. Since 2015, webinars have been held as a part of the CTF Educational Program with the goal of interacting with the FLS community of the CTF and disseminating perti-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

nent information about FLS and secondary fracture prevention.

With the help of the CTF mentorship program, organizations interested in launching a new FLS can interact with eminent FLS professionals. The initiative establishes a forum for the exchange of crucial knowledge and abilities between FLS champions and FLS in the early stages of development, locally and regionally. The mentorship program has been in operation since its launch in 2016, giving a combination of on-site training and FLS seminars to provide advice on FLS implementation. During the on-site training, a FLS champion (mentor) hosts a FLS candidate (mentee) and spends a day teaching them how to implement a FLS and apply to CTF by completing the BPF questionnaire. The content is customized to match the mentee's specific needs because the training is conducted one-on-one. Conversely, FLS workshops draw in a bigger crowd, frequently more than 15 FLS applicants from the same nation.

Measuring the effectiveness of FLS

Eleven patient-level key performance indicators (KPIs) for FLS have been developed by the IOF CTF® Campaign in collaboration with the Fragility Fracture Network (FFN) and National Osteoporosis Foundation (NOF) to help guide quality improvement. These 11 FLS KPIs that have been suggested, give a comprehensive picture of how the FLS delivers secondary fracture prevention at the patient level. The degrees of achievement correspond to those that economic models employ to show the anticipated advantages of secondary fracture prevention in the local context. For an FLS to realize its predicted ability to lower re-fracture rates through secondary fracture prevention, it must reach a green level of accomplishment across all KPIs. Up until this point, FLS should actively pursue quality improvement. In some regions, meeting these KPIs may rely on modifying local healthcare systems outside the purview of the FLS. These KPIs should be viewed as instruments for enhancing service provision while utilizing already available resources. They should also be used to communicate to payers the precise service gaps that exist and suggested targets for development. The reduction of secondary fracture rates is the ultimate objective of FLS (5).

The majority of individuals with reportedly fractured spines do not require secondary fracture prevention (48). Improved techniques for identifying people with spine fractures are being developed. Text analysis of radiological reports or medical records may be required (49). Although these techniques are precise, they might not be sensitive since they rely on radiologists, whose reporting of spine fractures is notoriously inaccurate (48).

Patients who are evaluated by the FLS after having fractured during therapy frequently need a different approach to treatment (50,51). Testing for specialized laboratory tests is another potential KPI. This is relevant given that laboratory testing has detected secondary causes in up to 35% of FLS patients with osteoporosis (52). Several national guidelines for the prevention of secondary fractures recommend a variety of laboratory testing, although there is little agreement among them. Testing for vitamin D is one instance. Given the effectiveness of regular supplementation (53) and the difficulty in interpreting results due to seasonal variation and changes brought on by acute inflammation, some guidelines pragmatically advise high-dose empirical supplementation over systematic testing for the majority of patients following a fragility fracture if oral AOMs are advised. However, some investigations have called into doubt the effectiveness and security of greater vitamin D doses (54), emphasizing the requirement to assess vitamin D status in many individuals. Nearly all clinical guidelines state that patients in need of AOM should receive calcium and vitamin D replenishment; however, calcium replenishment can be easily obtained by diet, over-the-counter supplements, or prescribed medications, making calcium replenishment measurement difficult. Additionally, clinical investigations have shown that calcium and vitamin D supplementation alone is ineffective in the post-fracture scenario to lower the risk of re-fracture (55,56).

The Hellenic experience

There are two reports of FLS implementation in Greece. The first one was conducted at the 251 Hellenic Air Force and VA General Hospital of Athens (17) and the second was a multicenter study involving four orthopaedic departments across the country (66). The recruitment efficacy was very low (29.3%), significant-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

ly lower than the first FLS Greek report (54.5%) (17), or other national programs, such as those in The Netherlands, Spain, and UK (5,9,10), despite the fact that a large number of patients were deemed eligible to participate in the program. The majority of eligible patients who volunteered to participate in this FLS had a hip fracture. Nevertheless, despite the surprisingly low recruitment rate, 99% of those who were recruited completed the study and showed up for the 12-month follow-up appointment (66). This is in contrast to the first FLS Greek report, which was conducted in a single hospital and found that the completion rate was <20% (17), but it is consistent with other studies that found that between 65% and 80% of patients adhered to their treatment plans and scheduled follow-up visits (7,9,10). This startling discrepancy in the two FLS structures can be explained by variances in the recruitment rate and the percentage of patients who ultimately completed the follow-up visits. In the first FLS program (17), the registered nurse who was explicitly tasked with this work and as a result was both motivated and committed, conducted the screening and recruitment of eligible patients. The treating physicians were required to be active in the recruitment of the eligible patients during their usual clinical work at the hospital in the current trial, in which Orthopaedic Departments were involved rather than hospitals, and this may have influenced the outcome. In other words, in addition to their often busy schedules, the orthopedic surgeons had the extra responsibility of patient recruiting. The relatively high percentage of patients (57.3%) receiving treatment for osteoporosis may have been another likely factor in the high percentage of uncooperative individuals. As a result, patients probably chose to be monitored by their own doctor rather than in a FLS environment. Furthermore, this large proportion of patients who had previously had osteoporosis follow-up could be a sign of population selection bias in the study. A likely yet not solid explanation for this would be the urban and rather central location of these University Departments, which is likely to make them easily accessible to patients with unrestricted access to health services and thus make them adequately treated for a variety of medical conditions. A patient in Greece can typically choose among the hospitals of his or her residential area. However, despite the low recruitment rate of eligible patients, the treating physician's contribution to the recruited patients' completion rate turned out to be crucial, as almost all of them followed through with the follow-up appointments for up to one year. These adherent individuals lacked any distinctive traits that could pinpointed, and neither their treatment within the FLS nor outside of it differed from other patients. Additionally, as this was a general finding across all four locations, it is not possible to be attributed to the FLS staff members' unique communication skills. Therefore, it makes sense to draw the conclusion that the patient remains under medical care anytime the treating physician is active in the process of recruiting and motivation.

The allocated personnel's commitment to spending time outlining the hazards of osteoporosis and the advantage of therapy appears to be a key factor in whether osteoporotic patients are successfully recruited. Similar studies (11,17) have demonstrated that FLS workers are typically not employed exclusively; rather, the task is performed in conjunction with the rest of their duties and is primarily voluntary. However, it is evident from the experience gained in Greece that even when a program as complex and time-consuming as an FLS is run by committed and motivated staff who are willing and able to thoroughly explain the risks of osteoporosis to patients and persuade them of the immediate need for treatment, the results are, on the whole, highly satisfactory and successful. Specific guidelines (57,58), unambiguous FRAX cutoffs for cost-effective treatment (59,60), and convenient access to BMD testing with adequate reimbursement promote osteoporosis management in Greece. The national registration and audit FLS programs, however, will perform poorly anytime there is a paucity of funding, at least in terms of disease awareness.

Osteoporosis requires preventative and ongoing therapy to lower the risk of future problems, just like other silent and asymptomatic chronic diseases like diabetes and hypertension. However, for a variety of reasons, treatment compliance is currently very low (61,62). According to a recent study, only 19% of patients with hip fractures were receiving therapy for bone-active osteoporosis prior to the fracture, and this number barely changed after the fracture, climbing to 21% (63). Given that there are effective medi-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

cines to prevent future fractures, this type of diagnostic gap is too great, which highlights the need for a more concentrated public health strategy (64,65). Hip fractures made up more than 50% of the eligible and ultimately included cases in this study, which may indicate a selection bias. This is explained by the fact that in Greece almost all hip fractures result in admission to an orthopaedic department, while less serious fractures may be treated in outpatient facilities that are either public or private. Therefore, a large proportion of hip fractures will be present in any Greek FLS that occurs in an orthopaedic department that receives trauma cases. The first Greek study revealed that a male relative younger in age with a single NVF other than the hip fit the description of osteoporotic patients reluctant to take part in an FLS program. Patients with a hip fracture and several comorbidities who were older than 75 also seemed to be more likely to give up on the endeavor. These are the patients who don't stick to therapy as well because they either don't understand how serious fractures are or have a tough time getting to an outpatient clinic due to a bad transportation system. Greece lacks a public non-emergency transportation facility that is patient-centered, which is essential for elderly patients, especially those who live alone. The ability to confirm whether the aforementioned characteristics applied to the included subjects was limited by the fact that pertinent data on the patients who rejected to participate or who were lost to follow-up were missing from this study. Finally, of the 392 patients who finished the latest Greek project, 12 additional fragility fractures developed during the follow-up visits of our current study (66). The numbers were too small to draw any firm conclusions, and the treatment duration was too brief to significantly affect the re-fracture rates, despite the fact that all of these fractures were documented in patients who had rejected or stopped anti-osteoporotic medication. This finding suggests a chance occurrence more than an occurrence directly linked to or motivated by the absence of anti-osteoporotic therapy.

Based on the knowledge gained from the FLS implementation in Greece, it is necessary to significantly enhance recruitment rates. The treating physician must be well-educated, driven, and capable of devoting the necessary time to persuading patients to enroll in order to increase both the recruitment and completion rates. Additionally, certain target populations require special consideration, including young people and older adults with comorbidities and/or polypharmacy. Additionally, there is an urgent need for a national fracture database, and HSSBM is working with the ministry of health and other medical societies to achieve this objective. All FLS activities will undoubtedly benefit from this, particularly at the national level. The operational structure of the FLS, which is a very labor-intensive and time-consuming effort, should be adequately and consistently supported by the national healthcare system for a vital role in the final outcome.

Conclusion

Fragility fracture care includes more than just stabilizing a shattered bone through surgery. Osteoporosis, the underlying condition that led to the fracture, needs to be actively managed as a disease. The majority of healthcare professionals do not thoroughly assess this underlying medical state and then develop a treatment plan for it, and this lack of action could have long-term financial repercussions. FLS offers a thorough method for not only identifying individuals who are at risk for secondary fracture but also for putting into practice evidence-based therapies to stop further fractures. For the FLS to be successful, doctors, nurses, administration and national healthcare systems must work together toward the common objective of protecting patients aged 50 and older from fragility fractures.

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REVIEW

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

The role of antiosteoporotic drugs in fracture healing

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ABSTRACT

This narrative review was carried out to investigate the effect of antiosteoporotic drugs (selective estrogen receptor modulators [SERMs], bisphosphonates, denosumab, teriparatide, romosozumab) in fracture healing process of vertebral, hip and distal radius fractures. The administration of bisphosphonates (BPs) didn't affect the fracture healing process and clinical results after distal radius and hip fractures. However, there no evidence for vertebral fractures. Denosumab doesn't seem to delay the process of fracture healing in patients with non-vertebral fractures in a study that was well documented and designed. There no human studies that appreciated the influence of SERMs and romosozumab in fracture healing process. In one study was reported that patients with distal radius fractures who were treated with teriparatide had shorter time of fracture healing, however this was not clinically significant. On one hand, in hip fractures, some recent studies suggested that in patients treated with teriparatide there was better improvement of pain and clinical outcomes of functionality. On the other hand, in vertebral fractures, there was no statistically significantly difference regarding the stability of fractures between teriparatide and control groups. Considering the fact that there is no evidence that antiosteoprotic drugs influence negatively the fracture healing, there is no reason to delay the initiation of antiosteoporotic treatment after the fracture.

KEYWORDS: bisphosphonates, denosumab, fracture healing, osteoporotic fractures, teriparatide

Introduction

The aim of anti-osteoporotic drugs is to prevent osteoporotic fractures (vertebral, hip, distal radius, humeral neck fractures etc.). Despite the fact, that diagnosis of osteoporosis is easy and there are a lot of anti-osteoporotic drugs available for prescription, evaluations and treatments of osteoporosis have not been adequately implemented [1]. This fact is called "care gap" and patients with a recent osteoporotic fracture are the therapeutic target group in order to decrease this gap in treatment [2,3]. In order to achieve the correct management of these patients, it is very important to understand how anti-osteoporotic drugs affect the healing of fractures.

Fracture healing is a complex procedure consisting of cellular interaction and new bone formation [4,5]. Delayed fracture healing or nonunion of fractures is a complicated issue which decisively influ-

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

ences the healing of fractures; when fracture healing is not achieved within six months we are talking about delayed union, while when fracture union has been late for over nine months it's about non-union [6].

Consequently, the purpose of this narrative review is to investigate how antiosteoporotic drugs affect the process of fracture healing.

Selective Estrogen Receptive Modulators (SERMs)

It is known that selective estrogen receptive modulators combine the advantages of estrogen in skeletal tissue without negative consequences in other organs [7]. In an in vitro study by Taranta et al [8], raloxifene which is the main representative of SERMs used in treatment of osteoporosis, contributed to the reduction of bone remodeling rate, and was instrumental in the weakening of osteoclastic activity while at the same time contributed to the preservation of osteoblast activity. In an ovariectomized rat study by Cao et al [9], both estrogens and raloxifene suppress to a mild degree hard callus remodeling and don't prevent the progress of fracture healing. In another two studies using mice, estrogen and raloxifene contributed to the creation of fracture callus with larger areas of chondrocytes, increased thickness of trabecular bone, reduced fracture healing time in comparison with controls [10,11]. These findings were seen in both the metaphysis and diaphysis of the bones. Despite of these, there no human studies assessing the effect of estrogen or raloxifene on fracture healing.

Bisphosphonates

Bisphosphonates (BPs), which are first line treatment for osteoporosis [12], act by inhibiting osteoclast activity [13]. BPs adhere to the hydroxyapatite binding sites on the surface of the bone, in particular active bone resorption surfaces. Consequently, there is concern that BPs may affect fracture healing or may have adverse effects on functional rehabilitation after fracture [14].Contrary to concerns, a satisfactory number of animal studies suggest that bisphosphonates are primarily remained to the point of the acute fracture site. On the one hand, bisphosphonates increase callus formation which contributes to mechanical functionality and stability, but on the other hand inhibit remodeling of the bone by modifying the morphology of callus [15]. Regarding the time of administration of bisphosphonates, the delayed for 1-2 weeks single intravenous administration of zoledronic acid contributes to the increase in the size and strength of the callus formation and at the same time improves mechanical properties of hard callus compared to weekly bisphosphonates [16,17]. These findings support that the single intravenous administration of zoledronic acid contributes to the production of larger and stronger hard callus [15].

The effect of bisphosphonates on fracture healing of the wrist has been studied since the beginning of 2000. Among the antiosteoporotic drugs, bisphosphonates have been studied the most so far [18]. A randomized controlled study by van der Poest Clement et al [19], which compared patients with distal radius fracture who received alendronate versus placebo, argued that there was no statistically significant difference between the two groups in fracture healing rate. Moreover, the group of patients who took alendronate showed an increase in bone mass. Furthermore, two studies from the same group patients compared patients receiving bisphosphonates with patients who had not received bisphosphonates and suffered from a distal radius fracture which was treated conservatively. In the studies no statistically, significant differences were found between the two groups regarding the healing time of the fractures and the clinical or functional results [20, 21].

Two other studies assessed the effect of the timing of alendronate administration on fracture union of distal radius fractures which were treated with open reduction and internal fixation and concluded that early administration of alendronate does not affect radiological or clinical results [22,23]. A multicenter randomized placebo-control trial was recently conducted in the United Kingdom in an effort to assess the effect of weekly alendronate in the treatment of fractures of the distal radius. The researchers administered alendronate 70mg on a weekly basis, fourteen days after a distal radius

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

fracture that was treated either conservatively or surgically. They concluded that the administration of alendronate in an early stage does not disadvantage fracture healing or clinical results [24].

In hip fracture patients, treatment with bisphosphonates showed decrease in biochemical markers of bone metabolism and anti-resorptive impact. In a study by Altintas et al [25], was supported that at the end of three months of risedronate treatment, a significant decrease in urinary N-telopeptide levels was observed. Furthermore, Cecilia et al [26], suggested that treatment with alendronate caused an increase in bone mineral density in proximal femur and a decrease in biochemical markers of bone metabolism. In a large multicenter study, a single intravenous administration of zoledronic acid in the first trimester after a hip fracture was not related with a remarkable delay in fracture union [27]. In another trial by Kim et al [28], the administration of risedronate at an early stage did not affect results of functionality and complication rate in patients with intertrochanteric fractures who treated surgically as in patients with distal radius fractures who were treated with operation. Despite of this, in a recent trial by Lim et al [29], was suggested that history of bisphosphonate administration was associated with an increased risk of delayed fracture healing at 3 months in patients with intertrochanteric fractures who were treated surgically.

The effect of bisphosphonates on vertebral fracture healing has not yet been adequately evaluated. In a prospective trial by Ha et al [30], current use of bisphosphonates did not affect clinical results to a significant extent. However, patients receiving bisphosphonates developed intervertebral fissures which could be an indicative factor of affected healing of osteoporotic vertebral fractures.

Denosumab

Denosumab is a strong inhibitor of bone resorption caused by osteoclasts, and is believed to have similar properties to bisphosphonates as far as the healing of the fractures [31]. As with bisphosphonates, denosumab does not seem to affect facture healing in experimental animal studies [15]. In denosumab treated animals, the volume of hard callus was raised at the fracture site and bone remodeling was delayed. Furthermore, in experimental animal studies with mouse femurs has been suggested that denosumab increases torsional stiffness [32].

Apart from the FREEDOM study data, there are few published clinical results involving fracture healing in patients treated with denosumab. In this large multicenter trial, 7808 postmenopausal women were randomized to receive either denosumab or placebo and 667 patients had sustained 851 non-vertebral fractures (e.g. hip fractures, humeral head fractures, distal radius fractures etc.) during the entire time period. In any person who had received denosumab six weeks before or after the fracture, delayed union or nonunion of the fracture was not observed. There was no statistically significant difference between the denosumab group and the placebo group in relation to the complication rates that were associated with the fracture or the intervention. The researchers concluded that denosumab does not delay fracture healing or play any role in causing complications even when given the time period around the fracture [33].

Teriparatide

Teriparatide is a powerful anabolic agent that contributes to the increase of bone mineral density (BMD) in patients suffering from severe osteoporosis. PTH contributes to increasing the activity and lifespan of osteoblasts and has as a consequence increased bone formation on all bone surfaces [34,35]. In addition, it contributes to the increase of connectivity of the trabecular bone as well as in the increase in thickness of cortical bone which strengthens the biomechanical properties of the bone [15]. In another animal study by Kakar et al [36], was suggested that teriparatide increases recruitment and differentiation of chondrocytes which are basic processes endochondral ossification at an early stage. Therefore, teriparatide affects both cartilage and mineralized callus formation in the process of healing of the fractures [37]. Regarding the timing of teriparatide administration, its early dosing within a week after the fracture, is associated with better fracture healing [38, 39].

In a clinical study by Aspenberg et al [40], was

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

supported that teriparatide appears to contribute to callus formation after distal radius fracutres. Anyway, the effect of teriparatide in healing of the distal radius fractures has not yet been well estimated [41]. Only one randomized prospective multicenter study seems to suggest that in patients with conservatively treated distal radius fractures, to whom teriparatide was given, had a better average time of union (about one to two weeks) compared with controls. Despite of these, there was not statistically significant difference between the two groups concerning improvement of pain and scores of functionalities [42].

The effect of teriparatide on hip fracture healing is unclear. In a randomized placebo-control trial by Bhandari et al [43] in patients with femoral neck fractures who were surgically treated with internal fixation, there was no statistically significant difference regarding the proportion of patients whose fractures were united or they needed revision surgery between the patients who received teriparatide compared with controls. Moreover, the administration of teriparatide didn't improve the radiological signs of fracture union neither reduce pain compared with controls. Anyway, two retrospective studies supported findings that contradict previous study. In a trial by Huang et al [44], was reported that patients received teriparatide after surgical stabilization for intertrochanteric fractures had significant improvement in pain and better quality of life. In another trial by Kim et al [45], was supported that in patients with unstable intertrochanteric fractures who were surgically treated with proximal femoral nail fixation, in patients treated with teriparatide in comparison with controls, the time to fracture healing, relief of pain and improvement of scores of functionalities were better.

The effect of teriparatide on osteoporotic fractures of the spine is controversial. In a trial by Tsuchie et al [46], there was statistically significant difference regarding the collapse of vertebral body and the change of kyphotic angle in patients with fractures of thoracolumbar spine who were treated with teriparatide. However, in another two studies was not reported statistically significant difference regarding these parameters of stability between the two groups [47,48].

Romosozumab

Romosozumab is an antibody that targets sclerostin, is a contemporary new treatment option and its target group is elderly women with severe osteoporosis. In a study by Takase et al [49], was supported that in fractures of ovariectomized rats, romosozumab and active vitamin D_3 increased trabecular bone volume, but they didn't accelerate the fracture healing process. The influence of romosozumab on fracture healing remains controversial and further trials must investigate the expression of sclerostin during the early and late phases of fracture healing.

Comparisons between drugs

The comparison of the role of teriparatide in fracture healing compared to other drugs such as bisphosphonates resulted from recent very widespread use of teriparatide in osteoporotic fractures. In a double-blind clinical study by Aspenberg et al [50], patients with trans- trochanteric femoral fractures who were treated with internal fixation, received either teriparatide or risedronate. The administration of teriparatide in comparison with risedronate was related to less pain and shorter time to complete the Timed Up-and-Go test in the time interval between six and twenty-six weeks. Despite of these, other clinical outcomes associated with rehabilitation after fracture, such as union rate of the fracture, time until fracture healing, scores of the physical function were similar between the two groups.

Most comparisons between teriparatide and bisphosphonates were conducted in patients with osteoporotic vertebral fractures. On one hand, in a trial by Tscuchie et al [46], was supported that in patients treated with teriparatide, less change in kyphotic angle and less vertebral body collapse were observed. On the other hand, Iwata et al [51], suggested that the stability parameters in fracture site were similar to a significant extent between the two groups. Furthermore, in a trial by Min et al [48], was mentioned that the height loss of vertebral body was less in teriparatide-treated patients while there was not statistically significant difference regarding the rate of fracture instability and

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

local kyphosis change between the two groups. In reference to the pain at fracture site, two studies supported that in patients treated with teriparatide there was less pain to a significant extent at last follow-up [46, 48]. In another trial by Kang et al, was reported that patients treated with teriparatide had less pain, but the clinical data were not different to a statistically significant extent [52]. Finally, in a trial by Hanji et al was suggested that clinical data related to pain were recorded according to pain assessment methods [53].

Conclusions

The administration of bisphosphonates does not affect the process of the facture healing after vertebral, hip and distal radius fractures. Despite the fact that clinical evidence is incomplete, denosumab does not appear to delay the healing process of non-vertebral fractures. In relation to the effect of SERMs and romosozumab on the process of fracture healing, there are no human studies. The administration of teriparatide in patients with distal radius fractures showed shorter healing time, while in patients with hip fractures, the healing time was unclear but was suggested that patients had minor pain and better clinical results in scores of functionalities. In patients with vertebral fractures, there were no evidence of clinical data that teriparatide shortens the healing time of fractures but was supported that there was greater improvement in pain at the fracture site. Considering the fact, that there is no evidence that antiresorptive drugs delay the healing of the fracture process and the fact that after the first osteoporotic fracture, the risk of subsequent osteoporotic fracture is particularly increased, there is no reason to delay the initiation of antiosteoporotic treatment after the fracture. Anyway, high-quality randomized controlled studies are needed to investigate further the role of antiosteoporotic drugs in fracture healing.

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

REVIEW

Vitamin D and musculoskeletal health

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ABSTRACT

Vitamin D is a steroid pro-hormone, with effects that are not limited to the metabolism of calcium and phosphorus, but are pleiotropic and involve cellular differentiation, the immune response, intermediate metabolism and the cardiovascular system. This fat-soluble vitamin plays a significant role in musculoskeletal homeostasis and its deficiency or mal-regulatory function leads to several bone metabolic disorders.

KEYWORDS: Vitamin D ; Metabolic bone disorders ; Musculoskeletal health

Introduction

Vitamin D belongs to the category of fat-soluble vitamins. There are two forms, vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol), of animal and plant origin respectively, which differ in chemical structure and pharmacokinetic properties. It is actually a steroid pro-hormone, with effects that are not limited to the metabolism of calcium and phosphorus, but are pleiotropic and involve cellular differentiation, the immune response, intermediate metabolism and the cardiovascular system.

Resources – Composition - Vitamin D Effects

Vitamin D3 is produced in the skin under the influence of ultraviolet radiation (UVB 290-315nm). Specifically, 7-dehydrocholesterol, upon exposure to ultraviolet radiation, is converted to provitamin D3 and then into its isomer, vitamin D3. Vitamin D then enters circulation, where it binds to its carrier protein, vitamin-D binding protein (VDBP). Other sources of vitamin D are foods (vitamin D2 - plant origin and D3 - animal origin). In this case Vitamin D is absorbed through the intestine and is transferred to systemic circulation through the lymph by chylomicrons. The two types differ in a methyl group at the C24 position and a double bond between C22-23. Despite they are equally absorbed from the digestive system, they differ in pharmacokinetics, with vitamin D2 due to less binding to VDBP, being eliminated faster. Therefore, vitamin D2, in equivalent intermittent doses, has only 30-40% of the bioavailability of vitamin D3. On the contrary, in daily administration of equivalent doses appear to have similar bioavailability.

The production of vitamin D in the skin, which constitutes at least 80% of the total daily produc-

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

tion - the rest comes from food - is affected by multiple factors, among which are sun exposure, the use of sunscreens (sunscreen with an SPF > 8 limits up to 90% the synthesis of vitamin D), clothing, the amount of melanin (black people show lower levels), the time of year (significant decrease during winter), the latitude (increase in latitude is accompanied by a significant limitation of the ability to synthesis), age (decreased ability to produce vitamin D in the elderly), obesity (reduced mobilization of vitamin D from adipose tissue)[1,2,3,4], as well as genetic factors (enzyme polymorphisms involved in the conversion of 7-dehydrocholesterol to provitamin D3 and mainly VDBP polymorphisms). Studies in monozygotic twins show that genes are involved in the synthesis, metabolism and transport of vitamin D thus, interpreting 5-10% of the variability of its levels[4]. A series of studies report that the daily vitamin D intake from food is less than 5 μg (200 IU) per day in most European countries except for the Scandinavian countries, while in North America it is less than 10 μg (400 IU)[4].

After the initial synthesis of vitamin D in the skin and its binding to VDBP, it is transported to the liver where it is hydroxylated at the 25-position to form 25(OH)D. The enzyme responsible is called CYP2R1, it is expressed in the liver and the testis, it belongs to the group of cytochrome p450 oxidases, and besides vitamin D it hydroxylates cholesterol and bile acids. Its activity decreases in severe liver failure.

Then 25(OH)D is transferred to the kidney where, under the influence of CYP27A1 (1-a hydroxylase), it is converted into the active form of vitamin D, 1,25$(OH)_2$ vitamin D. The "entry" of 25(OH)D into the epithelial cells of the renal tubule occurs both initial filtration from the glomerulus via the protein megalin, which is expressed on the tubular surface of the cell and the basolateral surface of renal tubular cells. Then 25(OH)D enters the cytoplasm, and with the intracellular binding protein of vitamin D it is brought to the mitochondria where it is hydroxylated by 1-a-hydroxylase to 1,25 $(OH)_2D$.

CYP27A1 (1-a hydroxylase) is a mitochondrial enzyme. The responsible gene is located on of chromosome 12. Alternatively, 25(OH)D is converted to 24,25$(OH)_2D$ by CYP 24A1 (24-hydroxylase) and then to calcitroic acid, which is excreted in the bile. Inactivating mutation of the 1-a hydroxylase gene causes vitamin D-resistant rickets type 1, while inactivating mutations of 24-hydroxylase causes idiopathic hypercalcemia of infancy, as well as PTH-independent hypercalcemia in adults.

Beyond the renal tubule, 1-a hydroxylase is present in many tissues, such as osteoblasts, intestine, monocytes, pancreas, prostate, breast, etc. where it participates in the local production of active vitamin D. Regarding the factors that increase the activity of 1-a hydroxylase in the kidney, the main ones are PTH, hypocalcemia, and hypophosphatemia, while it is reduced in hypoparathyroidism, hypercalcemia, hyperphosphatemia, as well as by FGF23 and 1,25 $(OH)_2D3$. The differences between 25 $(OH)D_3$ and 1.25 $(OH)_2D_3$ are shown in table 1.

Vitamin D exerts genomic and rapid non-genomic actions, which mainly involve ion transport[5]. Regarding the genomic actions, vitamin D, as a steroid hormone, acts through its receptor, the VDR. In particular, 1,25 $(OH)_2$ vitamin D after entering the cytoplasm or produced locally binds to its receptor, which forms a heterodimer with the retinoic acid receptor. The complex binds to a special region of DNA called VDRE (Vitamin D Response Element), near the promoter of the corresponding gene, which is regulated by vitamin D. Then by activating co-activators or co-repressors it causes the activation or suppression of genes with consequent modification of the levels of the corresponding protein. It is estimated that 3000 genes respond to vitamin D.

It should be noted that even 25(OH)D at very high levels can exert endocrine effects, as it binds to VDR, but with a much lower affinity than calcitriol. Such action occurs in the context of hypervitaminosis D as well as when administering cholecalciferol or ergocalciferol to patients with hypoparathyroidism, where the doses used are of the order of 50,000 IU daily or more.

The positive effects of vitamin D mainly target the intestine, bone, kidney and parathyroid. Particularly:

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 1.

Vitamin D metabolite characteristics

	25 (OH)D	1,25 $(OH)_2D$
Concentration	20-150 nmol/L (8-60 ng/ml)	50-150 pmol/L (20-60 pg/ml)
Half-life time	25 days	7 hours
External effects	Sunlight, season, nutrition	immobilization, calcium intake
Hormonal adjustment	T3	PTH, cortisol, estradiol, calcium, phosphorus, FGF23
Binding to VDR	1/100 of 1,25 $(OH)_2D$	Kd 10^{-10} to 10^{-11}M

– In the intestine it causes an increase in the intestinal absorption of Ca and P, through the induction of TRVP6 channels, calbindin D9k, PMCA1 and the NaP cotransporter IIb.

– In the bones, it causes an increase in osteoblastic and osteoclastic activity, through an increase in the production of RANKL by the osteoblasts, resulting in an increase in the release of calcium and phosphorus from the bones, while it also increases the production of FGF23 by the osteocytes.

– In the kidney, it suppresses 1-hydroxylase, induces 24-hydroxylase, and increases calcium reabsorption in the distal tubule.

– In parathyroids it inhibits the synthesis of PTH and the proliferation of parathyroid cells.

In addition to the above effects, vitamin D affects multiple functions of the human body which are related to inflammation, blood pressure and tumorigenesis.

Vitamin D is associated with suppression of cell growth, increase in cell differentiation, regulation of apoptosis, immune response, differentiation of skin and hair, regulation of blood pressure (reduction of renin), increase in insulin secretion, improvement of muscle function and effect on CNS function.

Vitamin D and musculoskeletal health

As early as the 17th century due to poor socioeconomic conditions of the industrial revolution, the characteristic skeletal disorders of rickets were described, while at the beginning of the 19th century the importance of exposure to solar radiation for the prevention and treatment of rickets was highlighted. At the beginning of the 20th century, exposure of the body and milk to ultraviolet radiation was used therapeutically. In the last decade the recognition of the importance of vitamin D for both optimal musculoskeletal health and its possible extra-skeletal role has led to the need to redefine its place in clinical practice. At the same time, a series of epidemiological studies confirmed the increased frequency of hypovitaminosis D in the general population. A particular study in Germany in a pediatric population reports that levels of 25 (OH)D < 12 ng/ml and < 20 ng/ml are found in 12.5% and 45.6%, while corresponding data in adults especially from northern countries (UK) describe percentages of the order of 22% and 55% [4,6].

Vitamin D pathophysiology deficiency

Although the exact sequence of pathophysiological changes in vitamin D deficiency has not been fully elucidated in humans, a common denominator regardless of the cause (Table 2) is a decrease in intestinal absorption of calcium and phosphorus and the development of secondary hyperparathyroidism. Studies in dogs[7] under 2 years of low calcium and vitamin D intake suggest a progressive decrease in calcium levels with a concomitant increase in PTH.

PTH increases the rate of bone remodeling, resulting in an increase in the release of calcium and phosphorus from bone, a decrease in renal calcium excretion and an increase in phosphorus excretion, and a concomitant increase in calcitriol production, at least in the early stages. The increase in calcitriol partially compensates for the decrease of calcium

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 2.

Causes of Vitamin D Deficiency
• Decreased skin complexion – Use of sunscreen – age (older) – Burns
• Decreased bioavailability – Malabsorption syndrome – Obesity
• Increased catabolism – Antiepileptic, glucocorticoids, HAART, isoniazid
• 25-hydroxylase deficiency – Liver failure
• Increased loss(es) – Nephrotic syndrome
• Decreased composition of 1,25 (OH)2 D – Chronic Kidney Disease
• Genetic Causes of Rickets – Resilient to Vitamin D Type 1,2,3 – XLHR – ADHR – ARHR
• Acquired hypophosphatemia disorders – TIO

TABLE 3.

Risk factors for rickets and osteomalacia
Maternal factors
Vitamin D deficiency
Skin colour
Full coverage of the body with clothing
Stay in high altitude in winter / spring
Other causes for low sun exposure (stay outside the house, restricted mobility, pollution)
Decreased dietary Vitamin D intake
Neonatal- infant factors
Infant vitamin D deficiency due to maternal Vitamin D deficiency
Lack of complementary nutrition or substitute
Skin colour
Full coverage of the body with clothing
Stay in high altitude in winter / spring
Other causes for low sun exposure (stay outside the house, restricted mobility, pollution)
Decreased dietary Vitamin D intake
Low calcium intake
Low income, malnutrition, special dietary habits.

and phosphorus, increases their intestinal absorption and bone release. Late, further depletion of vitamin D due to consumption leads to a decrease in calcitriol levels, resulting in an even greater decrease in calcium and phosphorus levels.

Vitamin D deficiency during puberty - childhood

Rickets is a disease of the developing skeleton and is characterized by disruption of chondrocyte apoptosis, delay or failure of the mineralization of connective cartilage and osteoid, resulting in its enlargement and the appearance of characteristic skeletal deformities[8,9]. The most common cause is the lack of vitamin D or the reduced intake / absorption of calcium, which leads to a decrease in the intestinal absorption of calcium and phosphorus, secondary hyperparathyroidism with consequent further worsening of phosphorus deficiency.

Hypophosphatemia leads to a decrease in the normal apoptosis of hypertrophic chondrocytes, a phenomenon that is necessary for the development of vascularization in the connective cartilage and its subsequent mineralization. The incidence of rickets increases significantly at 25(OH)D levels < 30 nmol/L (12 ng/ml), while in full clinical expression the levels are less than 12.5 nmol/L (5 ng/ml). As a rule, it manifests itself between the 6th-24th month of life in infants with reduced exposure to the sun or under exclusive breastfeeding.

The higher frequency in the neonatal age is attributed to the limited vitamin D pool in the neonate (it is estimated that 25(OH)D levels in the umbilical cord are 50-60% of maternal levels, due to low VDBP), to the low amount of vitamin D in breast milk and in the significant dependence of the intestinal absorption of calcium on vitamin D

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 4.

Recommended Vitamin D intake from the American Institute of Health and the Endocrine Society. (AI: adequate intake, EAR: estimated average requirements, RDA: recommended daily allowance, DR: daily requirement, UL: tolerable upper intake level) [10, 11]

	IOM recommendations				Endocrine Society	
	AI	EAR	RDA	UL	DR	UL
Infants						
0-6 months	400			1000	400-1000	2000
6-12 months	400			1500	400-1000	2000
Children						
1-3 years		400	600	2500	600-1000	4000
4-8 years		400	600	3000	600-1000	4000
Men						
9-18 years		400	600	4000	600-1000	4000
19-70 years		400	600	4000	1500-2000	10000
> 70 years		400	800	4000	1500-2000	10000
Women						
9-18 years		400	600	4000	600-1000	4000
19-70 years		400	600	4000	1500-2000	10000
> 70 years		400	800	4000	1500-2000	10000
Pregnancy - lactation						
14-18 years		400	600	4000	600-1000	4000
19-50 years		400	600	4000	1500-2000	10000

at this age[4,8,9]. The diagnosis is made on the basis of history, clinical picture, biochemical control and is confirmed by radiological control. International clinical guidelines for the prevention of nutritional rickets (Nutritional Rickets) have recently been published which briefly state[9]:

1. Vitamin D levels

a. Adequate: > 20 ng/ml (50 nmol/L)

b. Insufficiency: 12-20 ng/ml (30-50 nmol/L)

c. Deficiency: < 12 ng/ml (<30 nmol/L)

d. Toxicity: > 100 ng/ml (>250 nmol/L)

2. Calcium nutrients to prevent rickets

a. Neonates- infants: 0-6 months of age : 200 mg & 6-12: 260 mg

b. Children > 12 months calcium intake < 300 mg increases rickets risk.

c. Classification of nutrition calcium intake for children > 12 months of age

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 5.

Indications for testing for of vitamin D Deficiency [11,14]
• Rickets, osteomalacia
• Osteoporosis
• Adults with a medical history of falls, low energy fractures
• Chronic Kidney Disease
• Liver failure
• Malabsorption syndrome – Fibrocystic disease – Inflammatory Bowel Disease – Bariatric surgery – Radiation enteritis
• Hyperparathyroidism
• Medication
• Pregnancy - lactation
• Athletes (indoor sports)
• Obesity
• Granulomatous diseases
• Certain lymphoma

i. Adequacy: > 500 mg/day
ii. Insufficiency: 300-500 mg/ day
iii. Deficiency: < 300 mg/ day

3. Vitamin D administration to prevent rickets / osteomalacia

a. Neonates-infants 0-12 months: 400 IU (10 μg) day

b. children > 12 months: 600 IU (15μg) day via supplements or diet

4. Areas of population (Table 3)

a. Healthy children do not need Vitamin D preventive check up

b. Candidates for Vitamin D supplements after the age of 12 months old lacking in Vitamin D nutrition

i. Children with symptomatic Vitamin D Deficiency
ii. High risk Vitamin D Deficiency Children and Adults
iii. Pregnancy

5. Rickets treatment

a. Minimum dose of vitamin D 2000 IU/day and 500 mg calcium for 3 months

b. Oral administration of vitamin D is the most effective

c. Vitamin D2 and D3 in daily administration are equally effective

d. On intermittent administration D3 is more effective

a. Universal vitamin D supplements in all newborns and infants up to 12 months of age. After this age vitamin D supplements only in high-risk individuals and in pregnancy.

b. Monitoring the implementation of intervention strategies

c. Detection and intervention in high-risk populations

d. Implementation of informational programs at the population level

e. Evaluating the effectiveness and cost/benefit ratio of food fortification programs at the population level.

Corresponding to the above are the guidelines from the US Institute of Health for the prevention of rickets[10], while the American Endocrinology Society recommends an intake of 400-1000 IU up to 1 year and 600-1000 IU up to 18 years[11] (Table 4). Regarding the relationship between vitamin D levels and musculoskeletal health during childhood, a series of studies describe a positive association between higher levels of vitamin D and bone density, bone mineralization, intestinal calcium absorption and muscle function.

However, there are not clear data, for now, regarding children / teenagers.

Vitamin D Deficiency in adults

Osteomalacia

Osteomalacia is a disease of adults and is usually caused by long-term vitamin D deficiency. Histomorphometrically, it is characterized by an in-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

crease in volume and a decrease in osteoid mineralization[12]. Osteomalacia leads to significant bone loss in the cortical bone with an accompanying increase in the risk of falls and fractures. At a clinical level, it manifests itself with a series of symptoms and signs (osteomalacia syndrome) such as bone tenderness and bone sensitivity to palpation, muscle weakness and difficulty walking, which usually go unnoticed.

Imaging show osteopenia, an increase cortical porosity, a rarely fibrous cystic osteitis due to secondary hyperparathyroidism, while Looser zones are characteristic which appear on the pelvis, scapula or less frequently on the medial surface of the femoral neck or medial surface of the diaphysis of the long bones. Laboratory findings include low 25(OH)D levels, elevated alkaline phosphatase and secondary hyperparathyroidism. Regarding 25(OH)D levels below which osteomalacia occurs, most agree that 25(OH)D levels ≥ 20 ng/ml rule out osteomalacia.

Nevertheless, a recent study of bone biopsies in more than 600 subjects, who passed away of violent death, showed that a percentage of patients (» 20%) with 25(OH)D levels between 20-30 ng/ml have static histomorphometric findings of osteomalacia, while all patients with levels above 30 ng/ml had a normal biopsy. The treatment is recommended to correct hypovitaminosis D.

Osteoporosis

In recent decades the undisputed role of vitamin D in the musculoskeletal system has made both its determination and its use as a therapeutic agent a prerequisite in the evaluation and treatment of osteoporosis. Nevertheless, even today there is a dichotomy[10,11] regarding the ideal levels of vitamin D for optimal musculoskeletal health, due to the lack of consensus on the ideal endpoint (intestinal calcium absorption, PTH levels, bone density, rate of bone loss, fractures, falls) and, on the other hand, the conflicting results of several clinical trials. .

The definition of ideal levels of vitamin D and consequently the recommended daily intake varies according to the population being tested. Consequently, the US Institute of Health sets ideal levels of 25(OH)D ≥ 20 ng/ml (50 nmol/L)[10] in the general population, while the IOF[13] and the American Society of Endocrinology[11] set a goal of ≥ 30 ng/ml (75 nmol/L) in patients with metabolic bone diseases.

ESCEO[14] characterizes levels of 25(OH)D < 10 ng/ml as vitamin D deficiency, levels of 10-20 ng/ml as vitamin D deficiency, while levels > 20 ng/ml are considered sufficient, with the exception of some elderly individuals where values > 30 ng/ml probably lead to a better outcome regarding falls and fractures. 25(OH)D values > 50 ng/ml are likely to be associated with adverse effects.

The lack of unanimity regarding ideal vitamin D levels, therapeutic targets, and corresponding replacement doses is attributed to a lack of adequate data in the general healthy population regarding the effects of vitamin D deficiency, the absence of well-designed intervention studies with clear endpoints in specific populations, and in the lack of reliability of measuring the levels of 25(OH)D in daily clinical practice. For example, regarding intestinal calcium absorption, a study by Heaney[15] in postmenopausal women showed that an increase in 25(OH)D from 20 ng/ml to 34 ng/ml is associated with an increase in intestinal calcium absorption by 40-60%, while a recent, better-designed study found that increasing 25(OH)D levels from 20 to 66 ng/ml results in only a 6% increase in intestinal calcium absorption, which is significantly reduced at levels below 10 ng/ml[16].

The relationship between PTH levels and 25(OH)D is not linear, with PTH levels increasing exponentially at lower levels of vitamin D. At the same time, there appear to be significant differences depending on race (blacks show an increase in PTH at levels of 25(OH)D < 16 ng/ml vs. white 24 ng/ml), the duration of hypovitaminosis, the presence of pathological conditions (functional hypoparathyroidism in diabetes mellitus, smoking, hypomagnesemia, etc.).

Conversely, studies addressing the restoration of PTH levels by correcting hypovitaminosis have conflicting results, with some showing further PTH reduction at 25(OH)D values > 30 ng/ml and others not. It is possible that the differentiation of

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

the results is related, among other things, to the duration of the maintenance of ideal 25(OH)D levels as sufficient time (more than 6 months) is required for the correction of secondary hyperparathyroidism[17].

Studies concerning the relationship between 25(OH)D and other endpoints, more characteristic of osteoporosis, show an almost linear association between vitamin D levels and bone density as well as the rate of bone loss. In addition, a series of studies (generally case-control) show a significant increase in fracture risk in the context of hypovitaminosis D (clinical fractures, hip fractures, non-vertebral fractures) in the white race and in both sexes[18]. However, a recent WHI analysis does not confirm the association of low 25(OH)D levels and fractures in postmenopausal black women[19].

Regarding the intervention studies with the endpoint reduction of fractures and falls, the data are conflicting due to the different controlled populations (community, institutional patients, with or without osteoporosis), the different doses [400 to and above 800 IU daily, intermittent administration (weekly, monthly, yearly)], in the parallel administration of calcium as well as in the degree of compliance. Nevertheless, most meta-analyses conclude that the administration of vitamin D with calcium in doses between 480-770 IU/day and the achievement of 25(OH)D levels around 30 ng/ml are associated with a reduction in the risk of non-vertebral fractures by average 20%[13,20], while there is a reduction in the risk of falls by 18%[21]. In addition, in all clinical studies of approved osteoporosis drugs (calcitonin, bisphosphonates, SERMS, strontium ranelate, denosumab, teriparatide-complete parathyroid hormone) calcium and vitamin D were co-administered at doses of 400-800 IU daily.

Special conditions

Pregnancy – Lactation

The past few years, vitamin D deficiency in pregnancy and lactation is closely related to multiple endpoints for both the mother and the fetus – newborn baby[22]. During pregnancy, significant amounts of calcium are transferred from the mother to the fetus, especially during the 3rd trimester, where it is estimated that the daily transfer approaches 300 mg. Adaptation occurs through an increase in intestinal absorption of calcium. In contrast during lactation, where approximately 300 mg of calcium is transported per day, the adaptation occurs through an increase in bone mobilization of calcium through PTHrp.

It is noted that during pregnancy, 25(OH)D passes through the placenta, a transfer which determines the levels of vitamin D in the newborn, while in breast milk, in addition to calcium, calciferols (D2 and D3) are transferred and not 25 (OH)D. The prevalence of hypovitaminosis D is particularly high worldwide (18% to 80%) and has been associated with a higher incidence of preeclampsia, gestational diabetes mellitus, preterm delivery, caesarean section, low birth weight and reduced BMC/BMD of the newborn. Additionally, the effect of vitamin D deficiency on the intrauterine programming of the fetus is discussed given the pleiotropic actions of vitamin D.

However, Vitamin D Intervention studies have basically failed to prove effectiveness. Two recent studies, conducted in the EU[23]and the USA[24] describe a marginal benefit in infant wheezing and asthma with cholecalciferol administration during pregnancy at doses of 2800 IU/day vs. 400 IU/day and 4400 IU/day vs. 400 IU/day respectively.

Based on the above data, von Mutius E & Martinez FD in the editorial[25] that followed suggest that the administration of higher doses of cholecalciferol than recommended (≈ 2800 IU) to women at high risk for giving birth to children with asthma (e.g. history of asthma, eczema, allergic rhinitis) to be a trial strategy, subject to confirmation by new studies with sufficient sample size. Finally, the MAVIDOS[26] study was recently published, which concerns the administration of 1000 IU of vitamin D3 versus placebo during pregnancy, with the primary endpoint being the newborn's bone mass.

Vitamin D administration was not associated with a significant benefit in terms of bone mineral density, with the possible exception of neonates born in winter. It was also found that risk factors

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

for 25(OH)D levels < 20 ng/ml at the 34th week of pregnancy are: 1. Delivery in winter, 2. Weight gain during pregnancy, 3. Reduced 25(OH) levels during the 14th week, 4. non-white race and 5. Low compliance. The IOM recommends an intake of 600 IU/day in pregnancy and lactation, while the American Endocrinological Society 600-1000 IU for ages 14-18 and 1500-2000 IU for over 18.

Chronic Kidney Disease

Disorders of bone and mineral metabolism (CKD-BMD) occur early in the course of CKD and are characterized by secondary hyperparathyroidism, bone disease, and vascular calcifications. The main causes are related to phosphorus retention and disturbances in vitamin D metabolism.

The progressive decrease in calcitriol levels during the progression of renal disease is attributed to the decrease in 1-a hydroxylase activity due to a decrease in renal mass, increase in FGF23 due to hyperphosphatemia, to a decrease in the supply of 25(OH)D to the kidney due to a decrease in the expression megalin (protein which is responsible for endocytosis of 25(OH)D). Due to the high frequency of hypovitaminosis D in the context of CKD and its association even with mortality, the control of 25(OH)D levels is recommended in all patients with impaired renal function, with ideal values of 30 ng/ml[27]. Although there is not much intervention data, it seems that restoring ideal levels of vitamin D is safe, leading to a decrease in PTH levels up to stage 3 CKD, after which you usually require the administration of vitamin D analogues. Nevertheless, restoring vitamin D deficiency even stage 5 CKD is advocated due to its pleiotropic actions.

Pleiotropic effects of Vitamin D[28,29]

Apart from the proven bone activity of vitamin D, already at the beginning of the 20th century it was observed that children with rickets presented, in addition to the musculoskeletal disease, an increased frequency of respiratory infections. In 1903 Finsen (Nobel prize in medicine) used ultraviolet radiation to treat cutaneous tuberculosis (lupus vulgaris), while in 1915 Hofman observed that cancer mortality was higher in populations far from the equator.

The recognition in recent decades that calcitriol exerts important actions in multiple tissues beyond the classic ones (bones, intestine) such as in the skin, large intestine, breast, pancreas, brain, T and B lymphocytes, macrophages, where VDR is expressed, as well as that calcitriol can be synthesized locally dueto the local expression of 1-a-hydroxylase in the above tissues, linked the observation of hypovitaminosis D with a series of diseases such as neoplasms (cancer of the breast, colon, esophagus, prostate, pancreas), autoimmune diseases (multiple sclerosis, type 1diabetes mellitus), infections (tuberculosis), skin diseases (psoriasis), intermediate metabolism diseases (type 2 diabetes), CNS diseases (dementia) and cardiovascular diseases.

A series of in vitro studies document that vitamin D improves differentiation and inhibits cell proliferation, inhibits angiogenesis and induces apoptosis, increases insulin secretion, reduces renin, increases the production of cathelicidin, a peptide that facilitates the destruction of Mycobacterium tuberculosis.

To date, numerous epidemiological studies describe an important relationship between hypovitaminosis D and the above disorders, while some intervention studies describe a reduction in the occurrence of the above diseases by restoring vitamin D levels to values above 30 ng/ml.

Despite this, there is a lack of data from well-designed studies with endpoints in the above diseases, except for psoriasis, where topical vitamin D analogues are already used with good results.

Consequently, despite the abundance of basic research data and observational studies regarding the beneficial relationship of higher vitamin D levels with multiple non-skeletal diseases, such as malignancies, reproductive function, infections, cardiovascular diseases, neurological diseases, data from well-designed randomized trials with clearly defined endpoints, well-defined populations of interest, specific vitamin D dosing regimens, specific 25(OH)D target levels to test both the efficacy and safety of achieving higher 25(OH)D levels are lacking or failed to show significant effect.

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Treatment of vitamin D deficiency

The treatment of low vitamin D includes two phases, first the restoration of the lack/insufficiency and second the long-term maintenance of ideal levels. It is estimated that for every 100 IU (2.5 μg) of vitamin D administered, 25(OH)D levels increase by 1 ng/ml (2.5 nmol/L). Even today there are many questions regarding the form of vitamin D (D2 vs. D3) that is more effective, the dose, the route, and the intervals of administration.

From a pharmacokinetic point of view, the absorption from the digestive tract of calciferols (D2 or D3) is similar.

Administering calciferol during hypovitaminosis D leads to a rapid increase in its hydroxylation at the 25- position with a plateau at 25(OH)D levels of approximately 34 ng/ml[30]. Calciferols are then removed from the circulation, either metabolized and eliminated with faster metabolic clearance of D2, due to reduced binding to VDBP, or stored in adipose tissue (probably D3 is better stored than D2).

Regarding the use of vitamin D analogues (calcitriol and alphacalcidol) its use should be limited to patients with impaired renal function, patients with hypoparathyroidism as well as to patients with hereditary or acquired hypophosphatemic disorders. Their use to treat vitamin D deficiency is not indicated, as it does not increase 25(OH)D levels (possibly even reducing them) and it does not provide the necessary substrate for the formation of calcitriol locally in the tissues. Finally, the adequacy of replacement cannot be tested as, as mentioned, it does not restore 25(OH)D levels.

Regarding the effectiveness of the various regimens, it is clear that vitamin D3 in intermittent regimens (weekly, monthly) is superior to D2, due to the faster clearance of D2[31], oral administration is superior to parenteral administration, daily versus intermittent administration and the total dose. Studies concerning the route of administration show that 25(OH)D levels increase rapidly after administration of 300,000 IU D3 per os[32], while at least 2 months are required for 25(OH)D levels to increase after intramuscular administration.

Regarding the intermittent administration of vitamin D both for the restoration of hypovitaminosis and for the chronic maintenance of ideal levels, it probably excels in terms of compliance compared to daily regimens, nevertheless cumulatively significantly larger doses are required to achieve the same effect. In addition, there is increasing data regarding the safety of administering large doses of vitamin D either intermittently or in large daily doses to elderly patients.

In particular, a study in the elderly with oral administration of 500,000 IU D3 orally once a year[34] showed an increase in the risk of fractures and falls during the first trimester, a phenomenon that was attributed either to the rapid improvement in the mobility of the subjects and consequently an increase in falls, or in the rapid decrease in vitamin D levels after the initial large increase, a phenomenon possibly related to the seasonal distribution of fractures.

Another one-year study[34] in elderly community patients with satisfactory baseline vitamin D levels found that vitamin D3 administration at doses of 60,000 IU/month vs. 60,000 IU/month in combination with calcifediol vs. 24,000 IU/month for one year did not improve muscle function, but was accompanied by an increase in falls compared to the group receiving 25,000 IU/month. In this study achieving 25(OH)D levels between 44.7-98.9 ng/ml vs. 21-30 ng/ml was associated with a 5.5-fold greater risk of falls. Corresponding data were described in a recent study[35] with daily administration of vitamin D where correction of hypovitaminosis was accompanied by a reduction in falls, while achieving high levels was unexpectedly associated with an increase in falls.

These data raise serious questions regarding the safety of large single doses of vitamin D on a long-term basis in elderly subjects (monthly doses > 50,000 IU) and possibly also the target levels of 25(OH)D in these groups (values > 45 ng/ ml probably related to an increase in falls).

In any case, a prerequisite for the safe restoration of vitamin D deficiency is the previous determination of calcium and PTH. In vitamin D[11] deficiency, administration of 50,000 IU vitamin D3/week/8 weeks or 5000-6000 IU vitamin D/day/8 weeks

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

(D2/D3) is recommended.

An interval of at least 3 months is required from the start of treatment to assess the efficacy of the regimen by determination of 25(OH)D, while the restoration of PTH levels may be delayed even longer. Regarding the maintenance of ideal vitamin D levels, the recommended daily dosage varies according to the 25(OH)D target that is set.

If we aim for levels > 20 ng/ml, which are recommended by most international organizations, taking 800 IU/day is sufficient in most cases (probably longer doses are required for obesity, ongoing losses, malabsorption syndromes, etc.), while if we aim values above 30 ng/ml, then a higher total daily dosage of 1500-2000 IU/day or more is required, with an upper safe daily dose based on IOM of 4000 IU/day and 10000 IU according to the guidelines of the American Endocrine Society.

Hypervitaminosis D[36]

Hypercalcemia occurs in 0.2% and 4% of the general and hospitalized population, respectively, with the most common causes being primary hyperparathyroidism and hypercalcemia due to malignancy. Classically, hypercalcemia is divided into PTH-dependent and PTH-independent. Hypervitaminosis D refers to PTH-independent hypercalcemia, as PTH levels are low.

The frequency of hypercalcemia due to hypervitaminosis D is low, however, the widespread use of vitamin D supplements, vitamin D analogs as well as the identification of inactivating mutations in the metabolic pathway of vitamin D clearance (24-hydroxylase-CYP24A1) may lead to an increase in the frequency. In general, doses up to 10,000 IU for a short period of time appear to be safe, while hypervitaminosis D has not been described at vitamin D levels < 50 ng/ml (125 nmol/L).

Laboratory tests show an increase in calcium, phosphorus, 25(OH)D (usually > 150 ng/ml), hypercalciuria, suppression of PTH, while the levels of $1,25(OH)_2$ are not particularly elevated. Pathophysiologically, hypercalcemia is due to VDR activation by 25(OH)D, while the involvement of increased endogenous synthesis of 5,6-trans-25(OH)D_3 is also suspected, a derivative that can activate the receptor. In addition, hypercalcemia after administration of vitamin D can occur in the presence of granulomatous disease (sarcoidosis, tuberculosis, leprosy, systemic mycosis, Wegener's disease, Crohn's disease, etc.), inactivating mutations of CYP24A1, Williams-Buren syndrome, hypophosphatasia, etc.

Finally, hypercalcemia can be caused much more often during the administration of vitamin D analogs, especially when they are administered in large doses in combination with calcium. Treatment consists of stopping vitamin D, hydration or administration of furosemide, corticosteroids or, in extreme cases, extrarenal dialysis.

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

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REVIEW

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Osteoporosis of genetic origin: a literature review

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ABSTRACT

Numerous cases of genetic (primary) osteoporosis are reported in the literature, thanks to the in-depth investigation of suspicious scenarios, where a child or young adult presents with bone fragility. Thorough diagnostic work up is required in order to exclude more frequent, treatable, secondary causes of osteoporosis (e.g. leukaemia or Crohn's disease). When first line investigations exclude secondary osteoporosis and in the presence of specific clinical clues (e.g. blue sclerae, joint laxity) or of a suspicious family history of early onset osteoporosis, a genetic work up should be undertaken. There are many new genes implicated in the pathogenesis of primary osteoporosis, playing different roles in bone formation and/or resorption, depending on the metabolic bone path involved. The greater understanding of the complexity of bone metabolism opens new research roads for new, gene-specific treatments. Herein, the latest literature data on the osteoporosis of genetic origin are being presented. Emphasis is also given on the importance of lateral thinking, when it comes to children and young adults whose fracture history is remarkable and cannot be attributed solely to injury. Finally, the importance of not missing significant chronic disorders leading to osteoporosis is also highlighted.

KEYWORDS: osteoporosis, children, genes, metabolism, fractures

Introduction

Osteoporosis is the most frequent metabolic bone disorder, characterized by the presence of bone fragility, which predisposes to fractures, as a result of defective bone microarchitecture and reduced bone mass[1]. It is a multifactorial and complex disorder, affected by multiple factors which impair bone quality and quantity. Previously considered mostly a disease of the elderly, it is now increasingly diagnosed in younger populations, even in small children with chronic disorders that affect the skeleton or with intrinsic, heritable bone abnormalities.

The definition of osteoporosis varies, depending on the age group involved. In men>50 years old and post-menopausal women, where osteoporosis is more prevalent, according to the International Society of Clinical Densitometry (ISCD), a bone mineral density (BMD) T-score ≤ -2.5 , measured with dual X-ray absorptiometry (DXA) of the lumbar spine and/or hip, signifies osteoporosis[2]. In premen-

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 1.

Genes implicated in the pathogenesis of osteogenesis imperfecta.

Gene	Encoded protein	Type of inheritance
COL1A1	Collagen type I α1 chain	AD
COL1A2	Collagen type I α2 chain	AD
IFITM5	BRIL	AD
P3H1	Prolyl 3-hydroxylase 1	AR
CRTAP	Cartilage-associated protein	AR
PPIB	Peptidylprolyl isomerise B	AR
BMP1	Bone morphogenetic protein 1	AR
SERPINH1	Heat-shock protein 47	AR
SERPINF1	PEDF	AR
CREB3L1	OASIS	AR
SP7	Osterix	AR
TMEM38B	Transmembrane protein 38B	AR
WNT1	Wnt family member 1	AR
SPARC	Osteonectin	AR
TENT5/FAM36A	Terminal nucleotidyltransferase 5A	AR
MBTPS2	S2P	XLR

BRIL: Bone-restricted interferon-induced transmembrane protein-like protein, PEDF: Pigment epithelium-derived factor, OASIS: Old astrocyte specifically induced substance, S2P: membrane-bound transcription factor peptidase, site 2

opausal women and men<50 years old, the use of BMD Z-scores is preferred; values <-2 are considered as "low for age" [3]. Alternatively, according to the International Osteoporosis Foundation (IOF), it is possible to use T-score also for young adults; values <-2.5, in combination with history of chronic disease affecting the skeleton, are indicative of osteoporosis [4].

Regarding paediatric population, osteoporosis is rare but is now increasingly diagnosed in high risk patients; more and more cases are being discovered and treated. The growing skeleton is unique in that there is not only bone remodeling (continuous bone turnover cycle), but also bone modeling, i.e. accumulation of new bone, which gradually changes bone dimensions and enables growth. What is more important, is the fact that childhood is the "window of opportunity" for peak bone mass (PBM) achievement. Not surprisingly, it is estimated that a 10% increase in PBM may delay the onset of osteoporosis by thirteen years [5]. In other words, PBM achievement predicts bone health in adulthood [6].

However, children are not small adults, therefore the definition of osteoporosis in this age group is totally different. According to the paediatric ISCD guidelines [2], low DXA BMD Z-scores alone (<-2 in lumbar spine and/or total body less head, corrected for bone size, where appropriate) are not sufficient for diagnosis. A significant fracture history should also exist: either at least one non-traumatic vertebral fracture (regardless of BMD Z-score values) or at least three low-energy long bone fractures for those patients aged <19 years or at least two, if the patients are smaller (<10 years old). Admittedly, established osteoporosis is rare in children, but prompt diagnosis and treatment are crucial.

Depending on the underlying cause, osteoporosis is further classified into secondary (90% of cases), as a result of a chronic disease and /or its treatment (e.g. chronic use of systemic corticosteroids) and primary or genetic (10% of cases), attributed to a heritable bone disorder, thus occurring usually earlier, the so-called "early onset osteoporosis". When no identifiable cause is found after a comprehensive diagnostic work up, the term used is "idiopathic osteoporosis" and this is a diagnosis of exclusion, which is now

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

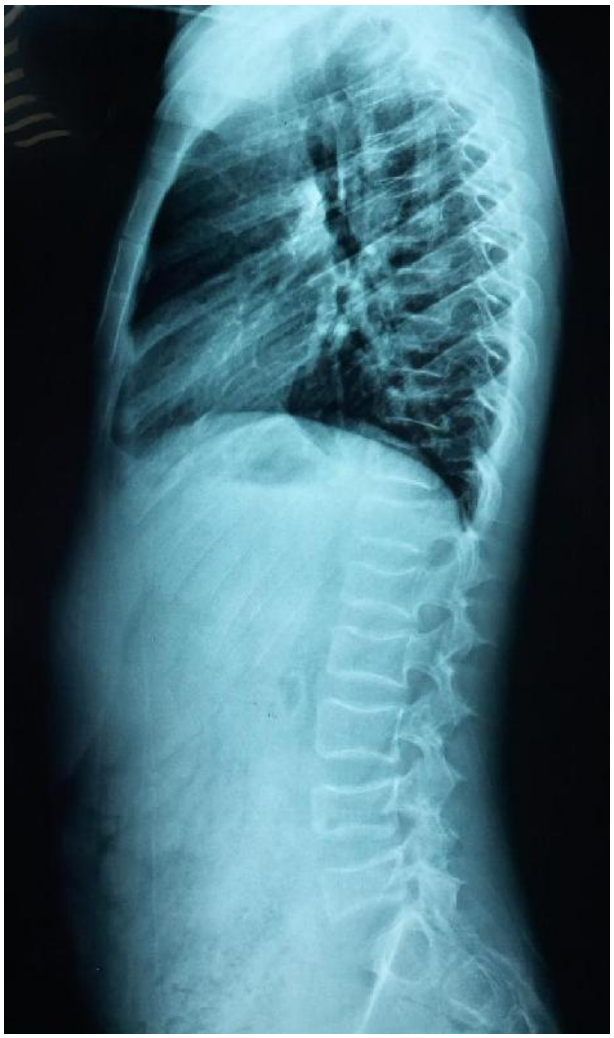

Fig. 1. *Multiple vertebral fractures of moderate severity in a 12-year-old boy with osteogenesis imperfecta (COL1A1 mutation) (Institute of Child Health archive)*

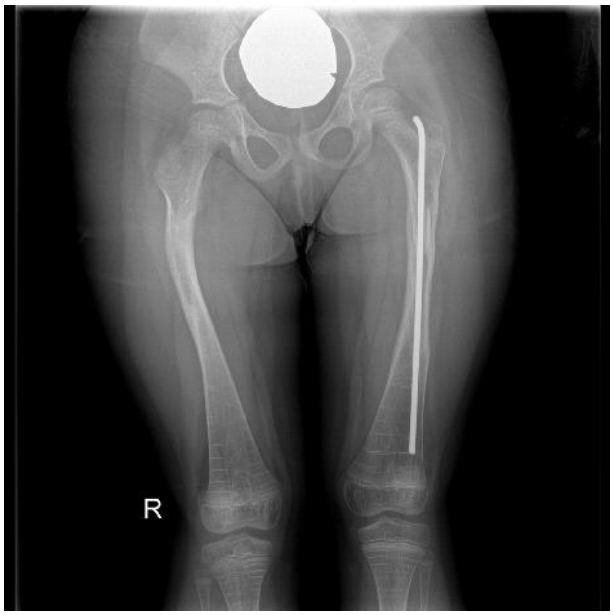

Fig.2. *Femoral deformities and rodding of left femur in a girl with osteogenesis imperfecta (COL1A2 mutation). Note the "zebra lines", due to treatment with zolendronic acid. (Institute of Child Health archive)*

less and less encountered, because of the discovery of new genes implicated in bone fragility [7].

This review will highlight the latest literature data on primary osteoporosis, which is genetic in origin and is suspected mostly in children and young adults. It is a group of heterogeneous inheritable disorders with different pathophysiology, depending on the gene involved. The intense research interest in these cases globally has enabled the scientific community to discover new metabolic bone pathways and diagnostic biomarkers and, most importantly, new treatments.

Types of primary osteoporosis and their pathophysiology

Genetic osteoporosis is attributed to monogenic disorders; however, with the advance in the diagnostic methodology, cases with a polygenic profile are also described.

Bone is a dynamic tissue; it undergoes considerable changes during growth. Even after growth plate fusion, bone remodeling continues for life and requires the complex coordination between the osteoblasts (bone formation), the osteoclasts (bone resorption) and the osteocytes. The differentiation and function of the aforementioned bone cells is regulated by specific signaling metabolic pathways. Moreover, the mineralization process is equally important for bone integrity and contributes to optimal bone quality.

Monogenic primary osteoporosis

The advent of extensive genetic testing not only of the index case but also of the whole family, has enabled the detection of > 35 monogenic disorders leading to early onset osteoporosis[8,9]. They show Mendelian inheritance and they are caused by mutations of genes which are very important in bone

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

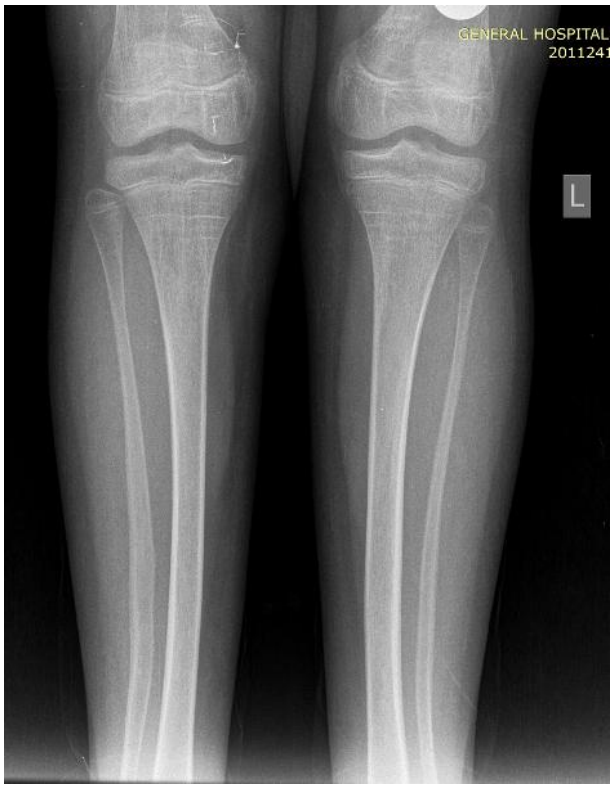

Fig.3. *Very slender and diffusely osteopenic tibiae and fibulae in a girl with osteogenesis imperfecta (COL1A1 mutation) (Institute of Child Health archive)*

homeostasis.

The most frequent entity of primary osteoporosis is osteogenesis imperfecta (OI) or brittle bone disease. It is an inherited connective tissue disorder, with prevalence of 1/10,000-1/20,000 births, caused mainly by mutations in COL1A1 or COL1A2 genes (85-90% of cases) [10]. These genes regulate the most abundant matrix protein, type I collagen [11], by encoding its two alpha chains. To date, eighteen other genes have been associated with the same phenotype and comprise the remaining 10-15% of cases. They are associated with the final stages of collagen modification or they play part in osteoblast differentiation or in the mineralization process. The list of OI genes is illustrated in table 1.

OI shows remarkable heterogeneity in terms of severity, even within the same family and this implies the existence of genetic modifiers affecting the spectrum of the phenotype. The impact of the mutation depends on the function of the affected gene and the type of pathogenic variant. OI patients show a ten-fold increase in the probability of fracture at a young age (0-19years), compared to the general population, according to Danish data [12]. Apart from the increased fracture rate (long bones and vertebral bodies, even in utero, in severe cases) (Fig.1, 2), these patients may also have bone deformities, severely osteopenic and slender bones (Fig.3), as well as short stature. OI is also characterized by its extraskeletal manifestations, such as deafness blue/grey sclerae, dentinogenesis imperfecta, joint laxity, basilar invagination, cardiac valve prolapse, easy bruisability and pulmonary hypoplasia in severe cases [13].

In terms of OI clinical types, the revised Sillence classification, which includes five different phenotypes, irrespective of the gene involved, is now used in clinical practice. Type I is the mildest form, type II is lethal, type III is the most severe form and type IV (no blue or grey sclerae) is of moderate severity. The new type V OI is distinct from the others in that there is calcification of the intraosseous membranes and hypertrophic callus post-fracture [14].

There are cases of genetic osteoporosis where there are no extraskeletal manifestations or severe bone deformities, despite a significant fracture history. These patients may be diagnosed later in adulthood, because their fractures are initially attributed to the active lifestyle of childhood, when in fact there are underlying mutations in specific genes, which play a pivotal role in bone metabolism. To date, the following genes have been described in more detail:

SGMS-2: This gene encodes Sphingomyelin Synthase-2, which is implicated in the synthesis of sphingomyelin. This phospholipid plays an important role in cholesterol metabolism, being a major lipid of the plasma membrane and thus important for cell signaling. Its exact mechanism of action with regards to bone turnover is still under investigation. Patients carrying mutations of this gene present with autosomal dominant osteoporosis, thin cortices of the long bone and calvarial doughnut lesions [15, 16]. Another potentially distinctive feature of this disorder is the presence of neurological symptoms as the main extraskeletal defect, particularly facial nerve palsy, which is usually transient [15].

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

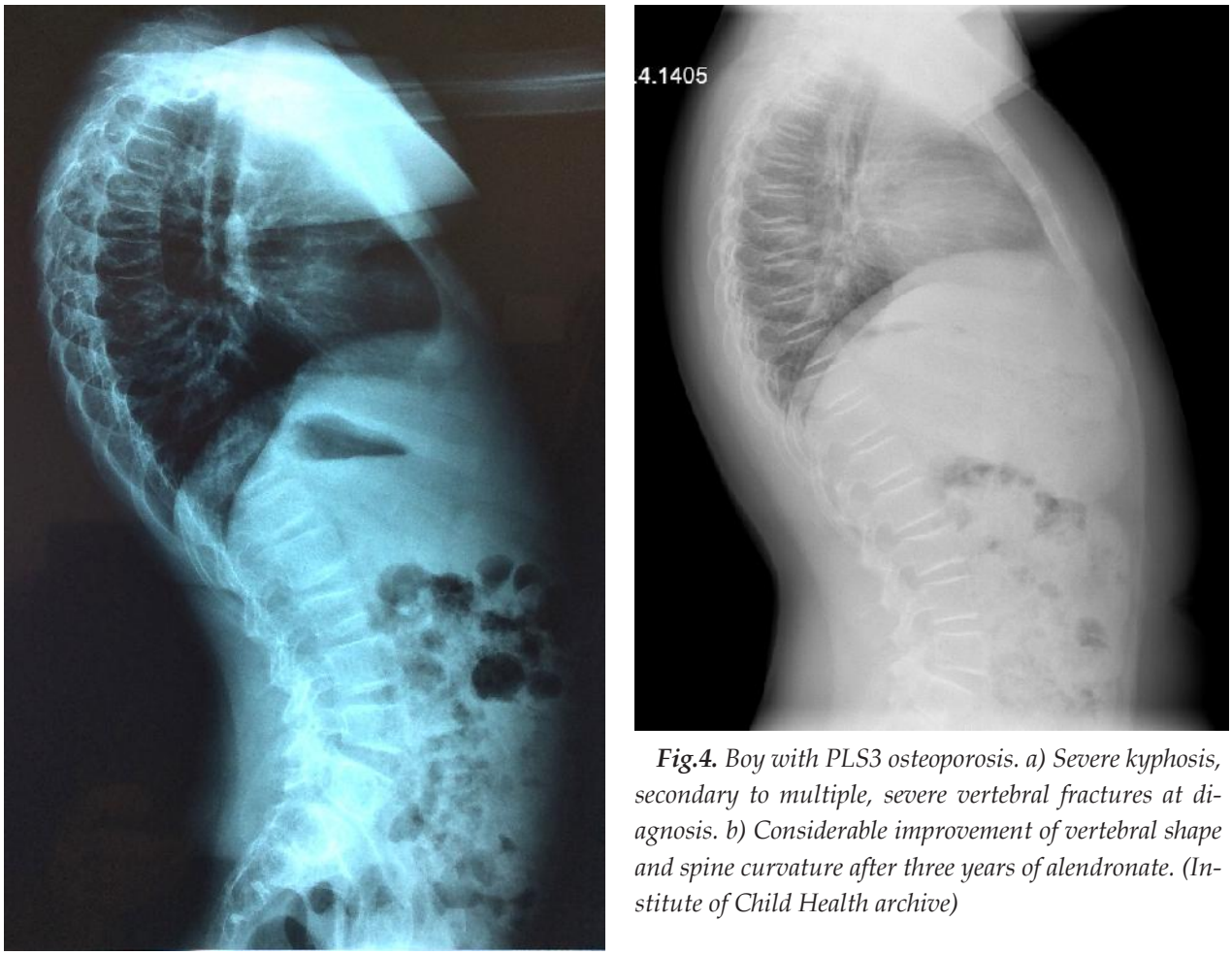

Fig.4. *Boy with PLS3 osteoporosis. a) Severe kyphosis, secondary to multiple, severe vertebral fractures at diagnosis. b) Considerable improvement of vertebral shape and spine curvature after three years of alendronate. (Institute of Child Health archive)*

PLS-3: Mutations of this gene cause X-linked osteoporosis, especially of the spine [17, 18]. As expected, male subjects show a more severe phenotype than their female counterparts, who can also present with fractures, usually at a later stage in life [19]. Plastin-3, the protein encoded by this gene, is implicated in the function of osteocytes, which serve as the mechanoreceptors of bone. This protein contributes to the integrity of the cytoskeleton, defining the shape of these bone cells [20].Dickkopf-1 (DKK-1), an inhibitor of the WNT signaling pathway, has been found increased in these patients and this contributes to their unfavourable bone profile [21].

WNT1: This gene is implicated in the WNT-β-catenin metabolic bone pathway, which controls mature osteoblast differentiation and bone development [22]. A gene dosing effect is apparently present. This is because the biallelic mutations of this gene lead to severe autosomal recessive OI, whose hallmark is the presence of ptosis [23], whereas its heterozygous mutations may cause autosomal dominant osteoporosis. There is low bone mass, long bone fractures and particularly slender fibulae during childhood [24] and vertebral fractures (with subsequent kyphosis) in adulthood [25].Surprisingly, a specific biomarker for this disorder is fibroblast growth factor-23 (FGF-23, both intact and C-terminal), whereas sclerostin and DKK-1, markers which are directly implicated in the WNT pathway, were not significantly different than controls in one study [26].

LRP5: LDL receptor-related 5 is a co-receptor for WNT ligands, therefore its mutations lead to abnormal bone metabolism and usually low bone formation markers [27]. Of interest, homozygous mutations cause osteoporosis-pseudoglioma syndrome, which is an important differential of OI, as

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

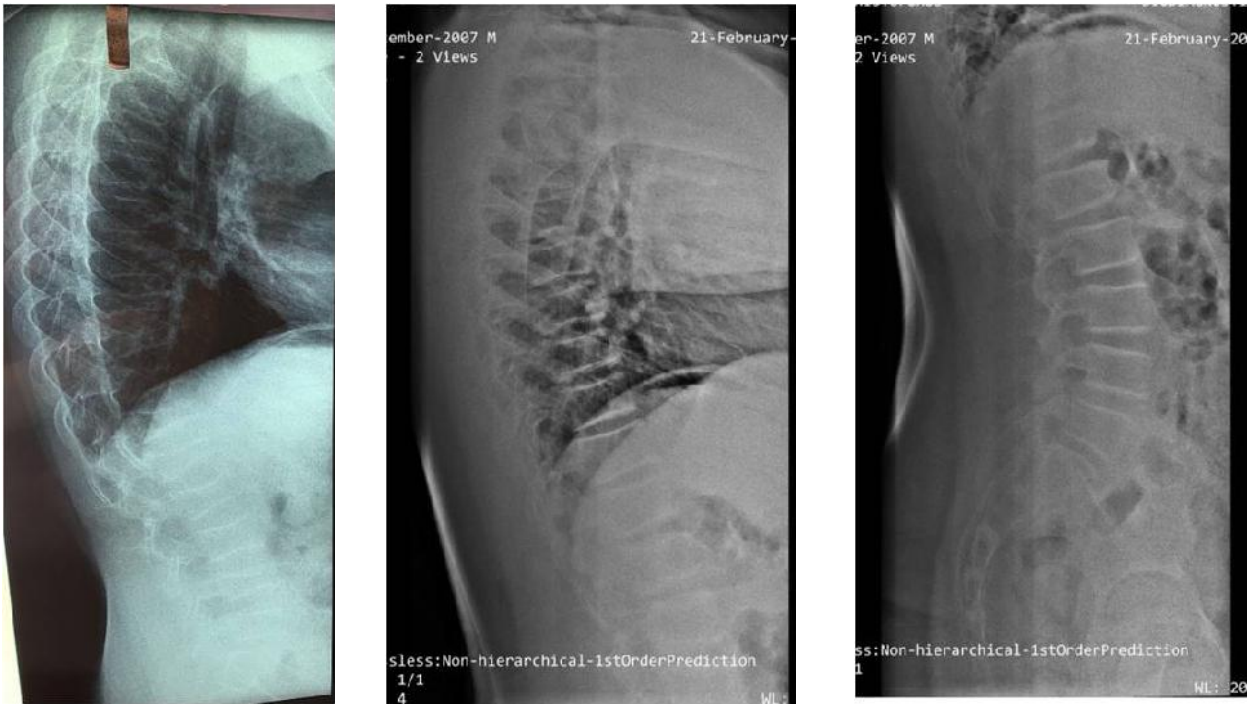

Fig. 5. *Boy with LRP5 osteoporosis. a) Kyphosis and severe, multiple vertebral fractures at diagnosis. b,c) Vertebral reshaping after three years on zolendronic acid. (Institute of Child Health archive)*

it combines early onset osteoporosis with blindness [28, 29]. On the other hand, heterozygous mutations cause osteoporosis with minimal or no eye involvement (Fig.5) [30].The presence of LRP5 variants is relatively common in cases with primary osteoporosis, estimated at 8.3%, according to a study of 372 patients [27]. These variants have also been associated with abnormal lipid profile and a tendency towards diabetes type II [31, 32].

NOTCH: Activating mutations of this gene enhance osteoclast maturation, through the RANK signaling mechanism, which in turn is affected by the NOTCH signaling pathway [33]. Hadju-Cheney syndrome results form autosomal dominant mutations of NOTCH2. Its main features are severe primary osteoporosis, combined with craniofacial dysmorphism and acroosteolysis [34]. Wormian bones may also be present. The key mechanism is the increased bone resorption, which is confirmed in specimens of bone biopsy [35].

TGF-β: Disorders TGF-β pathway lead to several skeletal diseases. This complex pathway is important for intracellular signal transmission, as it regulates cell activity in bone and cartilage. Depending on the mutations involved, the entities attributed to TGF-β disorders are Camurati-Engelmann disease, OI, Loeys-Dietz and Marfan syndromes [36-39].

For completeness, other monogenic diseases leading to early bone fragility are illustrated in table 2.

The polygenic aspect of primary osteoporosis

To assume that genetic osteoporosis is always monogenic is a rather simplistic approach and it does not account for the increased variability of phenotype amongst patients carrying the same disease variants. Thanks to genome-wide association studies, bone fragility is now considered multifactorial. In other words, genetic risk can be modified by the presence of common variants which explain the reduced bone mineral density [40, 41].

However, even in young patients who do not suffer from monogenic osteoporosis, their genetic profile maybe compatible with the presence of common fracture risk alleles [40]. In other words, it is possible that in some young patients their bone fragility is of polygenic rather than monogenic. This is a great diagnostic challenge; methods to quantify the polygenic contribution in cases of early-onset osteopo-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

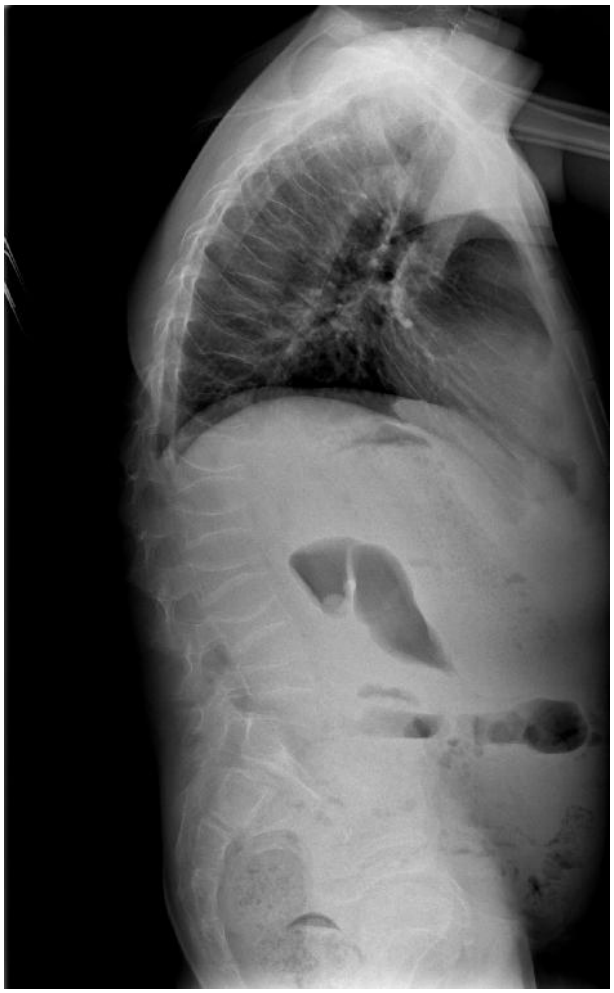

Fig.6. *Boy with severe osteoporosis (multiple, severe vertebral fractures), secondary to Crohn's disease. Of note, his first complaint was back pain. (Institute of Child Health archive)*

rosis are currently being explored. Epigenetics also contribute greatly to the understanding of osteoporosis occurrence. The term includes processes such as DNA methylation, non-coding RNAs (miRNAs) and histone changes. Collectively, they control gene expression without an effect on DNA sequences [42]. There is also the scenario of coexistence of two rare, different mutations in candidate genes for osteoporosis in the same patient; a case of a subject with both WNT1 and PLS3 pathologic variants has been reported [43].

When to suspect genetic osteoporosis

The earliest the primary osteoporosis is diagnosed, the better the outcome, especially in view of specific treatments available and also of the effect that such a diagnosis exerts on the patient and on the whole family. Given that this type of osteoporosis is considered "early onset", thus involving children and young adults, prompt intervention during the "window of skeletal growth" is of utmost importance. Referral should be made to a disciplinary team, led by a bone specialist, experienced in correctly diagnosing these rare disorders, carefully differentiate them from equally severe, secondary causes of osteoporosis (illustrated in Table 3) and aware of bone pathophysiology and growth potential.

A thorough history needs to be taken, starting from the prenatal period. Information of the presence of intrauterine fractures (reduced fetal movements), low bone mineralization and abnormal skeletal dimensions are clues to underlying, severe bone pathology. As a general rule, the smaller the age of the patient, the more likely the presence of genetic osteoporosis (after exclusion of non-accidental injury in non-verbal patients, i.e. infants and toddlers). Fracture history is obviously crucial and should be elucidated in detail (number of fractures, mechanism, location, treatment, review of all imaging studies available). The presence of vertebral fractures is also key to diagnosis; the patient is asked specifically for back pain. Lifestyle profile (exercise, diet) is explored, as well as past medical history for comorbidities and the use of medications known to affect the skeleton (e.g. corticosteroids). Growth parameters should be plotted on growth charts and pubertal status should be assessed. Lastly, family history is recorded meticulously, targeted not only on the presence of early osteoporosis in other members, but also on its complications, such as cardiac valve insufficiency, deafness, nephrocalcinosis and disorders of vision. Of note, the parents should be asked for their place of origin, in view of the fact that in closed, rural populations there might be consanguinity or particular gene mutations affecting the skeleton [44].

Special clues to the diagnosis of primary osteoporosis can be found during a head-to-toe clinical examination. Joint and skin laxity, grey or blue sclerae, tenderness on palpation of vertebrae, kyphosis

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 2.

Monogenic forms of osteoporosis

Syndrome	Gene	Encoded protein	Type of inheritance
Bruck 1	FKBP10	65kDa FK506-binding protein	AR
Bruck 2	PLOD2	Lysyl Hydrolase 2	AR
Hajdu-Cheney	NOTCH2	Notch receptor 2	AD
Ehlers-Danlos 1	PLOD1	Lysyl Hydrolase 1	AR
Ehlers-Danlos 2	FKBP14	FK506-binding protein 14	AR
Cole-Carpenter 1	P4HB	Prolyl 4-hydroxylase subunit β	AD
Cole-Carpenter 2	SEC24D	SEC24 homolog D	AR
Cutis laxa 2A	ATP6VOA2	ATPaseH+ transporting VO subunit	AR
Cutis laxa 2B	PYCR1	Pyrroline-5-carboxylase reductase 1	AR
Geroderma osteodysplasticum	GORAB	Golgin, RAB6 interacting	AR
Familial expansile osteolysis	TNFRSF11A	TNF receptor superfamily member 11A	AD
Gnathodiaphyseal dysplasia	ANO5	Anoctamin 5	AD

and skeletal malformations raise suspicion towards inheritable causes of osteoporosis rather than acquired. A very helpful finding in some cases is the presence of yellow-brown or grey, transparent teeth, suggestive of dentinogenesis imperfecta, therefore dental inspection should always be part of the clinical examination.

However, the differential diagnosis between the monogenic forms of primary osteoporosis can be challenging, as the clinical signs show significant overlap; nevertheless, as data are accumulating, it is possible to look for specific features. For instance, in PLS3 patients there seems to be a tendency towards severe vertebral fractures and kyphosis at a young age, as a hallmark [45] (Fig.4), whereas this type of fractures appears only in adulthood in the WNT1 osteoporosis [19, 46]. Another key differential is the presence of extraskeletal manifestations. For example, WNT1 mutations also affect the central nervous system, therefore neurological abnormalities, such as epilepsy, cerebellar hypoplasia and global developmental delay raise suspicion towards this direction [47].The same is true for SGMS2 cases, where nerve palsies are occasionally observed, e.g. transient facial palsy, along with global developmental delay [45].

Diagnostic work up

As mentioned in the introduction, there are specific diagnostic criteria for osteoporosis in children and young adults. When these criteria are met, the next important step is to exclude causes of secondary osteoporosis and child abuse in infants and toddlers with unexplained fractures. Diseases with special treatment and potentially life-threatening are not to be missed. For example, the first presentation of leukaemia and Crohn's disease can be a vertebral fracture (Fig. 6).On the other hand, there are high profile cases in courts where parents of babies with OI have wrongly been accused of non-accidental-injury and vice versa, i.e. small children being investigated for an underlying genetic disorders, when in fact they have been victims of abuse [48,49].

Therefore, after obtaining a comprehensive medical history and performing a thorough clinical examination, a laboratory evaluation of blood and urine is necessary, targeting known causes of secondary osteoporosis. As a general rule, basic bone profile is always performed (including 24h urine collection for calcium or spot sample for uCa/uCreat of a fasting, 2nd morning void), along with complete blood count, erythrocyte sedimentation rate, C-reactive protein, thyroid function tests and testosterone in boys. Thereafter, depending on the clinical scenario, other hormonal investigations can be undertaken, along with tryptase, ferritin and celiac screening, as

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 3.

Secondary causes of osteoporosis that need to be excluded in every patient with early bone fragility

Disease groups	Others
Endocrine Growth hormone deficiency or excess Hypogonadism Hyperthyroidism Hyperparathyroidism Diabetes 1 and 2 Hypopituitarism Cushing's disease/syndrome	Cerebral palsy HIV Chronic immobility Duchenne's muscular dystrophy Bone marrow transplantation Solid organ transplantation Renal failure Mastocytosis Pregnancy/Breastfeeding
Chronic inflammation Inflammatory bowel disease Systemic lupus erythematosus Rheumatoid arthritis Sarcoidosis	
Haematology Leukaemia Lymphoma Thalassaemia major Haemophilia Multiple myeloma Haemochromatosis	Medications Corticosteroids Chemotherapy Anticonvulsants HAART Proton pump inhibitors Heparin Aromatase inhibitors LHRH agonists Tamoxifen Thiazolidinediones
Malnutrition/malabsorption Cystic fibrosis Chronic liver disease Rickets Coeliac disease Short gut syndrome Anorexia nervosa	
Inborn errors of metabolism Gaucher's disease Hypophosphatasia Glycogen storage disease Homocystinuria Mucopolysaccharidoses Pompe disease	

HIV: Human Immunodeficiency Virus, HAART: Highly Active Anti Retroviral Treatment, LHRH: luteinizing hormone-releasing hormone

is shown in table 4. There is no paediatric consensus on the diagnostic use of bone turnover markers at a young age; however, they are valuable tools for monitoring of anti-osteoporosis treatment.

Imaging studies necessary for diagnosis include dual-energy X-ray absorptiometry (DXA), review of all X-rays available to check for fractures and deformities, as well as lateral X-rays of the spine, to look for vertebral fractures, especially if there is low BMD, kyphosis, height loss or tenderness on palpation of the spine. In cases where non-accidental injury is suspected, a skeletal survey of the whole skeleton is performed (baseline and follow up), in order to detect new and old fractures and pick up specific signs suggestive of an intrinsic bone defect (e.g. diffuse osteopenia, rachitic changes, slender bones, wormian bones), thus contributing to the differential diagnosis [50].

Ideally, a transiliac bone biopsy should be obtained in order to study the pathophysiology behind a particular phenotype, i.e. to differentiate between high and low bone turnover states, using histomor-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 4.

Diagnostic laboratory work up to exclude secondary osteoporosis in patients with early bone fragility	
First line, indicated in all patients	
Test	To exclude
Basic bone profile*	Disorders of calcium and phosphate metabolism, hypercalciuria, HPP
CBC	Haematological disorders
ESR, CRP	Inflammatory conditions
TFTs	Hyperthyroidism
Testosterone	Male hypogonadism
Glucose, HbA1C	Diabetes mellitus
Bone turnover (e.g. PINP, CTx)	Baseline before bone-active treatment
Second line, depending on history and examination	
Tryptase	Mastocytosis
Ferritin	Haemochromatosis
Sex hormones	Delayed/absent puberty
IGF-1	Acromegaly or GH deficiency
Urinary cortisol	Cushing's syndrome
Coeliac antibodies	Coeliac disease
Fat-soluble vitamins	Malabsorption

**: Basic bone profile includes (fasted serum and fasted 2nd morning void): calcium, phosphate, magnesium, alkaline phosphatase, creatinine, albumin, liver function tests, 25(OH)D, parathormone and urinary calcium/urinary creatinine, urinary phosphate/urinary creatinine*

CBC: complete blood count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, TFTs: thyroid function tests (free T4 and TSH), IGF-1: insulin-like growth factor 1, PINP: procollagen type I N-propeptide, CTx:carboxy-terminal cross-linking telopeptide of type I collagen, HPP: hypophosphatasia

phometry techniques. New, promising treatments target different bone metabolic paths, so this information could facilitate the best possible selection of treatment for each individual case. However, this diagnostic approach is too interventional, requires expertise and special equipment, therefore it is not at all popular in routine clinical practice.

When secondary causes have been excluded, appropriate genetic tests are the last resort, in an effort to reveal the underlying cause of osteoporosis. Suspicious family history and clinical signs pointing to a genetic cause show great variability, therefore it is necessary to confirm this suspicion with genetic work up. In addition, identifying the disease-causing mutation enables appropriate genetic counseling (and family planning, as a result), enables prognostication and allows treatment plans, tailored to the patient's needs. Taking into account that COL1A1 and COL1A2 mutations comprise 85-90% of the genetic cases, these two genes should be checked for in every analysis, as a minimum. With the advent of new, cost-effective diagnostic technology, it is now possible to screen for other monogenic forms of primary osteoporosis, by studying appropriate gene panels for bone fragility using next generation sequencing (NGS). These commercially available panels should be constantly updated, to include new candidate genes for osteoporosis. This pitfall may be avoided by using whole exome sequencing (WES).

As more and more genes are being discovered as causative factors of early osteoporosis, it is very important to have access to data which can be reanalyzed in due course. Performance of WES or whole genome sequencing (WGS) is now possible and contributes to the constantly accumulating knowledge on these rare disorders. By using these methods, the sequencing data are filtered appropriately to detect potentially disease-causing variants. It is hoped that

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

with time, these methods will be more and more accessible. In fact, with the contribution of bioinformatics, WGS may become standard practice in the future, because it may detect coding or non-coding or structural variants [51]. Until then, guidelines for genetic work up will vary between different centers and different countries, depending on the case load, local resources and available expertise. It should be noted that no genetic test is a substitute for detailed history and clinical assessment; in other words, a meticulous description of the phenotype and the family tree are prerequisites for the interpretation of genetic results, as they enable their filtering and interpretation. This is particularly true when a "variant of unknown significance" (VUS) is detected.In this scenario, the study of family trios can be proved very useful. According to this approach, the parents of the index case are also screened, to check the inheritance pattern of a specific variant.

Therapeutic approach of genetic osteoporosis

The rarity of the primary osteoporosis cases, combined with the usually small age of the patients leads to relatively few data from clinical studies, with regards to bone-active medications. Most research works focus on OI, whereas the other monogenic forms have not been extensively studied.In principle, a skilled multidisciplinary team, with expertise in bone disease in the young subjects, undertakes the challenging task of treating the patient using a personalized approach.

Lifestyle advice is always given. All patients with primary osteoporosis need to ensure adequate dietary intake of calcium and vitamin D and take supplements, where appropriate. In fact, small studies have shown a beneficial effect of calcium and vitamin D co-administration on bone mineral density [52, 53]. Exercise is equally important and plays a protective role for bone health [54]. In adolescents and young adults, advice on avoidance of smoking and alcohol use is offered, as these habits can have deleterious effects on the skeleton. Moreover, if there is a history of a comorbidity that affects bone health, it should also be addressed efficiently [7], e.g. a patient with OI and uncontrollable asthma, requiring frequent administration of oral steroids.

Supportive treatment is also crucial; it involves proper fracture management, aiming at improving mobility, as well as physiotherapy, occupational therapy, orthopaedic procedures to improve skeletal malformations (e.g. rodding, Fig.2) and mobility aids. Depending on the severity of osteoporosis, first line, bone active medications, with proved efficacy in improving BMD and quality of life (QOL) are bisphosphonates, which are used "off label" during childhood, in most countries. Thanks to the discovery of the aforementioned rare, monogenic forms of primary osteoporosis, new bone metabolic pathways have been investigated, allowing research on new drugs, with a view to a more individual approach towards the patient, for the best possible therapeutic results.

Bisphosphonates (BPs) are the first line treatment in primary osteoporosis. Most literature data describe their effects in OI patients and the majority focus in intravenous treatment with either pamidronate or zolendronic acid. BPs show an anti-resorptive effect on bone, i.e. they act on the osteoclasts, by binding to hydroxyapatite and inducing osteoclast apoptosis. They don't contribute to the accumulation of new bone; rather, they prevent bone loss, they promote vertebral reshaping (Fig.4, 5) and the net result is an increase in BMD. Their effects when given either orally or intravenously on fractures is less clear; a recent Cochrane review reports that no firm conclusion can be drawn regarding bisphosphonate use and fracture incidence [55].

Nevertheless, they are considered first line treatment of all forms of primary osteoporosis for the time being. On the other hand, there are major concerns surrounding their use. For example, BPs are retained in bone for many years, therefore it is important to discuss a future pregnancy with a female patient of reproductive age. Despite the fact that a small case study did not report major events during pregnancy, such as teratogenesis, neonatal complications cannot be totally excluded [56], therefore it is advisable to avoid BPs for at least a year before pregnancy [57]. Another vivid discussion in on the use of BPs and the risk of osteonecrosis of the jaw and also of atypical femoral fractures [58].

Another therapeutic agent which acts on osteo-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

clasts is denosumab, a monoclonal antibody which acts as a RANKL inhibitor; it increases BMD and has been approved for post-menopausal osteoporosis. As RANKL is involved in the osteoclast maturation, its inhibition by this monoclonal antibody blocks this process. Given that most primary osteoporosis cases are diagnosed in childhood, its use for this indication in this particular age group is thus far limited and research is ongoing. Important points for clarification are the rebound of increased bone turnover (risk of severe hypercalcaemia in young patients [59]), the occurrence of vertebral fractures after cessation of treatment, as well as the duration of the therapeutic effect [60]. In other words, more paediatric studies are needed for its use in genetic osteoporosis. Regarding pregnancy, it can be hypothesized that no major effects will be observed after stopping denosumab. This is because the drug is not retained in the skeleton.

There are also anabolic treatments available and are also being investigated in primary osteoporosis. Currently there is no formal consensus on their use in such cases, however they are mentioned here for completeness, given that the discovery of new genes implicated in osteoporosis has led to the study of new metabolic pathways, regulating bone formation rather than resorption.

Teriparatide (human PTH analogue) has been in use for many years; due to a black-box warning for risk of osteosarcoma in young rats, its use in paediatric patients is still contraindicated. There are numerous OI cases of young adults [58], where teripatide has been prescribed. It activates osteoblasts, therefore contributes to increased bone formation. The TOPAZ study looks into the effect of coadministration of teriparatide and zolendronic acid (or zolendronate) in adults with OI [61].

Growth hormone (GH) also shows an anabolic effect, as it stimulates bone growth; however, it is helpful when GH deficiency coexists and not in the OI scenario, when usually short stature is an intrinsic defect, correlated with disease severity. Nevertheless, it has been given off-label in cases of OI type I and IV [55].

Relatively new drug discoveries in the field of osteoporosis, with trials under way on genetic osteoporosis, are targeted towards the WNT metabolic pathway (anti-sclerostin antibodies, i.e. setrusumab and romososumab) and the TGF-β pathway (fresolimumab and losartan).

Sclerostin is a potent WNT inhibitor which is produced mainly by osteocytes and contributes to the control of bone formation [62]. The sclerostin antibody romosozumab was approved for osteoporosis treatment in 2019 and there are trials of this drug on OI patients [63]. Caution should be exerted with regards to its cardiovascular safety profile, given the contribution of WNT pathway in vascular calcifications and atherosclerosis [64]. Setrusumab is another sclerostin inhibitor and is also being investigated in adults with moderate OI [65].

Fresolimumab is related to the TGF-β pathway, which influences both bone formation (reduced osteoblast function) and-mostly-bone resorption, through stimulation of osteoclastogenesis [66]. It is a monoclonal antibody which blocks TGF-β. Animal studies have shown its efficacy in increasing bone mass and improving bone quality [67]. Currently it is being tried in adult patients with moderate or severe OI [68]. Losartan, an angiotensin II type 1 receptor blocker, may also inhibit TGF-β signaling [69]. This agent has been tried in Camurati-Engelmann syndrome [70].

Future developments in primary osteoporosis

As the effect of epigenetics on osteoporosis is more and more highlighted in the literature, numerous efforts are made towards identifying more specific and sensitive biomarkers for fracture occurrence. Non-coding RNAs, such as micro-RNAs (miRNAs) act as epigenetic regulators involved in the control of gene expression, affecting bone metabolism (both formation and resorption), amongst other biological processes [71].For diagnosis and treatment monitoring, the study of miRNAs is expected to modify our approach to osteoporosis. They can be easily measured in many different biological fluids (e.g. saliva [72] or urine [73] and reflect lifestyle and general health status for each individual, in relation to the osteoporosis risk.

Revolutionary treatments which are very hopeful and expected to change the therapeutic landscape

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

of primary osteoporosis, are stem cells administration and treatments aiming at correcting the gene involved. Back in 2005, adult mesenchymal stem cells (MSCs) were given to six children with severe OI and the results were encouraging, in terms of fracture rate and growth [74]. As a next step, an ambitious, two-armed study is under way (BOOSTB4), where fetal MSCs are administered as antenatal treatment in OI cases, i.e. in utero (1st arm, MSCs given during the 2nd and 3rd trimester) or postnatally (2nd arm, MSCs given after birth). The follow up period will last for ten years [75].Although the MSCs seem promising, they are not curative, as the patient will end up having a mixed population of bone cells, i.e. normal and abnormal. There is also the theoretical risk of the MSCs evolving into cancer cells. The research on these matters is in progress.

The efforts for a curative solution in the field of primary osteoporosis are ongoing, with the exploration of gene and cellular therapy approaches. Sophisticated, new technologies targeting the mutated gene are being developed, such as prime editing, zinc finger nuclease, TALEN and CRISPR-CAS [76]. Antisense oligodeoxyribonucleotides to silence the dominant allele in OI are tested on an experimental level [77].A detailed description of these methods is beyond the scope of this review.

Conclusions

The field of genetic osteoporosis is constantly expanding. Exciting developments are awaited, both diagnostic and therapeutic, as new metabolic bone paths are revealed. In all rare diseases, increased awareness shortens the patient's diagnostic journey and leads to prompt interventions, with the ultimate goal of improving quality of life. This is especially important, when it comes to children and young adults, i.e. the usual age group with primary osteoporosis.

Lateral thinking is crucial in the clinical scenario of a young patient with history of recurrent fractures, especially when they are low energy fractures of if they involve the vertebrae. Careful physical examination of all systems for possible clues of primary osteoporosis and detailed history, with emphasis on family tree may be revealing. It is equally important to exclude treatable, secondary causes of osteoporosis at the same time and non-accidental injury in infants and toddlers. With the advent of sophisticated technology in genetics and the hope that this will become more and more cost effective and accessible in medical centers worldwide, case numbers will probably rise and a greater number of patients will benefit from new treatments. A

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REVIEW

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Paget's disease of bone

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ABSTRACT

Paget's disease of bone is the most common metabolic bone disease after osteoporosis and affects 2-4% of adults over 55 years of age. Its etiology is only partly understood and includes both genetic and environmental factors. The disease may be asymptomatic and can be uncovered incidentally on x-ray or in biochemical tests performed for another condition. It can also manifest itself with bone pain, deformity, fracture or other complications. Paget's disease is diagnosed by x-rays and in general has very typical radiological features, but nuclear bone scans define the extent of the disease. Plasma total alkaline phosphatase activity is the most clinically useful indicator of disease activity. It is elevated in most untreated patients, but may be within the normal range in patients with monostotic or limited disease. Bisphosphonate therapy is indicated for patients with symptoms and should also be considered in patients with disease sites that suggest a risk of complications, such as long bones, vertebrae or base of the skull. Orthopedic surgery in Paget's disease patients includes almost the correction of fractures and arthroplasty.

KEYWORDS: paget's disease of bone, bone remodeling, bisphosphonates, alkaline phosphatase, treatment.

Introduction

Paget's disease of bone (PDB) is a chronic focal disorder of bone remodeling, affecting one (monostotic form) or more bones (polyostotic form) which are typically enlarged and deformed. The disease was first described in England, in 1877, by Sir James Paget who defined it with the name of "osteitis deformans" [1]. The disease mainly involves the axial skeleton, such that the pelvis (70%), femur (55%), lumbar spine (53%), skull(42%), and tibia (32%) are preferentially affected. Clinically,

the disease result in symptoms of bone pain, deformity, and pathological fracture. Osteoarthritis related to bone deformity and subchondral sclerosis is a common consequence and frequently requires arthroplasty. Patients with PDB also have

an increased risk of developing osteosarcoma, although rare (0.3% of PDB patients), and some families have been described in which PDB is accompanied by giant cell tumours [2].

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Epidemiology

PDB appears usually after the age of 40, being slightly more common in men than in women. It has been described almost worldwide, with an irregular geographical distribution. It primarily affects patients of British descent, being common (around 4%) in England , areas of Australia, New Zealand and North America and rare (less than 1‰)in Asia, Scandinavia and Africa.[3,4]. Most epidemiological studies

have documented a gradual decrease in the prevalence and incidence of PDB over the years, which is associated with a parallel decline in mortality and clinical severity[5],

Although the cause of this reduction is not completely understood, environmental changes, such as different migratory patterns, improved diet, sedentary lifestyle

and decrease in the exposure to viral infections and zoonoses, might play a role [4],

although no significant change in other regions such as Italy and the USA have been reported [6,7].

Etiopathogenesis

It is generally believed that the primary cellular abnormality in PDB is in the osteoclasts. Pagetic osteoclasts are mainly affected, experimenting an increase in number and size and containing more nuclei than normal osteoclasts and produce increased amounts of interleukin 6, and their precursors are hyper-responsive to 1,25-dihydroxy-vitamin D and receptor activator for nuclear factor κB (NFκB) ligand (RANKL) [8]. This results in an elevated metabolic osteolytic activity, coupled with increased bone formation by osteoblasts, which are apparently normal [9].

In PDB there is loss of the normal regulation of bone resorption and formation, with the process biased towards one or the other depending on the phase of the disorder.

There are three phases. The first is a lytic phase in which normal bone is resorbed by numerous, enlarged and more nucleated than normal osteoclasts and bone turnover is markedly increased. Secondly, a mixed phase of lytic and blastic activity characterised by rapid increases in bone formation from numerous osteoblasts.

The newly synhesised bone is abnormal with collagen fibres deposited in a haphazard way. There is both osteoblastic and osteoclastic activity, but formation becomes

dominant. Finally, there is sclerotic phase in which bone formation predominates, but the formed bone is disorganized (woven bone) and is weaker. The resultant bone has

altered and often abnormal architecture [10].

Despite the remarkable progresses of the last 2 decades, the pathogenetic mechanisms leading to these alterations in osteoclast phenotype and the development of PDB remain in part unknown and probably include either genetic or environmental causes.

Genetic factors

The presence of a familial predisposition in PDB has been known for many years.

Several genes and loci that predispose to familial PDB have been identified by a combination of linkage analysis in families and genome wide association studies (GWAS) in unrelated individuals.

Sequestosome 1 gene (SQSTM1): Mutations affecting the SQSTM1gene currently represent the major genetic cause of adult PDB and have been described in

approximately 25%–40% of familial cases and in up to 10%–15% sporadic cases in various patient series[11]. Despite SQSTM1 and other rarer mutations have been found in a relevant number of familial PDB-cases from different countries, their prevalence remains very low in patients with sporadic disease, and at up to 40%–50% of familial cases do not yet have a recognized mutation. This suggests the presence of

additional predisposition genes such as **Germline Mutations** associated with PDB and/or PDB related disorders such as: Tumour Necrosis Factor Receptor Superfamily Member 11A(TNFSRF11A) gene, Zinc Finger Protein 687 (ZNF687)gene, Profilin 1(PFn1)gene, Valosin containing protein(VCP)gene and **susceptibility**

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

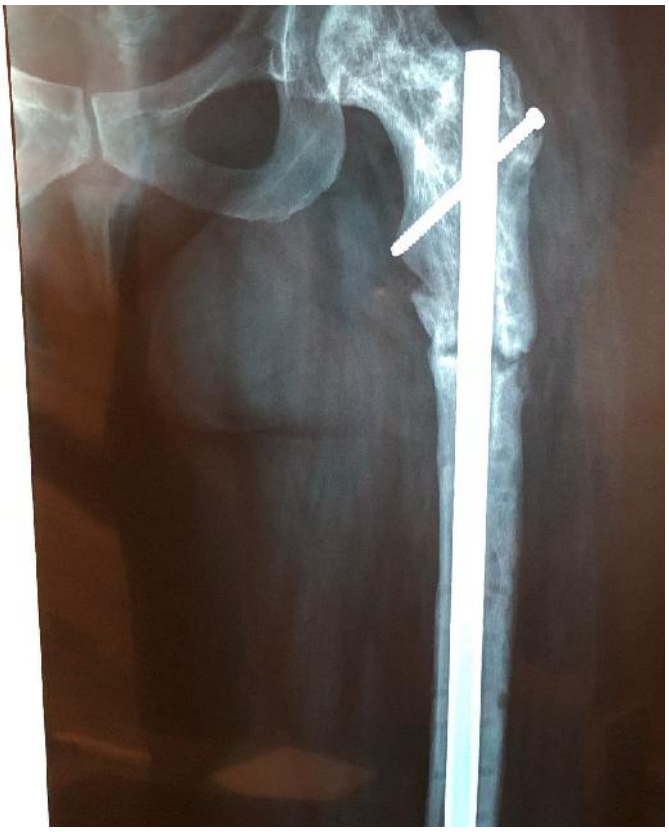

Fig.1. X-ray from a patient (37 years-old woman) with PDB affecting the left femur showing alternating areas of osteolysis and osteosclerosis with a pathologic fracture fixed intramedullary nail. (author's archive)

variants like: Optineurin(OPTN)gene, Colony Stimulating Factor 1(CSF1)gene, Ras and Rab Interactor 3(RIN3)gene, Promyelocytic Leukaemia Gene(PML)gene,Transmembrane 7 Superfamily Member 4(TM7SF4) gene[12]etc.

Enviromental factors

The possible involvement of viral factors in the pathogenesis of PDB has been reported since the early 1970s [13], when virus-like inclusions were demonstrated first in the nucleus and then in the cytoplasm of pagetic osteoclasts using electron microscopy. These inclusions consist of groups of microtubules, which are present either in a compact paracrystalline array or are scattered in a more random fashion. The pagetic microtubules are similar to the nucleocapsids of two paramyxoviruses, measles virus (MV) and respiratory syncytial virus (RSV), showed identical dimension, and have been found in several studies in the past years[14,15).

Other research groups have hypothesized an association between another paramyxovirus, the canine distemper virus (CDV), and PDB[16]. The nature of these bodies is still controversial, since other attempts which were made to replicate these findings in bone and blood samples from PDB patients, report negative results [17,18] It has been suggested that they could be protein aggregates resulting from the dysregulation of the autophagy system [19]. However, recent studies have shown that the MVNP protein is associated with the upregulation of IL-6 and IGF1 in osteoclasts from mouse models and PDB patients, which could suggest a role for measles virus in the alteration of bone formation seen in these patients [20, 21].

PDB has also been linked to other factors such as poor calcium and vitamin D intake, consumption of uncontrolled beef meat during childhood , consumption of not purified water[22], contact with dogs during early years [23], an excessive mechanical loading on the skeleton and exposure to some environmental toxics [24].

However, despite all these environmental factors have been associated to an increased risk of PBD in some patient cohorts, no conclusive evidence can be drawn and complicate our understanding of the genetic mechanisms of the disorder. In this respect, a potential unifying mechanism linking genetic and environmental factor in the pathogenesis of PDB, yet to be demonstrated as such, could be represented by

epigenetics and miRNAs, although currently there are small preliminary studies about their role in the pathogenesis of skeletal pagetic abnormalities[25,26].

Clinical features and complications

Many patients with Paget's disease of bone are asymptomatic, and the disease is discovered when a radiograph or bone scan is performed for another clinical indication or when an elevated serum ALP level is found on a multiphasic screening chemistry panel. Most of the clini-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

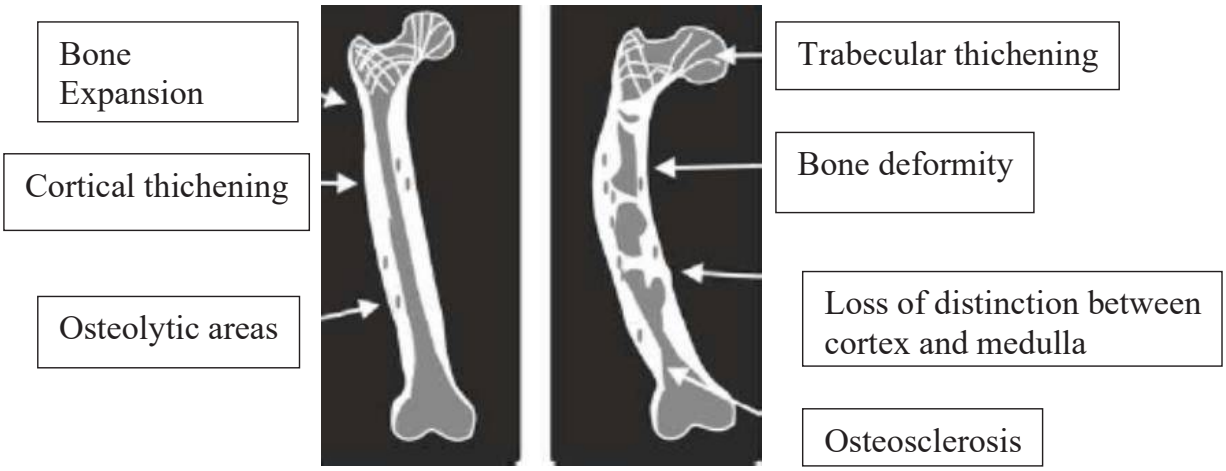

Fig.2 *Characteristic X-ray features of PDB*

cal manifestations of the disorder arise from the skeleton (Table1). In order of frequency, PDB affects the femur,spine, skull, sternum and pelvis, but can be found in any bone in the body [27]. The most common symptom is bone pain, which may be due to increased bone turnover or a complication such as osteoarthritis, spinal stenosis,or pseudofracture. Bone pain occurs in ~50% of cases presenting clinically and is usually mild to moderate in intensity and described as deep and aching. It can occur throughout the day and is often reported to be worse at night. Fractures with minimal trauma can occur through affected bone weakened by the elevated remodeling process with nonlamellar osteoid matrix. Approximately 10% of PDB patients sustain fractures. These fractures are termed "chalk-stick" or "banana"fractures because they are transverse and reflect the poor quality of the collagen matrix.(Fig 1). The most common neurological complication of Paget's disease is hearing loss associated with disease involving the

Skull. Originally thought to be caused by compression of the eighth cranial nerve, hearing loss is now believed to be due to cochlear damage [28]. With involvement of the skull, other cranial nerves can be affected. Rarely, basilar invagination may produce hydrocephalus. Paraplegia, quadriplegia, and other symptoms of spinal stenosis are rare, although the disease frequently involves vertebrae. Osteosarcoma is

a rare complication (present in less than 0.3% of cases) but should be suspected in patients who have a sudden increase in bone pain or swelling. Other rare complications include high-output cardiac failure, and hypercalcemia in patients who are immobilized. Clinical signs include bone deformity and warmth of the skin overlying an affected bone.

Diagnosis

A diagnosis of PDB is incidental in most cases, when an elevated level of alkaline phosphatase (ALP) is detected in the absence of liver disease in analyses that were performed for various reasons or the presence of suggestive radiographic changes ordered by other medical problems [29]. Other possible causes of increased ALP need to be excluded, including vitamin D deficiency, hyperparathyroidism, hyperthyroidism, renal osteodystrophy and malignancy. However, normal levels of alkaline phosphatase do not rule out the diagnosis[30]. Tests for specialized markers, such as bone-specific alkaline phosphatase(bALP) or procollagen type I N-terminal propeptide (P1NP), can be useful in patients with coexisting liver disease but otherwise offer little advantage over measurement of the total serum alkaline phos-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

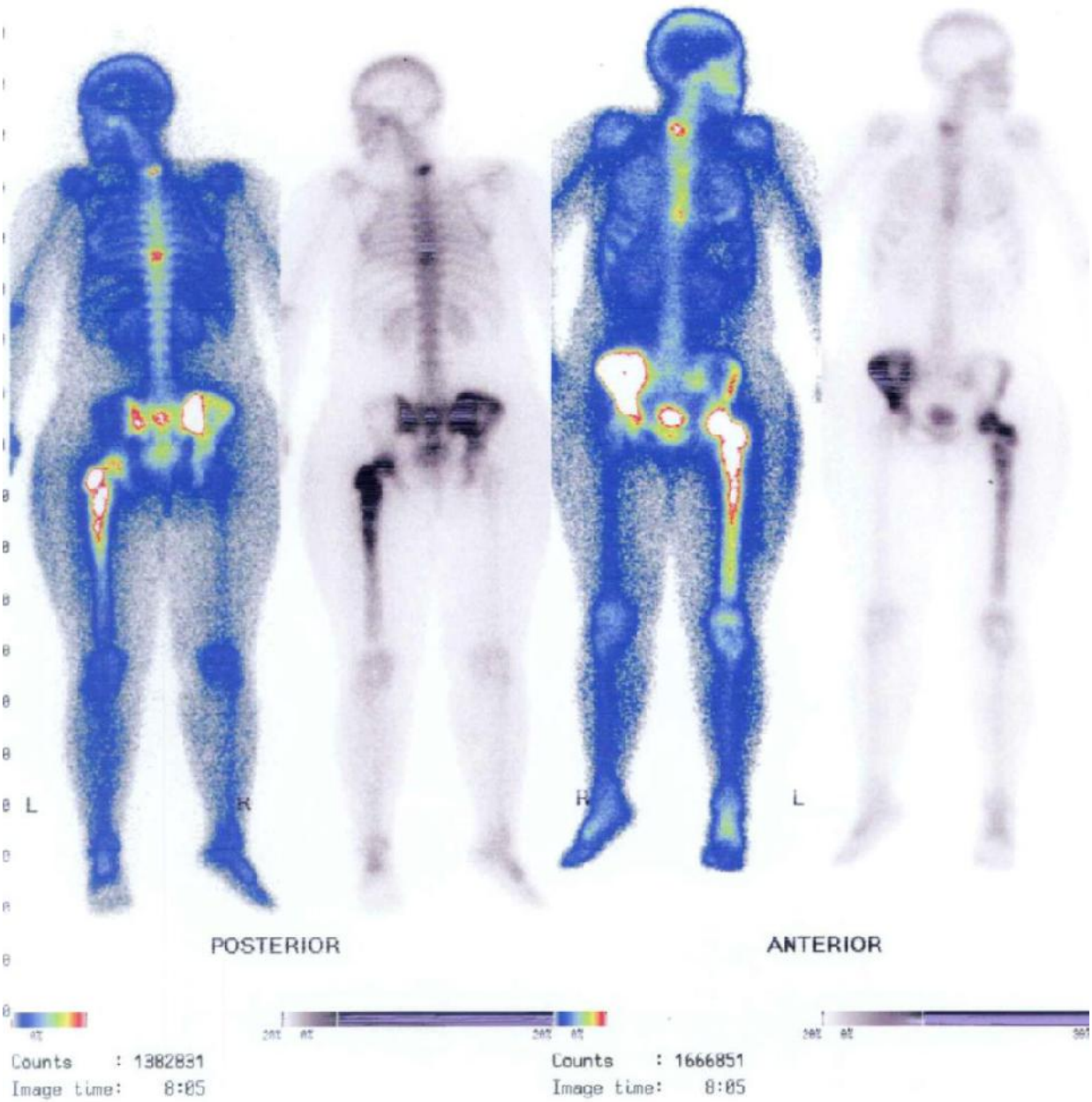

***Fig.3**. A radionuclide bone scan from the same patient of figure 1 shows intense tracer uptake in the upper part of the left femur. (personal archive)*

phatase level for the purpose of diagnosis [31]. Plain radiography is often the basis for diagnosis as its features are easily recognizable (focal osteolysis with coarsening of the trabecular pattern, bone expansion, and cortical thickening Fig.1and Fig.2). The differential diagnosis includes hyperostosis frontalis interna (a benign condition characterized by sclerosis of the frontal bones of the skull), fibrous dysplasia, pustulotic arthrosteitis (which can be manifested as sclerotic lesions of the clavicle and ribs), and osteosclerotic metastases. However, Paget's disease of bone is seldom confused with these other disorders, and biopsy of an affected site is rarely required for diagno-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

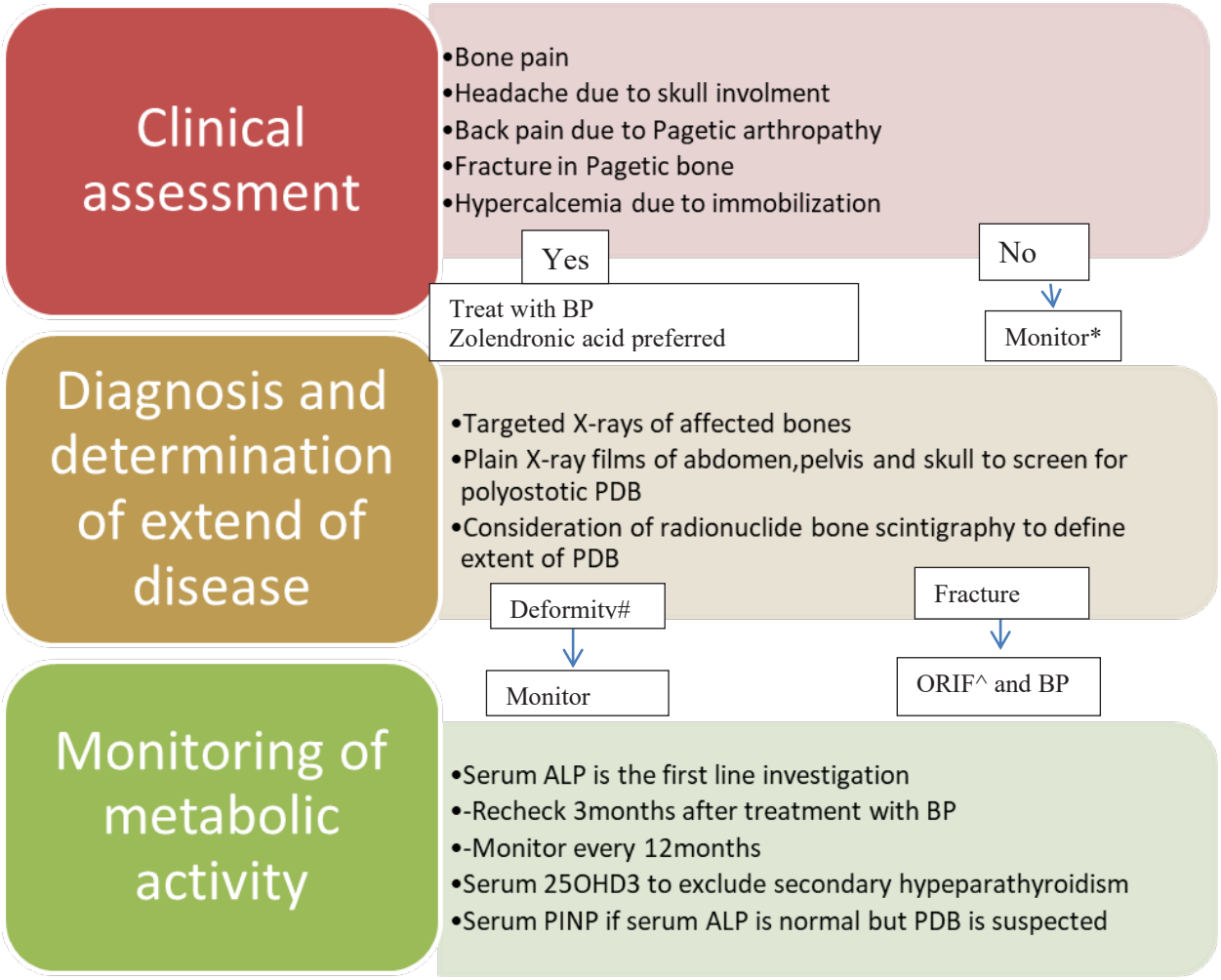

Fig. 4. *Management and treatment algorithm for Paget's disease of bone*

**Monitor serum ALP every 12 months, while treatment is indicated for symptomatic PDB.*

#There is insufficient evidence to recommend bisphosphonates to prevent bone deformity or progression of osteoarthritis in PDB.

^ORIF is recommended in treating fractures of pagetic bone. There is insufficient evidence to support use of pre-operative bisphosphonates to reduce intraoperative blood loss.

ALP, alkaline phosphatase; BP, bisphosphonates; ORIF, open reduction and internal fixation; PDB, Paget's disease of bone; P1NP, procollagen type 1amino-terminal propeptide

sis. Because a majority of the lesions of Paget's disease are asymptomatic, radionuclide imaging of the skeleton rather than a general x-ray survey has become the standard means to document the extent of skeletal involvement of Paget's disease [32]. Fig 3.

Other radiological modalities, such as computerized tomography, magnetic resonance imaging, and positron emission tomography, may be useful in individual patients, particularly if a neoplasm at a pagetic site is suspected, but they are not used routinely in the evaluation of patients with Paget's disease [33].

Further laboratory testing should include as-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 1.

Symptoms and Complications of Paget'sDisease of Bone

SYSTEM	COMPLICATION
Musculoskeletal	Bone pain (52%) Bone deformity (22%) Osteoarthritis of adjacent joints (73%) Acetabular protrusion Fractures (9%) Spinal stenosis
Neurological	Spinal stenosis Neurological Hearing loss (9%) Tinnitus Cranial nerve deficits (0.4%) Basilar impression (2%) Increased cerebrospinal fluid pressure Paraplegia, quadriplegia, vascular steal syndrome
Cardiovascular	Congestive heart failure (3%) Increased cardiac output Aortic stenosis Generalized atherosclerosis Endocardial calcification
Metabolic	Immobilization hypercalciuria Hypercalcemia Hyperuricemia Nephrolithiasis
Neoplasia	Sarcoma (osteo/chondro/fibro) (0.3%) Giant cell tumor

sessment of renal function and measurement of levels of calcium, albumin, and 25-hydroxyvitamin D; Vitamin D deficiency is a common finding, probably reflecting the fact that Paget's disease of bone predominantly affects older people, among whom vitamin D deficiency is prevalent and liver function should be assessed to rule out the possibility that elevations in the alkaline phosphatase level are of hepatic origin [34].

Management

The primary goal of PDB treatment is to restore normal bone turnover in order to relieve symptoms such as bone pain and possibly prevent complications that result from the abnormal resorption and overgrowth of pagetic bone (table 2). most guidelines, including Endocrine Society Clinical Practice Guidelines, suggest antiresorptive treatment, **mainly bisphosphonates,** for most patients with active disease who are at risk for future complications [27]. However, it should be mentioned, there is no clear evidence that asymptomatic patients benefit from antiresorptive therapy. A recent trial in a large cohort of 1324 PDB cases form UK, the Paget's Disease, Randomized Trial of Intensive versus Sympto-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 2.

Indications for treatment
1 Bone pain
2 Preparation for orthopedic surgery
3 Reversal of neurological deficit associated with vertebral disease
4 Hypercalcemia due to immobilization
5 High-output congestive heart failure
6 Prevention of complications including deformity and hearing loss

TABLE 3.

Bisphosphonates Used in the Treatment of Paget's Disease of Bone.

Drug	Dose	Common Adverse Effects
Oral		
Risedronate#	30mg/day for 2mo Retreatment may be required between 1 and 5 y	Dyspepsia, esophagitis
Alendronate# §	40mg/day for 5 mo	Dyspepsia, esophagitis
Intravenous		
Zolendronic acid¶	5mg single infusion. Retreatment is seldom required within 5 y	Acute phase response Hypocalcemia

 # This drug should be avoided in patients with an estimated glomerular filtration rate (GFR) of less than 30 ml per minute per 1.73 m2 of body-surface area.

§ Alendronate is not licensed for the treatment of Paget's disease of bone in the United Kingdom or other European countries.

¶ This drug should be avoided in patients with an estimated GFR of less than 35 ml per minute per 1.73 m2 of body-surface area.

matic Management (PRISM) study, compared the effects of a treat to target strategy aimed at normalizing bone turnover (as assessed by total alkaline phosphatase) with a strategy aimed at controlling symptoms. Most patients had previously been treated with bisphosphonates and a consistent proportion of them already presented complications such as hearing loss (22%), fractures (39%), bone deformity (36%) or had a previous surgery for PDB (16%).

The use of any licensed bisphosphonate was permitted, but risedronate was chosen as the first-line treatment because this was the most potent bisphosphonate available at the time when the study began. At 3 years, both strategies showed similar effects on the occurrence of fractures, or-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 4.

Surgery in patients with paget's disease.
1 Total hip replacement
2 Total knee replacement
3 Femoral and tibial osteotomy
4 Correction of spinal stenosis or nerve root compression
5 Vertebroplasty for painful vertebrae
6 Ventricular-peritoneal shunting for hydrocephalus
7 Suboccipital craniectomy and cervical laminectomy for basilar impression

thopedic procedures, hearing loss, bone pain, quality of life and adverse events [35]. A 3-year extension study of the trial was performed on 502 patients in which the same treatment strategies were continued but where the most potent bisphosphonate zoledronic acid was used as the treatment of first choice in the intensive arm. In keeping with the original trial, there were no clinically relevant differences in quality-of-life measures or bone pain between the treatment groups. However, intensive treatment arm was associated with a nonsignificant increase in fractures (HR 1.90; 95% CI 0.91-3.98), orthopedic procedures (HR 1.81; 95% CI 0.71-4.61), and serious adverse events (RR 1.28; 95% CI 0.96-1.42).

Thus, it was concluded that long-term intensive bisphosphonate therapy to suppress bone turnover confers no clinical benefit over symptomatic therapy.

Agents used to treat PDB are antiresorptive in nature and mainly nowadays are bisphosphonates although Calcitonin has been the first antiresorptive agent to be used for effective treatment of PDB and is still approved for the treatment of PDB in several countries.

Even these drugs may also reduce bone pain, symptomatic treatment with analgesic agents or anti-inflammatory drugs may be required in some patients. Moreover, since hypocalcemia and secondary hyperparathyroidism are common after the suppression of bone turnover, daily supplements of calcium and vitamin D should be also recommended to PDB patients in addition to antiresorptive therapy.

While all bisphosphonates have been shown to be effective in PDB (alendronate, risedronate, pamidronate, neridronate, ibandronate and zoledronic acid),Table 3 summarizes the bisphosphonates currently used in treatment.

Denosumab is an alternative antiresorptive therapy used for patients with osteoporosis; however, it has been less studied in PDB than bisphosphonates.

While case reports of its use in PDB show its effectiveness in reducing bone turnover markers for up to five months after administration, its effect on bone pain, fracture risk and progression of pagetic lesions is less clear. At this stage, it is not recommended as treatment for PDB but

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

may considered for the treatment of giant cell tumor(GCT) complicating PDB when the tumor is nonresectable[37].

Treatment response is best assessed by measuring serum total ALP 3–6 months after treatment and then annually once levels are normalised. If there are osteolytic lesions, the plain film should be repeated at 12 months to assess for improvement.

A single infusion of zoledronic acid has long-term benefits, with sustained remission rates of 87% at 6.5 years[36]. If symptoms recur and serum ALP rises above the normal range, retreatment with zoledronic acid should be considered [27].

Surgery

Although there no randomized trials, various surgical procedures have been beneficial for many patients. Table 4 lists the variety of procedures that have been used in the management of patients with Paget's disease.

Conclusion

Since the description of the first case, in 1877, PDB has remained for many years a challenging disorder either concerning the pathogenesis or the necessity of effective treatments, able to prevent disease progression and complications. Over the last two decades, thanks to the development in technology, remarkable advances have been provided on either the pathogenetic mechanisms or the clinical management of the disease. Despite these remarkable advances in the genetics of the disease there are still major gaps in knowledge, particularly concerning the understanding of the exact molecular mechanisms underlying osteoclast dysfunction and the occurrence of pagetic lesions in the presence of all these mutations. Importantly, since the development of more potent antiresorptive compounds such as aminobisphosphonates

PDB has become a treatable disorder, particularly after the recent introduction of

zoledronic acid which now allow a long-term remission in the majority of patients [38,39].

A graphical summary of the recommendations for diagnosis and management of PDB is shown in Fig 4.

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READY - MADE CITATION

Trovas G. Paget's disease of bone. *Acta Orthop Trauma Hell* 2023; 74(2): 52-63

REVIEW

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

The Orthopaedic Assessment of Children with Osteogenesis Imperfecta

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ABSTRACT

Osteogenesis Imperfecta (OI) is an inherited skeletal dysplasia characterized from bone fragility and skeletal deformities. OI presents with heterogenous features and variability in severity. Multiple systems are affected, since the disease involves the synthesis of collagen type I. Diagnosis is mainly based on the incidence of fractures. Severe osteoporosis, repeated fractures and fragility affect the skeleton and severe deformities are the result. Spine deformities are common. Muscle function and mobility is affected. Medical treatments including biphosphonates, denosumab, TGFb inhibitors are reported to increase bone mass, but fractures remain the main consideration of OI. Surgical treatment with the use of intramedullary expanding rods increases bone strength, correct deformities and provide stability for the mobilization of the affected patients. These procedures have a high rate of complications but have significantly improved the quality of life of the affected children.

KEYWORDS: Osteogenesis ; Imperfecta

Definition

Osteogenesis imperfect (OI) is a rare bone dysplasia, covering a broad area of connective tissue disorders that is characterized from bone fragility, fractures and bone deformities. It is estimated with an incidence of 1/ 15000 live births. In our area in north of Greece, we have 6 children with OI under our orthopaedic care.

OI is due to mutations in the genes that are responsible for the synthesis of the chains of the type 1 collagen. Osteoblasts appear primarily affected. Increased function of TGFb (Transforming Growth Factor beta) signalling that exhibit increased bone turnover and low bone mass, is found. Initially lesions in chromosomes 17 and 7 affecting COL1A1 and COL1A2 where identified, but today there is an increasing number of involved genes. We have described a new mutation in a severely affected girl with OI. The mutation is an autosomal dominant one but may appear as recessive or X-linked disorder. More than 50% of cases are new mutations. This is clinically important regarding the proper assessment of relatives for children affected from OI. [1-8]

Diagnosis

Diagnosis is mainly based on the feature of bone

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

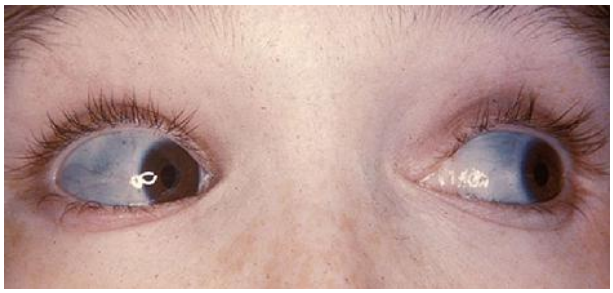


Figure 1: *Blue sclera of a patient with OI*

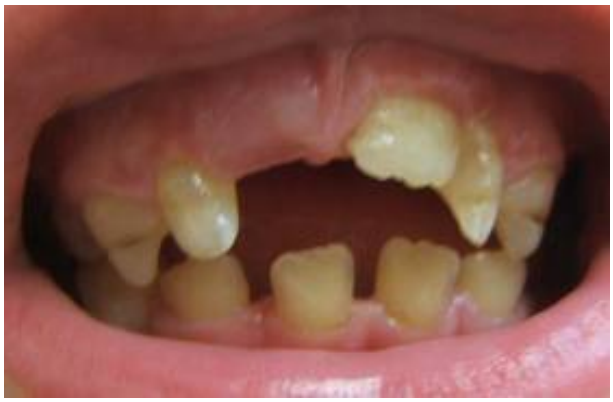


Figure 2: *Severely affected teeth in a patient with OI*

fragility. There are characteristic radiological elements of osteoporosis and alterations of bone morphology but are not unique for OI. Biochemistry bone measurements and bone mineral density measurements are helpful. Clinical picture with extra skeletal manifestations add to the accuracy of the diagnosis. Fractures of long bones, with minimal violence remain the main feature for the diagnosis of OI. Transverse type of fracture in the diaphysis of a long bone is the most typical pattern of a fragility fracture. [1,2,9,10]

Classification

Classification of a disease with a wide variety of clinical presentation is difficult. Initial classification was proposed from Silence, in four types, according to the severity of clinical and radiological manifestations. Type I was the no deforming type of OI characterized from blue sclera. Type II was the lethal perinatal OI, presenting with prenatal fractures and short life expectancy. Type III was the severe progressive type with deformities and multiple fractures. Type IV was described as a moderate form with less incidence of fractures and mild deformities.

Recent progress in genetics of OI has created a tendency to classify OI according to genetic defects. There is no correlation between the genotype and phenotype presentation of the disease. Mutations in the genes affect collagen structure either as an amount of pathological collagen either as changes in the structure of type I collagen. Genetic analysis of the OI cannot be linked with the clinical picture of OI.

Today Silence classification is used, while a 5th type of OI was added, characterized from calcification of the interosseous membrane of the forearm. [10-14]

Clinical Manifestations

OI is characterised from bone fragility, in all types of the disease. Since the genetic lesion affects the collagen structure, many clinical manifestations in almost all the human organs, may appear.

OI **type 1** has bleu sclera. Fractures are rare at birth but there is an increase in number, as the child grows. Usually, they are transverse fractures of long bones. Deformities are rare. There is decreased bone mass. Fractures are rare in vertebrae.

On **type 2**, short and deformed long bones appear in the prenatal ultrasonography. Reduced length of the femur is the most reliable parameter to detect skeletal dysplasia. Rib fractures are observed in uterus. The vast majority of patients die in the first month of life. Decreased ossification of the skull and the facial bones is found.

Type 3 OI is the most severe type, with multiple fractures and severe deformities of the long bones. Fractures appear from birth. Children have short stature. Growth plate appears elongated, leading in short bones. There are problems with dentinogenesis. Vertebral fractures may be found. Children present problems with scoliosis. Blue sclera is found and occasionally there is an increase of the intensity of the coloring, before fractures. As OI is a collagen disease there are several clinical manifestations. There is increased ligamentous

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

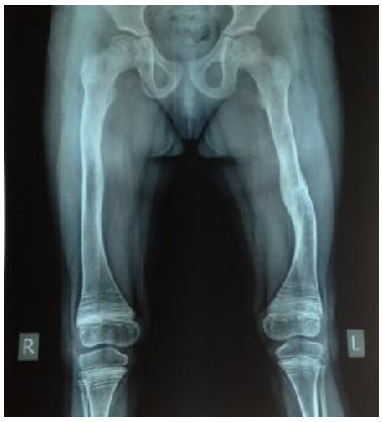


Figure 3: *Thin cortices and osteoporotic long bones, with a healed fracture of the left femur*

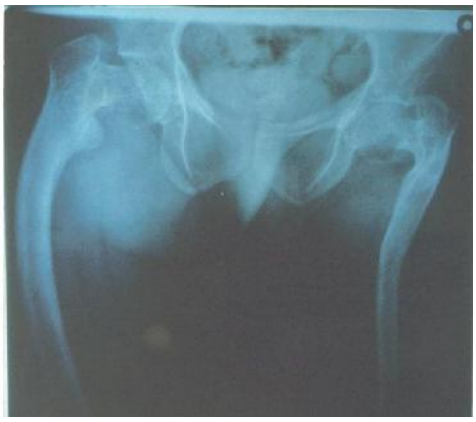


Figure 4: *Deformed femora and protrusion of the left acetabulum, with thin cortices*

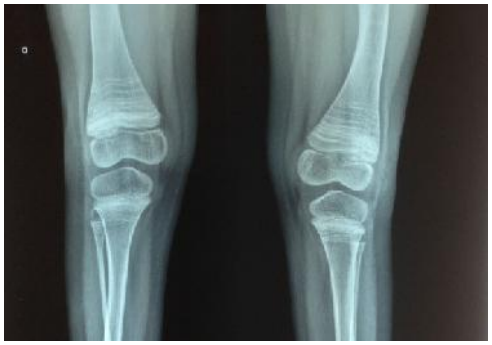


Figure 5: *Zebra lines in the metaphysic of the long bones*

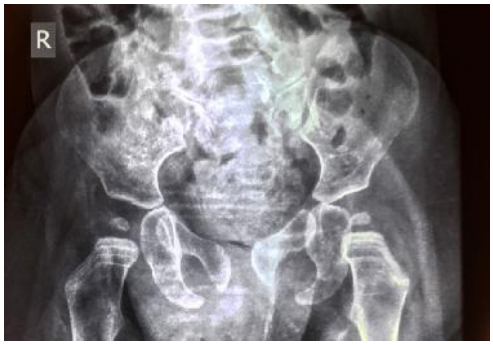


Figure 6: *Zebra lines in the metaphysis of the femur*

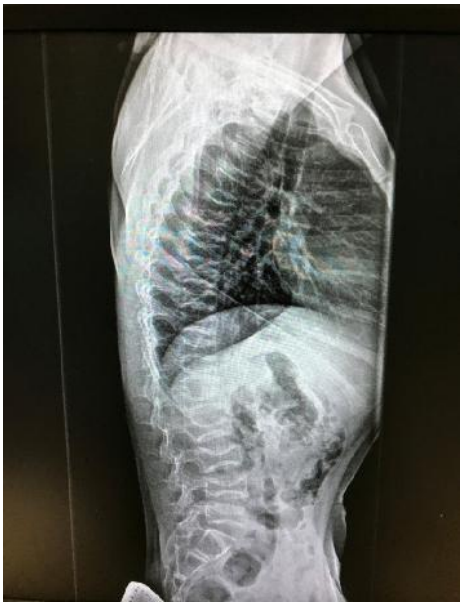


Figure 7: *Severe osteoporosis of the vertebrae that are markedly biconcave in shape.*

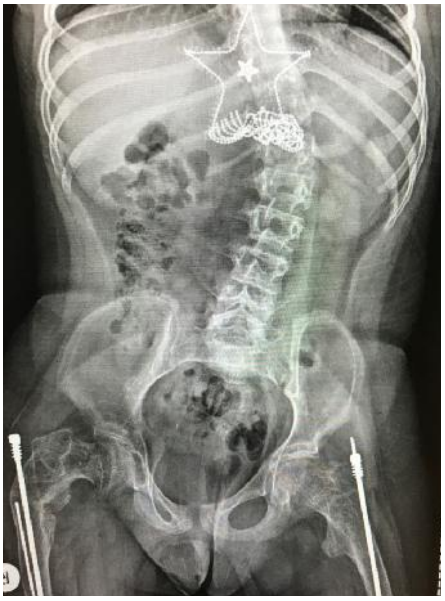


Figure 8: *Scoliosis in a child with OI*

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

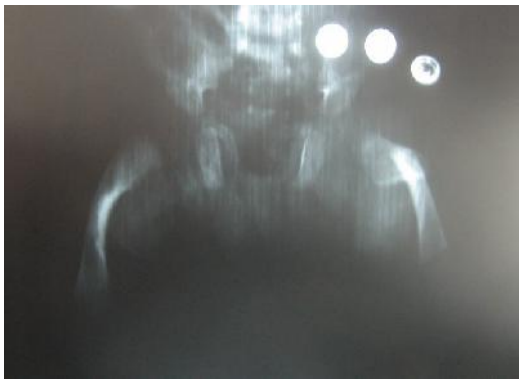


Figure 9: *Neonatal fracture of the left femur in a girl with OI.*

laxity. The head has a frontal prominence and there is an ageing appearance, the patient looks old. Craniofacial structures appear abnormal. Hearing problems are common. Children have normal intelligence.

Type 4 has a mild form of the disease. There are frequent fractures, but less severe deformities. Blue sclera is absent.

Type 5 had increasing ossification of the intraosseous forearm membrane. [1,2,10-14]

Radiology

Severe osteoporosis is the main characteristic. Cortices are thin. Severe deformities appear with almost complete bending of the long bones, similar to semicircle. There is thinning of the cortices with reduced width of the intramedullary canal.

Protrusion of acetabulum may appear later. Vertebrae have a characteristic biconcave shape, leading further to scoliosis. A most prominent sign is the zebra line phenomenon that is seen in children with OI, no matter whether they are under treatment for the osteoporosis. Bone mass index remains in low prices, in OI. [1,2,10]

Neonatal fracture

A neonatal fracture of a long bone may be the initial manifestation of OI. The severe lethal type 2 OI may appear on prenatal screening with bowing of femora and reduced length of the femur. The fracture is found in an uncomplicated normal delivery. On radiological examination apart from

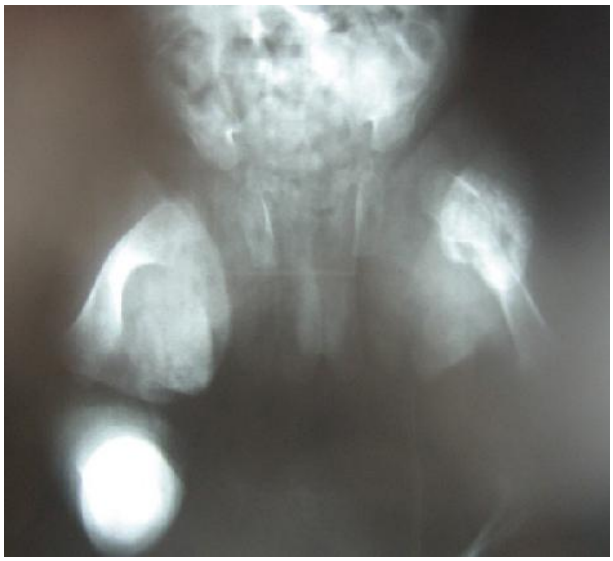


Figure 10: *Callus formation of the fractured left femur, deformity of the right femur*

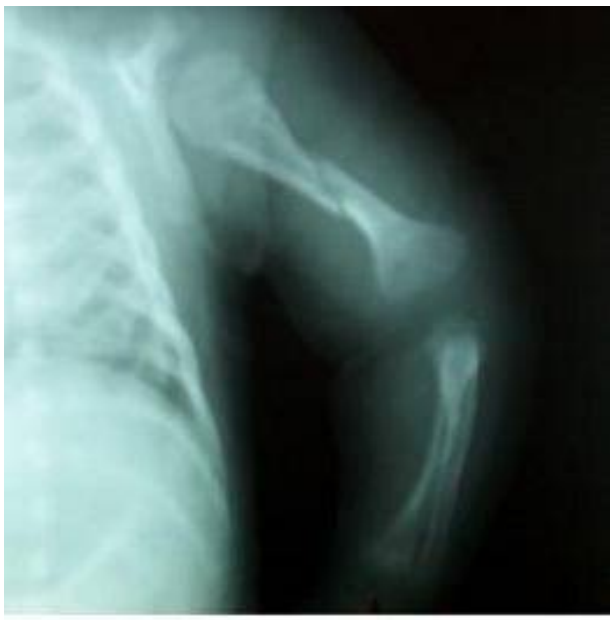


Figure 11: *Fracture of the humerus, as the first fracture of a neonate with OI*

the fracture, the cortices are thinned and deformed. Fractures usually affect the femur and the humerus but even fractures of the tibia, ribs or vertebrae have been reported. Treatment of the fractures follows the general principles for neonatal fracture, with skin traction (Gallow's traction) for the femur and appropriate splinting for the humerus. [15-18]

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

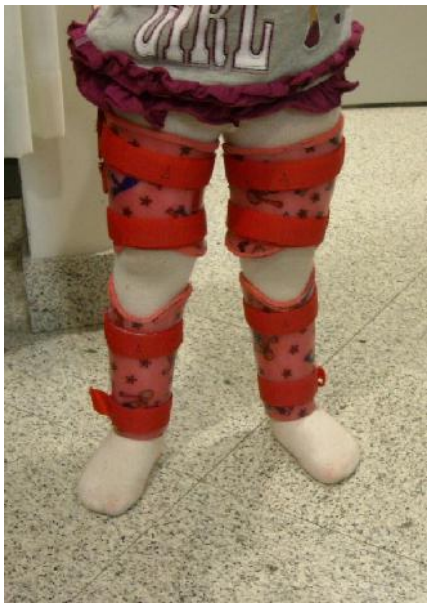
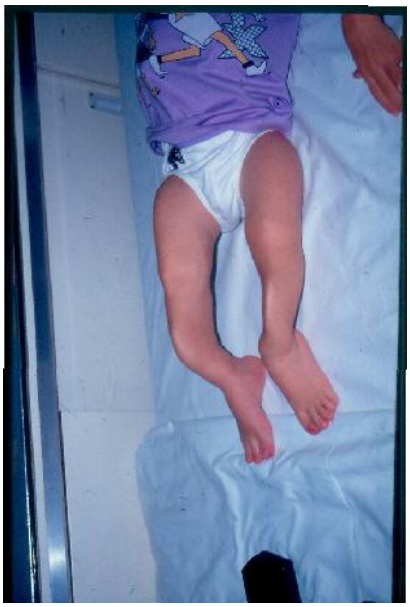


Figure 12: *Casts applied for protection in the preschool age, in a child with OI*



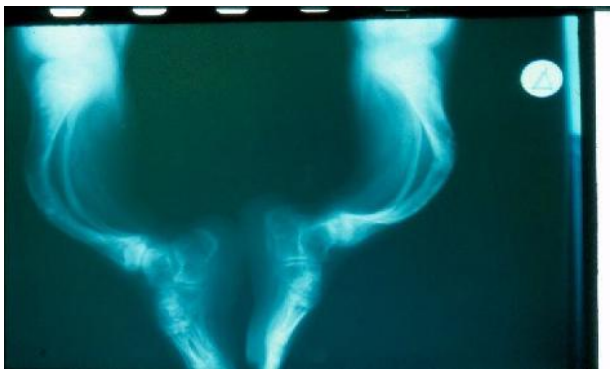


Figure 13, Figure 14: *Clinical picture and radiological image of a boy with severe type 3 OI. Note the semi-circular appearance of the tibiae.*

Deformities - Fractures

Repeated fractures and reduced bone strength lead in severe deformities of the long bones. Even in supported passive standing position, the fragile long bones sustain deformities that lead in an almost circular shape of the femur or the tibia. Same deformities are found in the upper arm. The bone healing is not impaired but the callus formation consists from poor bone quality in OI. Refractures and delayed bone union are reported in OI. [11,19]

In the initial stage appropriate functional casts are used to protect the shape of the limbs and provide support for the children, in order to walk independently.

Spine Scoliosis

Lesions of the vertebrae are common in OI. Early vertebral fractures in the first years of life are among the initial findings of OI. Vertebrae appear on radiological assessment with severe osteoporosis, thinning of the cortices and biconcave shape. Scoliosis is a common finding in OI female children. Scoliosis is another cause of gait disturbance in cases of a spine that is out of balance. Use of custom-made cast with elasticity is initially used in order to reduce the increase of the curvature. Commonly used casts for the adolescent scoliosis that use pressure cannot be applied in children with OI. Surgical treatment of severe scoliosis in OI is a great challenge for the spine surgeon. Fixation of pedicle screws may require the use of cement. Spine fusion is impaired in those children that are under regular bisphosphonate treatment.

Atlantoaxial abnormalities have been reported as complications in children with OI. Radiological manifestations include basilar invagination or impression and platybasia. Neurological symptoms with weakness of the limbs must be investigated for craniocervical lesions with appropriate MRI

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

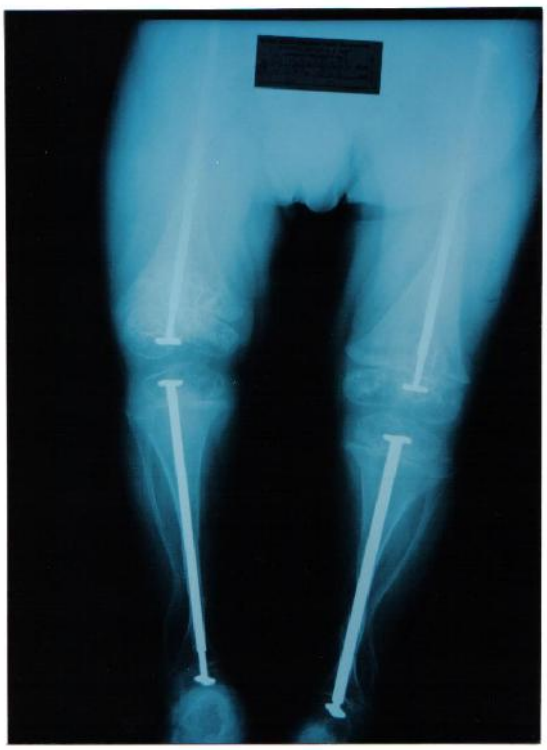


Figure 15: *Correction of both femur and tibia, with telescoping Sheffield rods, with multiple osteotomies. Impressive restoration of the axis of the lower limbs.*

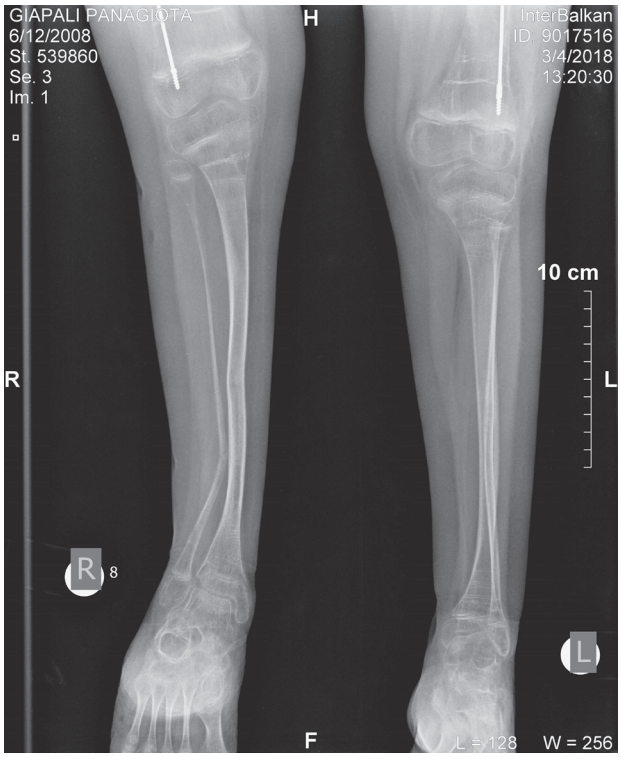
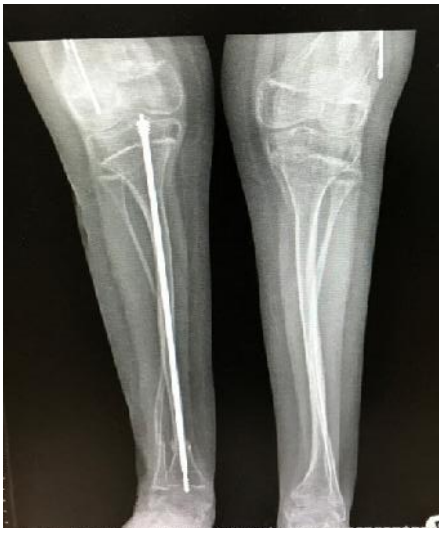


Figure 16: *Deformity of the right tibia, with delayed union of the transverse fracture of the tibia diaphysis. Notice the reduced width of the canal*



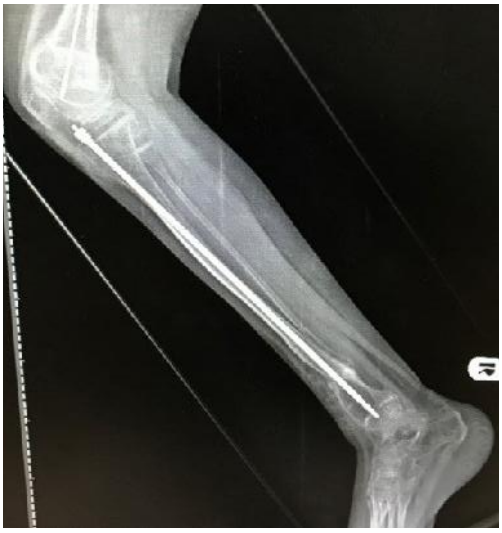


Figure 17, Figure 18: *X-ray examination AP and lateral of the corrected right tibia, with Fassier Duval expanding rods. Surgery performed the year 2018*

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

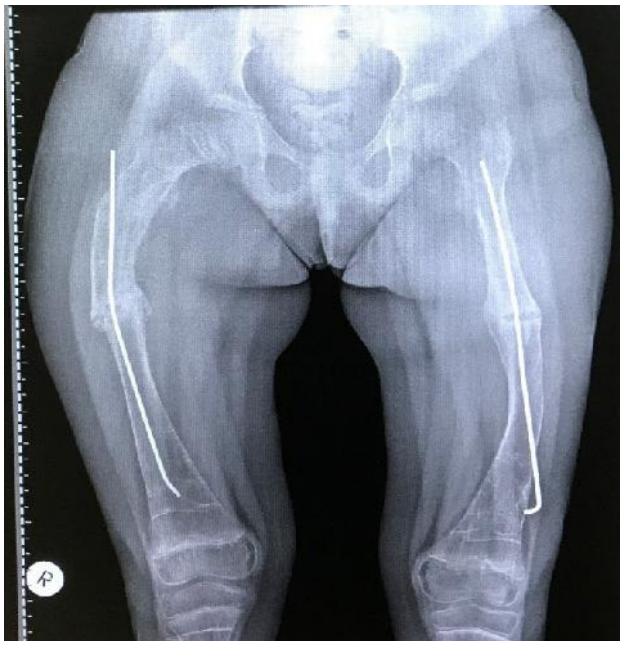


Figure 19: *Initial stabilization of fractured femur with intramedullary nails, year 2016*

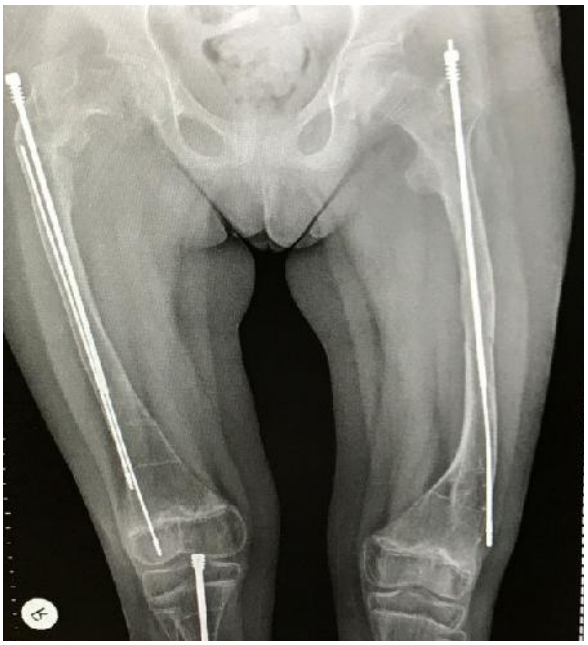


Figure 20: *repeated surgical stabilization with expanding rods Fassier Duval, year 2020*

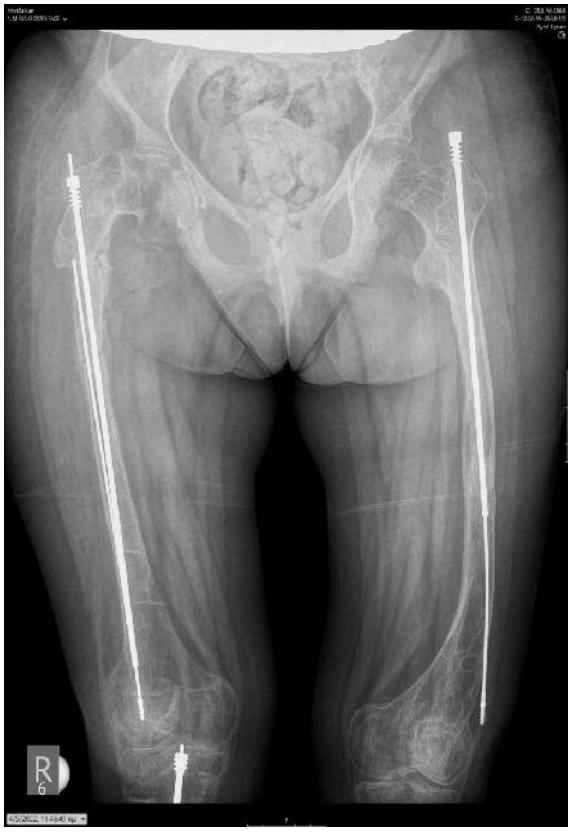


Figure 21: *Correction of recurrence of deformity of the right femur, with new osteotomy, on 2022*

evaluation. Regular assessment of the cervical spine in a year basis is recommended after the 6th year. Spondylolisthesis has been reported in OI children. [20-25]

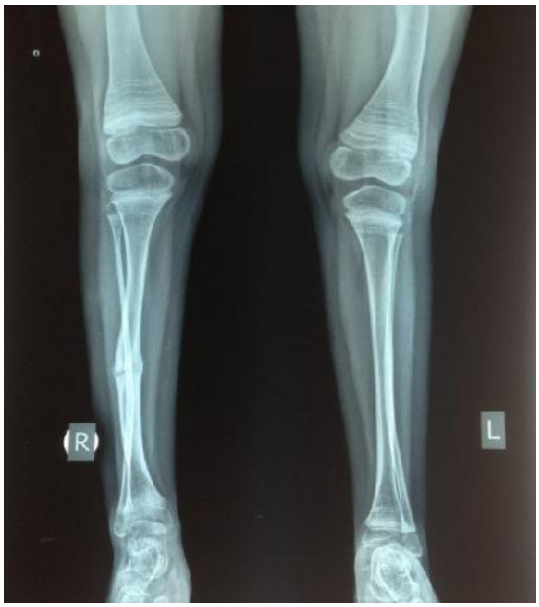
Muscle Lesions

Muscle weakness is an important feature and gait disturbances with increased motor disability affect the patient, further adding to the difficulties from the bone deformities. Patients have reduced mass muscle and muscle function is impaired. Collagen type I is found in the tendons and ligaments and the disturbance of collagen synthesis affect the connective tissue. Tendon ruptures are found in OI. Children have decreased mobility; this is another factor predisposing to reduced muscle strength. It is important with appropriate physical therapy to keep children in standing and walking activities. Increased ligamentous laxity is a common feature in OI, leading in joint dislocation. [2,10,26,27]

Mobility

Children with OI type 3 are severely affected on their motor ability. Deformities of the upper and lower limbs are occasionally extremes and children

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023



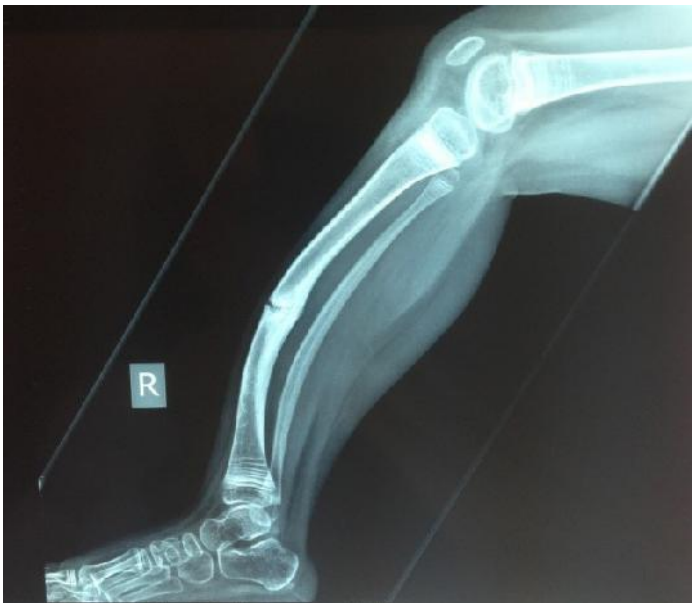
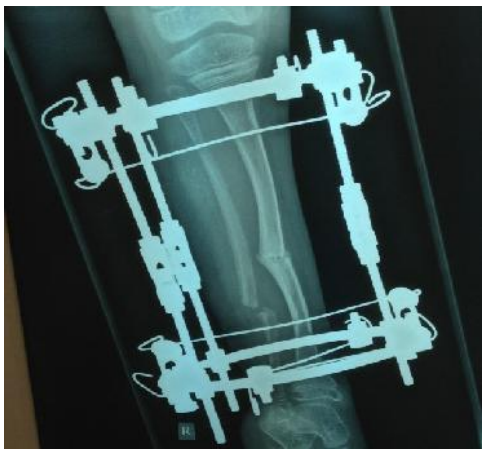


Figure 22, figure 23: *Anterior bowing and delayed union of the fracture of the right tibia, 2014*



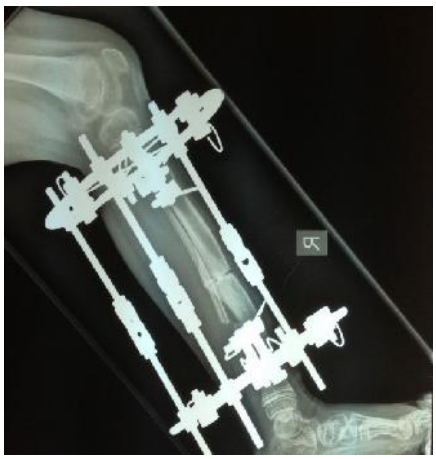


Figure 24, Figure 25: *Correction of the deformity, with application of Ilizarov device, 2014, note the osteotomy of the fibula.*

cannot achieve the upright position. Muscle weakness as already described is an important factor for the decreased mobility. Respiratory and cardiovascular deficit add to motor disturbance. [28,29]

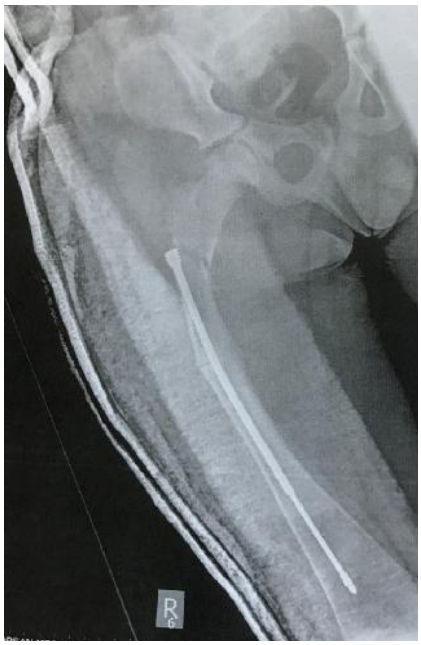
Medical treatment

The standard care for paediatric patients is the use of bisphosphonates. Intravenous use increases the bone mass and reshaping of the vertebra has been found. The number of fractures is not significantly reduced and deformation of the long bones remains a severe problem.

Denosumab, and anti-RANKL antibody that act by inhibiting osteoclast differentiation is currently studying for OI in children. It has shown to improve bone mineral density. There is a risk of increased hypercalcemia.

The use of sclerostin inhibition and TGF beta inhibition are reported with promising results. Anabolic agents as teriparatide have been also used, but it was not effective in severe forms of OI. Progenitor cell therapy, with transplantation of healthy stem cells, has been recently reported. [30-37]

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023



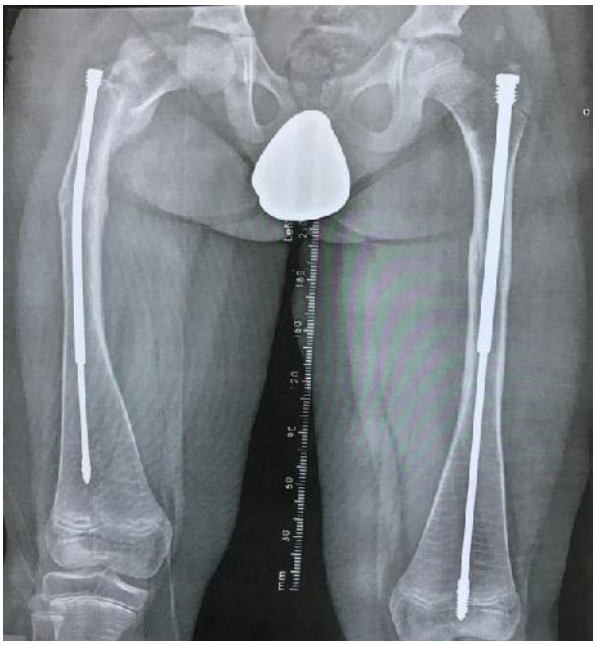


Figure 26, Figure 27: *Fracture in the subtrochanteric region, just above the rod. Treatment with immobilization in a spica and union of the fracture*

Surgical treatment

Surgical treatment is an essential part for the management of the children with OI. The aim of surgery is to straighten a deformed bone, providing adequate support in order to sustain appropriate loading during the standing and walking phase. The development of the expanding rods (Fassier Duval) has completely altered our approach for the surgical management of OI. Rods can support the weak bone in order to reduce the incidence of fractures and provide adequate support for preventing displacement of the fractured bone. Early surgery can prevent severe bone deformities.

Correction of deformities

Long bones appear as almost semi-circular shapes. In order to become straight several segmental osteotomies are required. Intramedullary canal is reduced in size and appropriate preoperative planning is required for the correct size of the rod. Longitudinal extensive incisions are required, with careful periosteal elevation and several segmental osteotomies. In the severe type 3 OI the feeling of the cortical bone is like trying fixing pieces of sand. Expanding rods are secured in the epiphysis of the bones, enabling the introduction of the male in the female part of the system. As the child grows, the telescoping rods are elongating.

Osteotomies can be performed subcutaneously, under image intensifier, with controlled type of osteotomies. Preoperative planning can be performed today threw a computer assisted method, in order to achieve accurate correction of the deformities. [38-44]

Severe deformities are mainly affecting the femur and tibia. But similar deformities affecting the humerus can be surgically treated with multiple osteotomies and rodding. [45,46]

In older children, locking plates with unicortical screw fixation have been recently reported, in cases with delayed union or pseudoarthrosis of the osteotomy.[47]

Tibia -Illizarov - Rods

Use of Ilizarov device is well established method for correction of deformities, with immediate weight bearing. Fixation of the wires in a bone with severe osteoporosis can be a problem in the use of the device. Leg lengthening procedure with Ilizarov

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

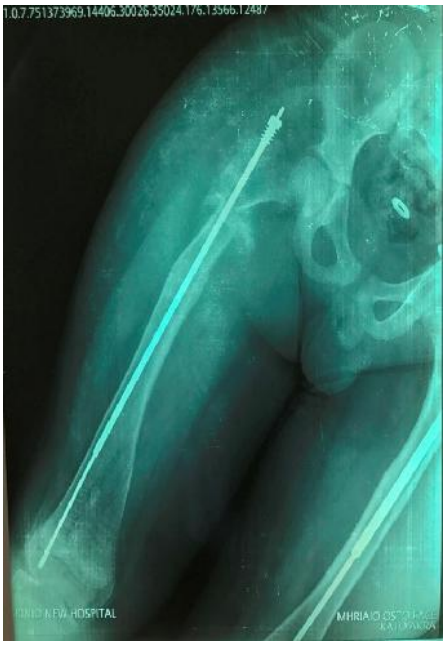
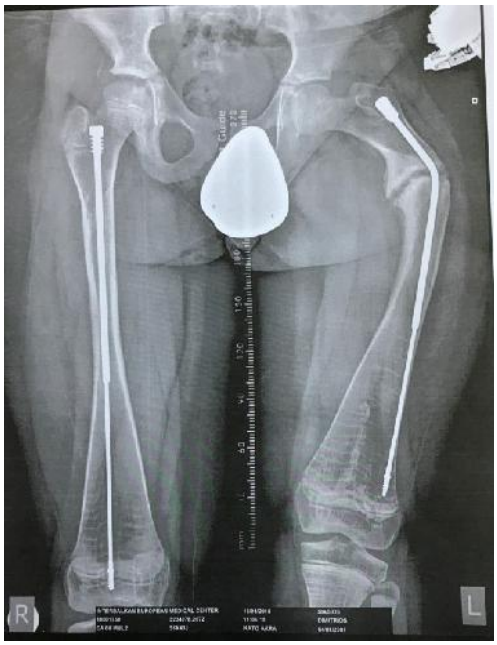


Figure 28: *Surgical correction after the union of the fracture, with subtrochanteric osteotomy and application of a new expanding rod Fassier Duval.*

device may encounter problems with the fixation of the wires and the stability. We have used the Ilizarov device for the accurate correction and stabilization of the deformity of the tibia that presented with a transverse fracture in the diaphysis. Bone healing was delayed as was expected in the fracture in the diaphysis of the tibia and not because of the underlying OI. Union was achieved and the device was removed. But the deformity recurred with further transverse fragility fractures and we treated the patient with the use of expanding rod (Fassier Duval)

Complications

Children with OI, even in milder forms as type 4, continue to sustain fractures, despite surgical stabilization with rods and appropriate medical treatment. Minimal activities or even absence of trauma, just as children are standing or walking, may trigger the fracture. Clinical signs of pain of the femur or cortical thickening occasionally are prenominal features for the fracture, similar to the atypical femoral fractures that are reported in anti-osteoporotic treatment. The presence of the rod acts



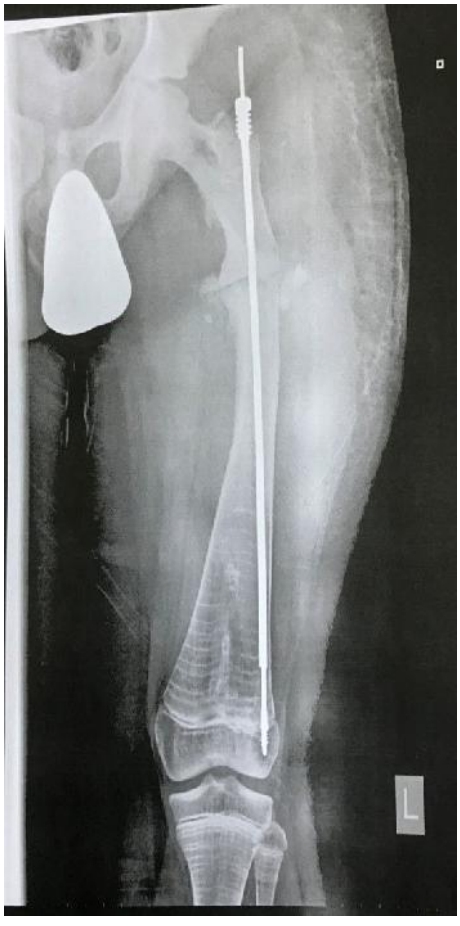


Figure 29, figure 30: *Pseudoarthrosis of the osteotomy of the left femur, with bending of the rod. Surgical treatment with realignment of the femur and insertion of a new rod.*

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

as an internal splinting, reducing the angulation of the femur and treatment with appropriate bed rest is adequate for the healing of the fracture, and since the fracture healing is not impaired in OI. Fractures may appear in the top of the rod, leading to varus deformation and bend of the rod. Treatment provided was the revision of the rodding, with adequate subtrochanteric osteotomy, in order to re-establish the axis of the femur. Another patient presented with bending of the rod and delayed union and was treated with open procedure with removal of the rod, reduction of the femur and insertion of a new expanding rod.

There is concern regarding the union of osteotomies and fractures in children that are treated with bisphosphonates. We have used a period of drug vacancy of 3 months for those that are scheduled for an elective procedure. We are using osteotomes instead of power saw in order to reduce the heat necrosis of the bone. In those treated in emergency for the fracture, we discontinue the use of bisphosphonates for 6 months. [48-52]

Blood loss

Patients with osteogenesis imperfecta (OI) have been reported to be at risk for significant surgical bleeding, secondary to abnormalities in platelet function. The younger patients are at increased risk. Increased number of osteotomies may lead to severe blood loss. It is important to secure blood units before the surgical procedures. With minimal surgical incisions and minimal periosteal elevation, femoral rodding can be performed without excessive blood loss. [53]

Conclusions

Surgical treatment must be considered as an early procedure in young children, with the severe form of OI, in order to prevent severe deformities. The increasing number of fractures is an indication for surgical intervention. The mobility status of a young patient can be reserved with early intervention, since the straight bones that are increased in strength with the rod, can permit their independent walking. Surgical treatment with expanding rods is a procedure that can improve the mobility of children with significant deformities. There is a high rate of revision procedures, reported up to 50% of patients. This is mainly related to the growth of the young patients, repeated fractures and migration of the rods. [41-43]

Individuals with severe type III OI, are more often treated with intramedullary rods, simultaneously in both lower limbs and present improvement in their mobility. With appropriate orthotics they can become independent ambulators.

Severe types of OI are associated with severe mobility disorder, as already reported. But appropriate medical and surgical treatment can improve the quality of life of the patient and the family. Genetic interference is expected to further improve the status of OI.

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CASE REPORT
VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Oncogenic Osteomalacia: A Case Report and Literature Review

Kapetanou A, Konstandinidis J, Kapetanos G.

ABSTRACT

Oncogenic Osteomalacia or Tumor Induced Osteomalacia (TIO) is a rare paraneoplasmatic syndrome characterized by multiple automatic pathological fractures as well as by severe hypophosphatemia. The etiology is not known, but its pathophysiology is associated with a very small mesenchymal tumor which is related to the Fibroblast Growth Factor 23 (FGF 23). Clinically the patient has numerous automatic fractures of the upper and lower limbs and of the spine, with bone and muscular pains. Hypophosphatemia, phosphaturia and increased alkaline phosphatase are the laboratory findings. Finding the tumor can be a major diagnostic challenge and the radical excision is the treatment of choice. A female patient, 47 years old, senior nurse, healthy in general, revealed a progressive weakness of the lower legs during the last two years, generalized myopathy and pathological fractures in pelvis, hips, humerus, sternum, clavicles, spine, radius and knees, symmetrical in both sides, left and right. Phosphorus and vitamin D were found very low and FGF 23 very high. Scan, CT and MRI were normal. The PET revealed a very small lesion in the base, under the tongue. The tumor was removed and the biopsy confirmed the phosphaturic mesenchymal tumor. Very soon the patient recovered, the fractures were united and today five years postoperatively, she is very well and free of the disease.

KEYWORDS: Tumor induced osteomalacia, hypophosphatemia, hyperphosphaturia, fibroblast growth factor.

Basic Knowledge and Related Literature

Tumor induced osteomalacia (TIO), is a very rare paraneoplasmatic syndrome. The prevalence of the disease is not known. It is estimated that more than 900 cases of TIO have been reported in the literature (1,2). In pathophysiology, TIO is characterized by severe hypophosphatemia and the most common cause of this is the phosphaturic disorders (1) which was demonstrated in mice (2). In humans this is confirmed by Miyachi et al (2). FGF23 was identified as strong phosphaturic substance (3) and was found in very high concentrations in TIO. FGF23 is also a regulatory hormone of 1,25 vitamin D and leads to a decrease concentration of this vitamin in the blood (3,4). Histopathologically, these tumors are usually very small, less than 1 cm, and of mesenchymal origin(2,5) with neoplasmatic cells. Mitotic activity of these cells is usually absent or very mild (2). While these tumors in vast majority are benign, malignancy and metastases can occur in some cases. (6) Infiltration of the surrounding tissue is typically present, so the surgical removal should be wide, in order to avoid persistence or recurrence.

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

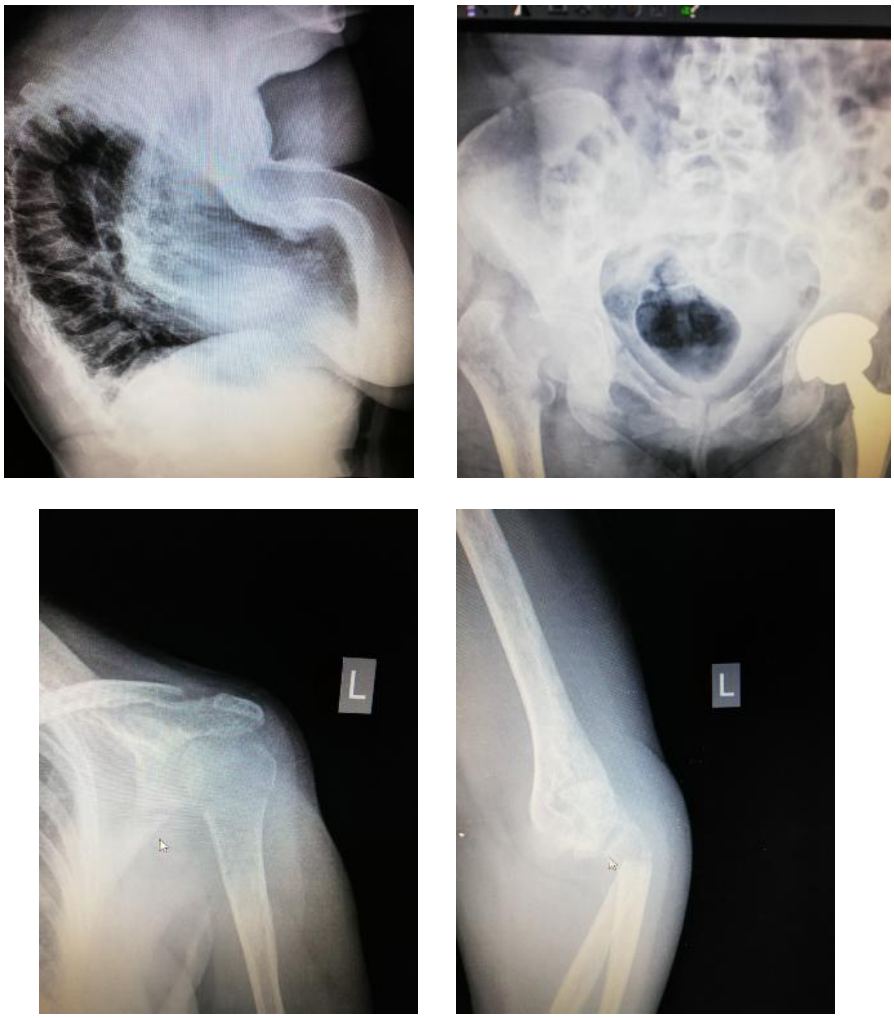

Figure 1. *Fractures of the sternum and spine (A), hip (B), clavicle and humerus (C), and elbow (D).*

The majority of the tumors is found in males (56%) and the mean age of diagnosis is the 45,3 years (2,4). Most tumors occur in the thigh and the femur (22,7%) and in craniofacial region (20,7%) and the rest in all the bones and soft tissues of the body. Very few cases were reported in organs such as the liver, the tongue, the thyroid and the lungs (7).

Clinically, common complaints are bone pain, muscle weakness and mainly the pathological automatic fractures, primary in vertebral bodies, ribs and femoral necks. In laboratory we have hypophosphatemia, caused by impaired renal phosphate, hyperphosphaturia, low levels of vitamin D, increased alkaline phosphatase and normal prices of the Calcium and Parathormone (PTH) except in the cases of secondary hyperparathyroidism. The very high prices of FGF23(1,2,6) confirm the diagnosis.

In differential diagnosis should always include renal Fanconi's syndrome as primary disorder or as complication of myeloma, amyloidosis or Sjogren's syndrome. It is also very useful the exclusion of genetic causes such as XLHR, ADHR and ARHR, by performing genetic tests (3,6,7).

The most challenging problem in this disease is to find the location of the tumor. This is due to the very small size and the fact that this tumor can be anywhere from the head to the toes in any bone or soft tissue, even subcutaneously and also has a very slow growing, through years. (7,8) Therefore we usually perform Total body Magnetic resonance (MRI), Computed tomography(CT), Scintigraphy(Tc99m) and positron emission(PET\CT) (8,9).

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

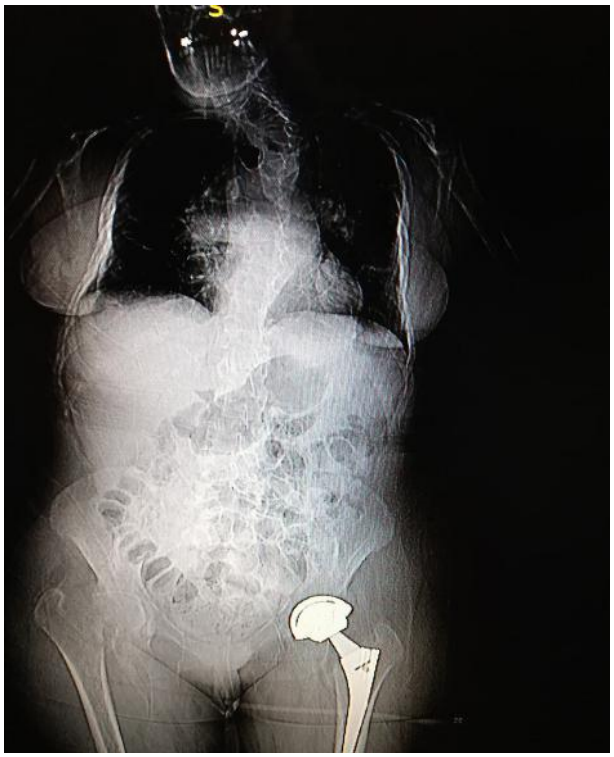

Figure 2. *Total body x-ray.*

The treatment of choice for TIO is the resection and removal of the tumor with a wide margin for complete tumor removal, as recurrences have been reported (10). After the removal of the tumor the patient feels much better immediately (within days or weeks). FGF23 disappears from the circulation rapidly, phosphorus and vitamin D return to the normal five days postoperative and bone healing starts immediately. In case of incomplete removal, radiotherapy can be used to avoid recurrence or metastasis. Radiofrequency ablation (RFA), octreotide and antibody for FGF23 have also been reported in combination with regular conservative treatment, such as the administration of phosphate and vitamin D, to have beneficial effect.

Case Report

A 47-year- old, female, senior nurse, healthy in general without any family or personal medical history, was complaining during the last two years of progressive weakness and musculoskeletal pain in the spine and limbs. The last author visited her at home and found a lady practically immobilized in bed, with severe weakness due to the generalizing myopathy and deformities, and in great pain in the limbs and the spine due to the fractures. The patient was admitted in the University Orthopaedic Department for further clinical and laboratory examination.

Clinical examination revealed scoliosis and kyphosis of the spine, weakness in muscles, deformities of the limbs and pain with palpation and movements. The neurological and endocrinological examination was normal and excluded parathyroid disease and myeloma.

Bone mineral density (DEXA) was normal (1000 mgr./cm2) and x-rays revealed osteomalacia with Looser's zones multiple fractures in different stage of union of the limbs, symmetrical in both sides. In detail there were fractures in clavicles, scapulae, humerus, radius, hips, knees, pelvis and also in sternum and at least in five vertebrae (20 fractures in total) (fig.1 and2).The first ultrasounds of thyroid, spleen, pancreas, kidneys ,liver and prostate were normal. The CTs, MRIs, the whole body scintigraphy with Indium 111 were normal as well in the beginning. All these investigations confirmed the fractures and osteomalacia but they could not reveal the cause of all these.

Laboratory examinations showed only low values of phosphorus in the blood (2,00 mg%, with normal values 2,5-4,9), very low vitamin D (3,0 gr/ml with normal values 18-65) and increased alkaline phosphatase (319,19 u/l with normal values 40-150u/l). All the other values were normal. The first possible diagnosis was Ongogenic Ostemalacia. The value of FGF23 was very high, 838(normal:<180pu/ml) and the diagnosis was confirmed. High doses of phosphorus and vit. D were administrated and the patient felt impressively well. The last MRI in the cervical spine revealed a small tumor (41x34x17 mm) beneath the right base of the tongue and eventually the PET/CT confirmed the diagnosis (fig.3). The tumor was removed from the second of authors on 26/4/2017 and the histological conclusion was 'Phosphaturic mesenchymal tumor '. The patient, even from the first week, had a very quick recovery from weakness and the levels of phosphorus and vitamin D came back to normal values. The progress of fractures' union was also impressive.

This case report is presented for the following reasons: 1) The Tumor Induced Osteomalacia (TIO) is very rare. Less than 1000 cases have been reported all over the world. 2) The appearance in the tongue is

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

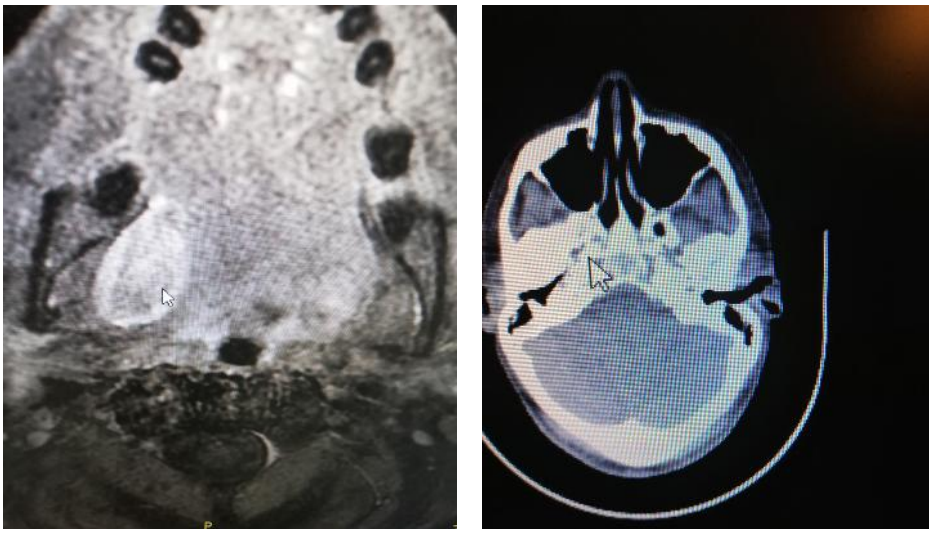

Figure 3.*The TIO in PET (A) and MRI scan (B).*

much rarer. 3) TIO is always a diagnostic and therapeutic challenge. In half of the reported cases, the final diagnosis and the finding of the tumor were delayed for some years. In addition, the removal of this tumor in some cases was very difficult and was not reachable. 4) In our case we had many pathological fractures, more than twenty. These fractures in the limbs were symmetrical. 5) The recovery after the tumor's excision was impressive and today five years from removal the patient is free from the disease.

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CASE REPORT
VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Ochronotic knee in a patient with Alkaptonuria

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ABSTRACT

A patient with a not known history of alkaptonuria was admitted for knee osteoarthritis and total joint replacement treatment. During the operation the dark colour of the knee cartilage resembled the clinical manifestation of Ochronosis. Postoperatively the patient was informed and laboratory and imaging studies put the diagnosis of Alkaptonuria. Alkaptonuria is a rare metabolic disorder affecting the connective tissue. Ill patients are usually suffering from joint arthritis and seek for orthopaedic advice and treatment.

KEYWORDS: Alkaptonuria, Ochronosis, Arthritis.

Introduction

Alkaptonuria is a rare inherited genetic disease which is caused by a gene mutation for the enzyme homogentisate 1,2-dioxygenase (HGD). The body accumulates an intermediate substance called homogentisic acid in the blood and tissues. Homogentisic acid and its oxidized form alkapton are also excreted in the urine. All above products give a dark blue-black colour in the tissues especially the connective tissues and the cartilage. This special colour is also known as Ochronosia.

Alkaptonuria was described by Archibald Edward Garrod, as being the result of the accumulation of intermediates due to metabolic deficiencies. He linked ochronosis with the accumulation of alkaptans in 1902, [1-4] In the same period, the genetics of it was also studied by William Bateson .[5] However, the genetic basis was elucidated in 1996, when HGD mutations were demonstrated. [4,6]

A 1977 study showed that an ochronotic Egyptian mummy had probably suffered from alkaptonuria.[7,8] In most ethnic groups, the prevalence of alkaptonuria is between 1:100,000 and 1:250,000. [4] In Slovakia and the Dominican Republic, the disease is much more common, with prevalence estimated at 1:19,000 people. As for Slovakia, this is not the result of a single mutation, but due to a group of 12 mutations in specific "hot spots" of the HGD gene.[4]

Pathophysiology

ll people carry in their DNA two copies (one received from each parent) of the gene HGD, which contains the genetic information to produce the enzyme homogentisate 1,2-dioxygenase (HGD) which can normally be found in numerous tissues

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

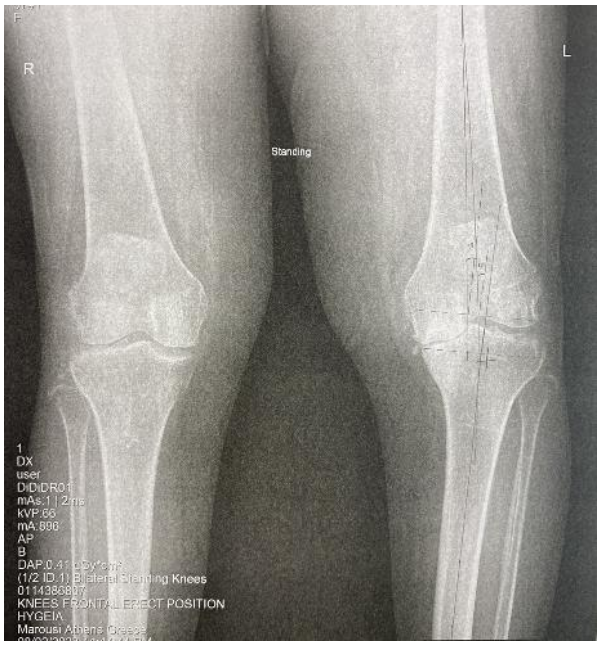

Fig 1. *Pre-operative x-ray showing the severe left knee arthritis and varus deformity*

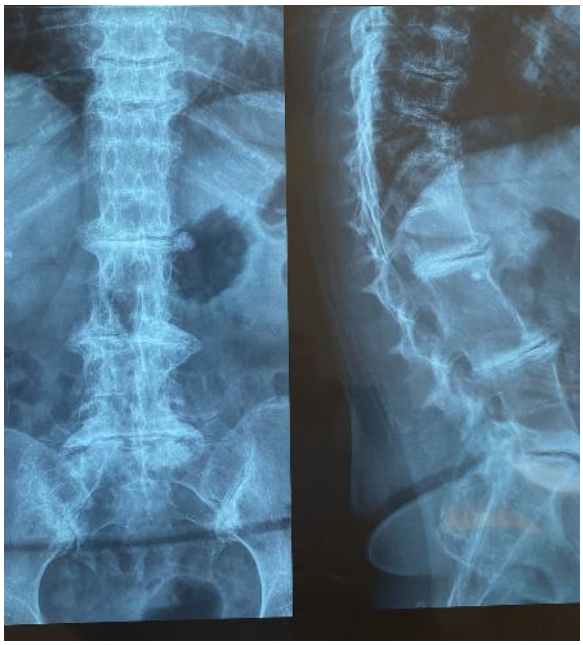

Fig 2. *Lumbar spine x-ray showing the fusion-like vertebral bodies deformity.*

in the body (liver, kidney, small intestine, colon, and prostate). In people with alkaptonuria, both copies of the gene contain abnormalities and the body cannot produce an adequately functioning enzyme. HGD mutations are generally found in certain parts (exons 6, 8, 10, and 13), but a total of over 100 abnormalities has been described throughout the gene. The normal HGD enzyme is an hexamer that is organized in two groups of trimers and contains an iron atom. Different mutations may affect the structure, function, or solubility of the enzyme. Very occasionally, the disease appears to be transmitted in an autosomal-dominant fashion, where a single abnormal copy of HGD from a single parent is associated with alkaptonuria.[1]

The HGD enzyme is involved in the metabolism of the aromatic amino acids phenylalanine and tyrosine. [9] Normally, these enter the bloodstream through protein-containing food and the natural turnover of protein in the body. Tyrosine is specifically required for a number of functions, such as thyroid hormones, melanin and certain proteins, but the vast majority (over 95%) is unused and is metabolized through a group of enzymes that eventually generate acetoacetate and malate. In alkaptonuria, the HGD enzyme cannot metabolize the homogentisic acid (generated from tyrosine) into 4-maleylacetoacetate, and homogentisic acid levels in the blood are 100-fold higher than would normally be expected, despite the fact that a substantial amount is eliminated into the urine by the kidneys. The homogentisic acid is converted to the related substance benzoquinone acetic acid which forms polymers that resemble the skin pigment melanin. These are deposited in the collagen. Therefore, the ochronotic connective tissue is stiffened and unusually brittle, impairing its normal function and causing structural damage.[10]

Clinical manifestations

The paediatrician will be the first physician that will put the diagnosis as dark stains on a baby's diaper are one of the earliest signs of alkaptonuria. The urine may turn dark brown or black when it's exposed to air. [10] By the second and third decades of life the patient may notice signs of early-onset arthritis of the spine or the large joints.

Pigmentation may be noted in the cartilage of the ear and the sclera and corneal limbus of the eye.[10-12] After the age of 30, people begin to

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

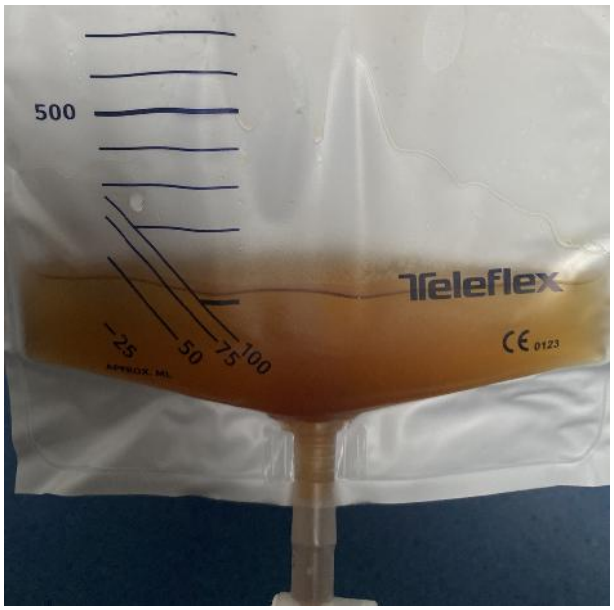

Fig 3. *Orange colour of the urine.*

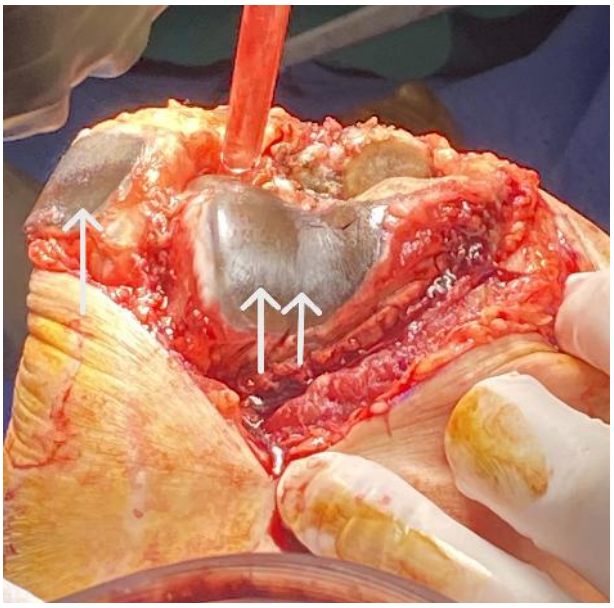

Fig 4. *Ochronosia with an ink- like colour of the patellar cartilage (single arrow) and the trochlea (double arrow).*

Fig 5. *Ochronosia with an ink-like colour of the lateral femoral condyle (single arrow) and severe arthritis without cartilage tissue of the medial femoral condyle (double arrow).*

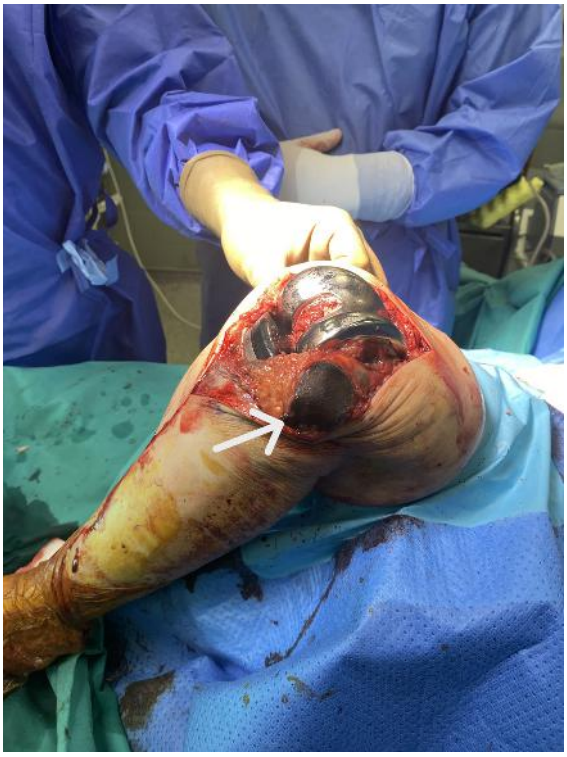

Fig 6. *Despite the ochronotic appearance of the patella cartilage, it was stable and very smooth and the surgeons decided to leave it untreated (arrow).*

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

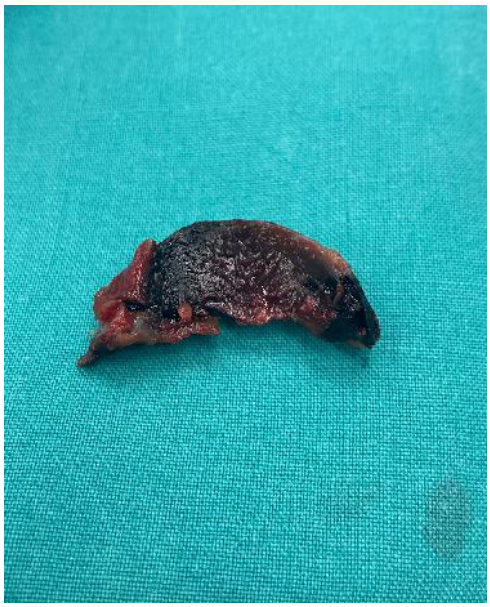

Fig 7. *Black coloured medial meniscus resected.*

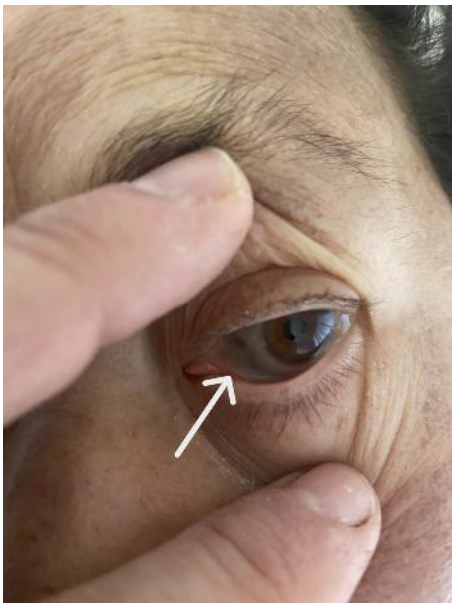

Fig 8. *Black stain of the eye's sclera (arrow).*

develop pain in the weight-bearing joints of the spine, hips, and knees. The pain can be severe to the point that interferes with activities of daily living and may affect the ability to work. Joint-replacement surgery is often necessary at a relatively young age. During such operation, the orthopaedic surgeon is taken by surprise of the dark colour of the cartilage. In the longer term, the involvement of the spinal joints leads to reduced movement of the rib cage and can affect respiratory function. Bone mineral density may be affected, and osteoporosis will increase the risk of bone fractures. Rupture of tendons and muscles may also occur. Valvular heart disease, mainly calcification and regurgitation of the aortic and mitral valves, may occur, and in severe and progressive cases, valve replacement may be necessary. Irregularities in the heart rhythm and heart failure affect a significant proportion of people with alkaptonuria (40% and 10%, respectively). Hearing loss affects 40% of people. Finally, there is a propensity to developing kidney stones exists, gallstones and stones in the prostate and salivary glands (sialolithiasis).[10]

Diagnosis

If the diagnosis of alkaptonuria is suspected, it can be confirmed or excluded by collecting urine for 24 hours and determining the amount of homogentisic acid by means of chromatography. No assay of HGA in blood has been validated. The severity of the symptoms and response to treatment can be quantified through a validated questionnaire titled the AKU Severity Score Index. This assigns scores to the presence of particular symptoms and features, such as the presence of eye and skin pigmentation, joint pain, heart problems, and organ stones.[10]

Treatment

No treatment modality has been unequivocally demonstrated to reduce the complications of alkaptonuria. Main treatment attempts have focused on preventing Ochronosis through the reduction of accumulating homogentisic acid. Such commonly recommended treatments include large doses of ascorbic acid (vitamin C) or dietary restriction of amino acids phenylalanine and tyrosine. However, vitamin C treatment does not have definitively proven effectiveness and protein restriction has not shown to be effective in clinical studies.[10]

Several studies have suggested that the herbicide nitisinone may be effective in the treatment of alkaptonuria. Nitisinone inhibits the enzyme 4-hydroxyphe-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

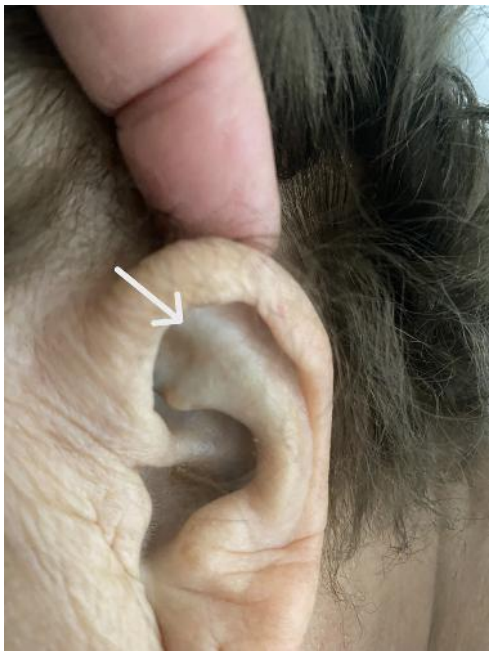

Fig 9. *Blue discoloration of the ear's cartilage (arrow).*

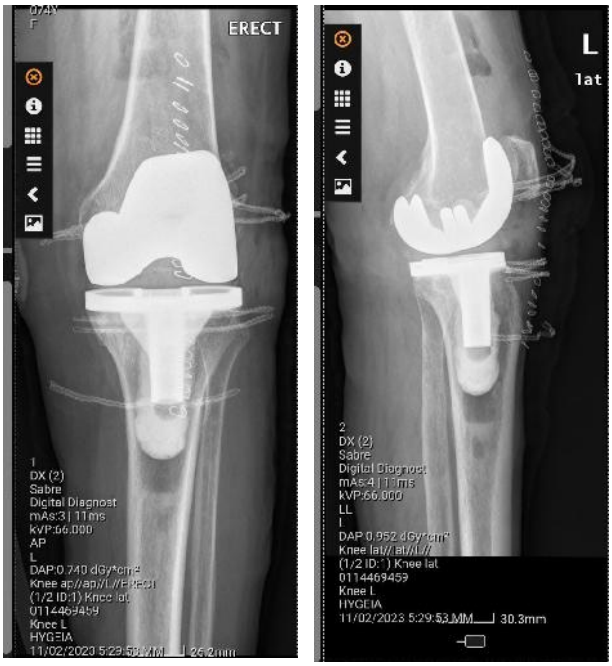

Fig 10. *Postoperative x-rays. (9a and 9b)*

nylpyruvate dioxygenase, responsible for converting tyrosine to homogentisic acid, thereby blocking the production and accumulation of HGA. Nitisinone has been used for some time at much higher doses in the treatment of type I tyrosinemia. Nitisinone treatment has been shown to cause a larger than 95% reduction in plasma and urinary HGA. The main drawback is accumulation of tyrosine, the long-term risks of which are unknown; a particular concern exists about damage to the cornea of the eye. Long-term use requires frequent monitoring for complications.[10] In 2020 the European Medicines Agency approved Orfadin (nitisinone) for the treatment of alkaptonuria in adult patients[13]

In terms of prognosis, alkaptonuria does not appear to affect life expectancy, although the latest study on the topic is from 1985.[10] The main impact is on quality of life; many people with alkaptonuria have disabling symptoms such as pain, poor sleep, and breathing symptoms. These generally start in the fourth decade. The typical age at requiring joint replacement surgery is 50–55 years.

Case report

A 74-year-old lady was admitted for elective total knee replacement due to left knee arthritis. (Fig.1) She had a medical history of hypertension, diabetes mellitus, hyperlipidaemia, and rheumatoid arthritis. Preoperative spine x-rays showed an awkward fusion-like deformity of vertebral bodies (**Fig.2**) Preoperatively, bladder catheterisation demonstrated and orange colour of the urine (Fig.3). During the operation the knee cartilage and the menisci were black in colour and the surrounding soft tissues -especially the quadriceps and the patellar tendons - appeared an ink-like colour. (**Fig.4-7**) The surgeons realized that the patient had ochronosia. They also noticed black stains at the eye's sclera (**Fig.8**) and a blue-black discoloration of the ear cartilage (**Fig.9**). All above phenotypic manifestations set the diagnosis of alkaptonuria. A total knee arthroplasty was then performed **(Fig.10)**. Postoperatively, the patient was informed. The final diagnosis was set with the high levels of homogentisic acid in urine. We recommended the patient to seek for further genetic investigation.

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

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ACTA

YOUNG SCIENTISTS' PAGES

Return to play following spinal cord injury

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ABSTRACT

Approximately 9% of spinal cord injuries (SCI) occur during sports. Decisions concerning return to play (RTP) have to be made for all the injured athletes at all levels of competition.

This study aims to review the existing literature concerning RTP on athletes with SCI regardless of the level of competition and to assess guidelines and protocols concerning RTP after SCI. Through the online PUBMED, CINAHL, EMBASE and AMED databases and following the PRISMA guidelines, studies regarding RTP after SCI were identified.

In total twelve studies were included. Four studies assessed RTP of athletes after a SCI, whereas, the remaining eight studies dealt with RTP protocols and guidelines.

RTP after a SCI must be individualized based on the mechanism of injury, the anatomical site of injury, the imaging studies, and the athlete's recovery response. Future studies providing evidence on thoracic and lumbar injuries are needed in order to achieve stronger recommendations and protocols for a safer RTP.

Key Words: spinal cord injuries, sport injuries, return to play

Introduction

Spinal cord injury (SCI) is a serious medical condition, which often results in severe morbidity and permanent disability. It occurs when the axons of the nerves running through the spinal cord are disrupted, leading to a loss of motor and sensory function below the level of injury [1]. Approximately, 250,000 to 500,000 patients can suffer a SCI every year. Most of these cases are due to preventable causes such as violence and motor vehicle accidents. In the United States, there are approximately 17,000 new cases of SCI every year, and around 282,000 people are estimated to be living with a SCI. The leading cause of SCI is motor vehicle accidents, accounting for 38% of new SCI cases every year. Thirty percent of SCI cases are due to falls, 13% to violence, 9% to sports injuries, and 5% are due to medical and surgical complications. The age group with the highest risk for SCI is 16 to 30 years of age. Males represent the majority of patients with sports injury related SCI. [2]

Regardless of the cause of injury, decisions on the return-to-play (RTP) have to be made for the injured athletes. Since SCIs are among the most devastating injuries in all of sports and the stakes can be so high for the athlete, returning to play after a SCI is one of the most difficult decisions in sports medicine.

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Standardized protocols have been, or are currently being, developed for RTP after anterior cruciate ligament (ACL) reconstruction, concussions, and many other musculoskeletal injuries treated both operatively and conservatively. However, there is no such consensus for RTP after an injury to the spine and the spinal cord. The reasons for the lack of guidelines are multifactorial due to the more complex anatomy and wide spectrum of injuries to the spine, as well as the decreased incidence of these injuries over the past 40 years. The myriad spinal conditions, injuries, and surgical options highlight the need to evaluate RTP guidelines after a SCI according to each specific injury and its respective treatment modality. Most would agree that the athlete returning to sport following a SCI must be asymptomatic, have full strength, and have full active range of motion (ROM); however, each case is unique.

The aim of this study is to review the existing literature concerning return to play of athletes after SCI regardless of their level of competition and to assess guidelines and protocols concerning returning to following after a SCI. This review adheres to the guidelines set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). A literature search was conducted in the following databases; PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine (AMED) and Embase, using the terms "spinal Cord injury" AND 'return to play'.

Study inclusion criteria: The literature research main focus was on recent publications concerning the impact of SCI in RTP. As far as the primary goal of the study was concerned, only case studies were included. The target population was male and female athletes who suffered a SCI during sport participation. Only articles written in English that had their whole text accessible were included. In addition, only articles that were recently published (1990-2020) and presented clinical results of RTP after SCI were included. Concerning the second aim of the study, reviews with guidelines and criteria for RTP after SCI were included. Only recently published articles (1990-2020), written exclusively in English and having their whole text accessible were included.

Study exclusion criteria: Articles that that did not meet the above-mentioned criteria were excluded from the study: articles not written in English, with no access to the whole text and not recently published were excluded. Case reports were excluded too (Table 1).

Discussion

The electronic database search resulted in a total of sixty two articles. One study was excluded as a duplicate. Seven studies were excluded due to lack to full-text access. Thirty four full-text studies were excluded due to lack of relevance. Additionally, eight more studies were excluded: three were not performed to humans, two were case-reports and three were systematic reviews. The final studies that met the study criteria were twelve. Four of those studies assessed RTP after SCI and eight of those assessed guidelines and recommendations for RTP.

The four studies that assessed RTP after SCI included one hundred and thirty three SCI patients (Appendix 1). All patients were athletes and sustained their injury during sports. Most of them were males. Football was the leading sport. All injuries occured between 1974 and 2022. The age range was between thirteen and thirty three years. Most of the injuries were cervical and cervical cord neuropraxia. Some patients had undergone operative treatment and others conservative. All patients were assessed for RTP and some of them were followed up after RTP.

A recent study by Poudel and Sherman included 14 cases of football-related SCI. Eight out of 14 patients had suffered a vertebral fracture-dislocation, whereas two had concomitant traumatic brain injury. Neurologically, 54% had tetraplegia, 39% paraplegia, and 7% suffered from hemiplegia and sensory deficit. Two patients regained the ability to walk with orthosis and four (28.5%) regained full mobility and RTP. The overall mortality was 14%.[4] In 2012, Brigham and Capo reviewed the case history, physical examination, and MR images of 4 professional athletes who suffered from cervical cord contusions. None of them had an acute disc herniation, fracture, instability or focal cord compression. All underwent anterior fusion at the level of their contusion and were later oncontacted by phone to assess symptoms at a minimum follow-up of

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

2 years after the injury. All athletes returned to active competition (100% RTP). During follow-up, 2 athletes developed new contusions. One athlete suffered a new contusion adjacent to the fusion approximately 5 years later and the second athlete suffered a contusion away from the fusion site approximately 2 years later. None of the athletes developed permanent neurological damage.[9] In 1997, Torg et al. reviewed 110 cases of cervical cord neurapraxia. Overall, 60% of them returned to sports participation at their previous level of competition. Of the patients returning to contact sports, 35 (56%) experienced a recurrent episode.[15] Maroon et al. studied five elite football players who had experienced episodes of neurapraxia. All patients experienced bilateral paresthesias. Three patients experienced paresthesias in all four extremities and two in the upper extremities, lasting from a few minutes to more than 24 hours. Transient motor deficits occurred in two patients with no permanent sequelae. In all cases, neuroimaging confirmed the presence of herniated discs and focal cord compression but no parenchymal changes. All patients underwent anterior cervical microdiscectomy and fusion, and cervical plates were placed in four patients. After aggressive rehabilitation and confirmation of fusion ranging from 9 weeks to 8 months postoperatively, all players were allowed to return to active play (100% RTP). Two of them developed recurrent career-ending disc herniation, one above and the other below the fusion level. One player required repeated spinal cord decompression.[16]

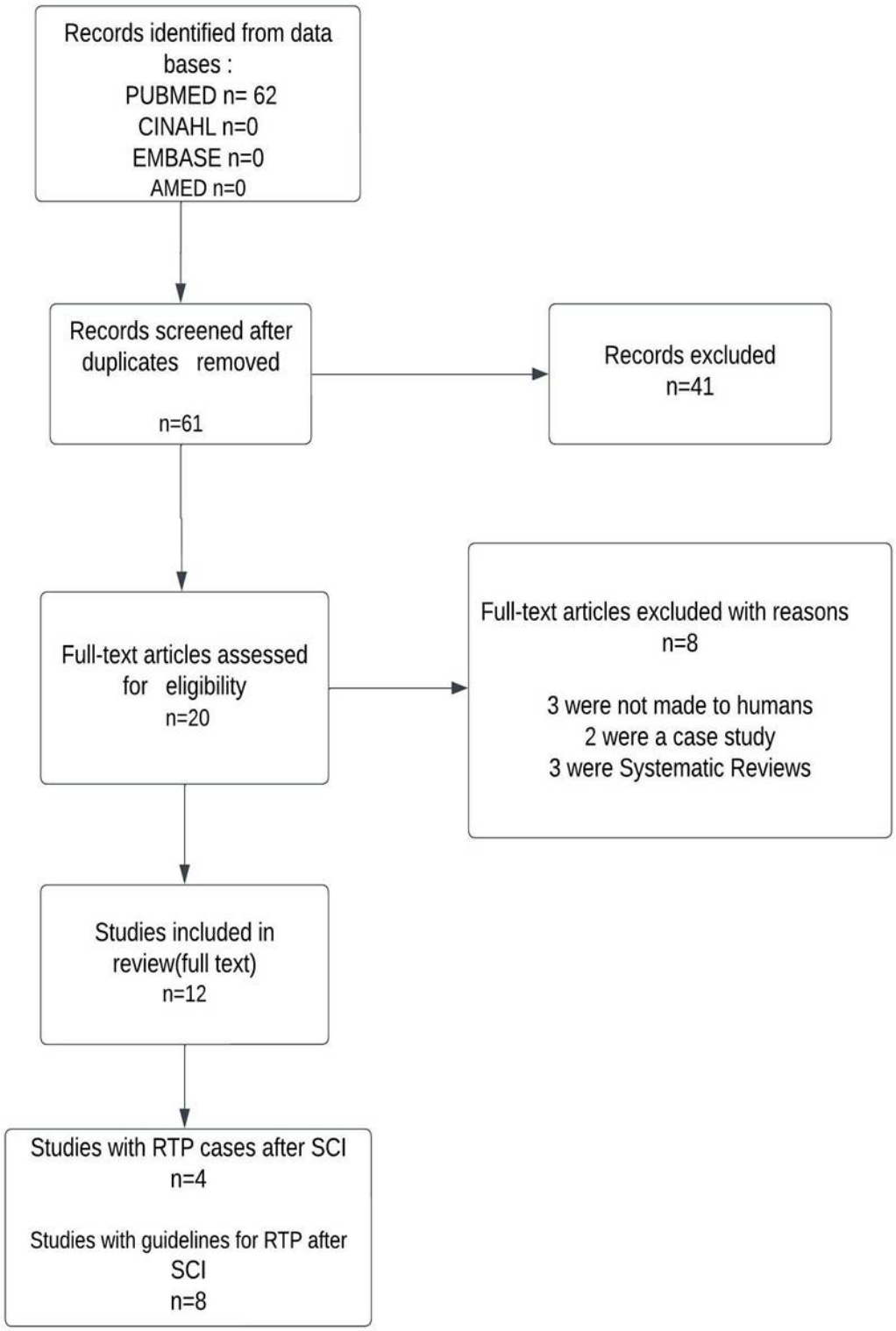
Concerning the second aim of the study, to reassess the guidelines for RTP, eight studies were included and evaluated. Only six articles presented guidelines for RTP following cervical SCI. One study assessed recognition and management of SCI in sports while another study presented RTP recommendations following cervical, thoracic and lumbar SCI. [6]''A study conducted by Robert C. Cantu et al. concluded that RTP following cervical spine injury is complex, often controversial, and patient specific. There are no universally accepted RTP criteria. The decision to RTPt after a cervical spine injury must be individualized based on the mechanism of injury, anatomical site, imaging studies, and athletes' recovery response. [5] A study conducted by Philip Huang et al concerning RTP recommendations following cervical, thoracic and lumbar SCI concluded that there are no standardized consensus guidelines for RTP after spine injuries. However, there was a good general agreement on 4 fundamental criteria that must be met for a player to return to sport; (i) the athletes should be pain free, (ii) have full range of motion, (iii) regain full strength, and (iv) show no evidence of neurologic injury. [6] In their survey, John C. France et al., suggested a consensus among surgeons for allowing patients with relatively normal imaging and resolution of symptoms to return to high-contact activities; however, patients with cervical stenosis or clinical symptoms continue to be a challenge for future management [7]. Robert Brian Bettencourt and Michael M. Linder concluded that research best supports that, in the absence of cervical spine instability or cervical spine stenosis (CSS), temporary cervical cord neuropraxia (CCN) and transient quadriparesis (TQ) are not associated with a significantly increased risk for permanent or catastrophic SCI. However, investigators' opinions vary widely on return-to-play criteria after TQ or CCN in the setting of CSS [8].

Another study conducted by Alexander R Vaccaro et al., concluded that the issue of RTP for an athlete after a cervical spine injury is controversial. It was also emphasized that there are no firm criteria for return to play, although most authors agree on many specific issues. Tremendous extrinsic pressures may be exerted on the physician from noninvolved and involved parties in regards to returning an athlete to competitive activities. The decision to permit the RTP to a particular sport should be based on the mechanism of injury, objective anatomical injury (as demonstrated by clinical examination and radiographic evaluation) and athlete's recovery response [10]. In their study, Jeffrey A. Rihn et al. stated that despite significant efforts to develop guidelines for RTP for cervical spine injury, the issue remains controversial. Currently, no set of guidelines for RTP exists for cervical lesions. This issue is often complicated by extrinsic pressures placed on the physician from coaches, players, families and other involved parties. Injured players desiring to return to play must be evaluated thoroughly to minimize the risk of recurrent injury. Evaluation includes a detailed history and physical examination

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

TABLE 1

Flow diagram of studies though the review



VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

and a complete neurological examination. The patient must be able to demonstrate a full, painless cervical range of motion and have no evidence of neurological deficit prior to returning to play [11]. In his study, Charles H. Tator stated that the issue of return to play presents a specific management challenge in athletes. In general, the treating team should use the same return-to-play guidelines for professional and amateur athletes, although professionals often treat themselves differently from the general population. Practitioners should be prepared for resistance from some relatives, coaches, trainers, league officials, and players' agents and should be prepared for a higher percentage of noncompliance from professional athletes. Many factors need to be considered when advising athletes about return to play after spinal injuries. Although there have been good attempts to develop return-to-play guidelines for spinal injuries, there is still a great deal of uncertainty. The decision about return to play depends primarily on the nature of the injury and the nature of the activity in which the athlete is engaged. [12] A study contacted by Robert C. Cantu concluded that return-to-play decisions after traumatic spine or spinal cord injury are not always clear and often require individualization. The study attempted to provide a framework for these decisions. Type 1 athletic injuries are those with permanent neurologic injury and preclude further participation of the player in contact sports. Type 2 injuries consist of transient neurologic disturbances with normal radiographic studies. If the complete workup reveals no injury, these players may return to competition once they are symptom free. Type 3 injuries are heterogeneous, including all players with radiographic abnormalities. Those athletes with significant bone or ligamentous spinal instability, spinal cord contusion, or significant spinal stenosis are advised not to return to contact sports. Other radiographic abnormalities, such as spear tackler's spine, posterior ligamentous injury, congenital fusion, herniated disks, or degenerative spondylitic disease, require consideration on an individual basis. [14]

From the twelve studies that were included in this review only four assessed patients' RTP following SCI, while the other eight assessed existing guidelines for RTP after a SCI. Based on the number of such events, there is limited evidence regarding RTP following SCI. Future prospective multicenter studies are needed to better address our purpose and key questions. Eight studies addressed cervical SCI. Only the study by Huang et al provided guidelines for RTP after thoracic and lumbar SCI. This is due to the fact that the number of cervical SCIs in sports is significantly higher than thoracic and lumbar SCIs. Out of the one hundred and thirty three cases included in this review only four cases were non cervical. Due to the low number of thoracic and lumbar SCIs in sports, more studies need to be published.

One of the aims of our study was to assess guidelines for RTP after a SCI. In a recent study, the authors concluded that there are no universally accepted RTP criteria and that RTP after a cervical spine injury is complex, controversial and patient specific. The decision to RTP after a cervical spine injury must be individualized based on the mechanism of injury, the anatomical site, the imaging studies and the athlete's recovery response. In general, athletes can return to contact sports after cervical spine injury when they are asymptomatic, demonstrate full ROM, have regained pre-injury neck strength, and their imaging shows no evidence of spinal stenosis, disc disease or instability. [5,6,10,11,14] Another recent study concluded that advances in on/off field evaluation and management, rehabilitation strategies and return-to-play guidelines have improved the care of athletes that sustain cervical injuries. Continued surveillance of cervical injuries in football and other contact sports will hopefully lead to further improvements in preventative strategies. [11]

Most of the cases included in this review (one hundred and fifteen) where episodes of Cervical Cord Neuropraxia (CCN). In their study, Torg et al concluded that CCN is a transient neurological phenomenon and that individuals with uncomplicated CCN may be permitted to return to their previous activity without an increased risk of permanent neurological injury. They also concluded that congenital or degenerative narrowing of the cervical canal is a strong risk factor, increasing the overall recurrence rate after RTP to 56% and that the risk of recurrence is strongly and inversely correlated to the canal's sagittal for future CCN episodes (p;0.001). These data enable the physician to counsel individuals regarding a predicted

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

risk of recurrence based on canal measurements. [15]. In another recent study, the authors concluded that the athlete with previous transient CCN must accept that his injury was not necessarily benign and that returning to play to contact or collision sports carries an apparently small, but nonetheless present, risk of permanent SCI [16]. Torg et al reported that cervical stenosis was predictive of another episode of CCN (53%) but not predictive of a catastrophic injury [3]. Dailey et al concluded that return to full participation in high-energy contact sports could be based on radiographic findings: patients with transient neuropraxia without stenosis could return to sports (strong recommendation), whereas stenotic patients could not return to sports (weak recommendation). Furthermore, a strong recommendation was made to permit players to return to full participation after decompression with a single-level anterior cervical fusion. [17]

Limitations:

This review presented the following limitations: (a) the small sample size of 12 articles that met the eligibility criteria, which could be overcome by searching additional databases; (b) studies were only published in English language, which should be taken into consideration when interpreting the conclusion of the study.

Conclusion:

There is limited evidence on the current practice standards RTP following SCI. More studies need to be made in order to have stronger recommendations and protocols for a safer RTP after SCI especially in thoracic and lumbar SCI where the evidence is extremely low. Most of the studies included in this review agree that RTP after a cervical spine injury is complicated, often controversial, and patient specific. The decision to return an athlete to a sport after a cervical spine injury must be individualized based on the mechanism of injury, anatomical site, imaging studies, and the athlete's recovery response. There are some strong recommendations about safe RTP after CCN without spinal stenosis but further studies need to be made too.

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APPENDIX 1

Data extraction list

Study	Year	Population	Intervation	Results
Football (soccer)-related spinal cord injury—reported cases from 1976 to 2020(Manoj K. Poudel, Andrew L. Sherman)	2020	Fourteen cases of football-related SCI	Eight of 14 individuals had vertebral fracture/dislocation, whereas two individuals had concomitant traumatic brain injury. Neurologically, 54% had tetraplegia, 39% had paraplegia, and 8% each suffered from hemiplegia and sensory deficit. Two cases could regain ability to walk with orthosis and four had full mobility with "Return to Play" (RTP). Themortalitywas 14%.	More than 50% of the individuals with football-related SCI were able to walk or RTP after rehabilitation. Further studies are required to establish universal RTP criteria and formulate preventive measures.

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Cervical Spinal Cord Contusion in Professional Athletes(Craig D. Brigham et al)	2013	4 professional athletes 27 year of age .	All athletes had documented cervical cord contusions. None of the athletes had an acute disc herniation, fracture, instability, or focal cord compression. All athletes were contacted by telephone to assess symptoms at a minimum follow-up of 2 years after injury.	Return-to-play guidelines should emphasize the athletes' history of symptoms in context with their MR image because there is poor correlation between the finding of a contusion and the clinical presentation. Recurrence of symptoms is common and the long term consequences of repeated episodes remain unknown
Cervical cord neurapraxia: classification, pathomechanics, morbidity, and management guidelines (Joseph S. Torg et al)	1997	One hundred ten cases of the transient neurological phenomenon, cervical cord neurapraxia (CCN), are presented. One hundred nine males and one female were included in the study; the average age of the participants was 21 years	All episodes occurred during sports participation; 87% occurred while the patient was playing football. Follow-up review lasting an average of 3.3 years was available for 105 patients (95%)	1)CCN is a transient neurological phenomenon and individuals with uncomplicated CCN may be permitted to return to their previous activity without an increased risk of permanent neurological injury; 2) congenital or degenerative narrowing of the sagittal diameter of the cervical canal is a causative factor; 3) the overall recurrence rate after return to play is 56%; and 4) the risk of recurrence is strongly and inversely correlated with sagittal canal diameter and it is useful in the prediction of future episodes of CCN (p , 0.001). These data will enable the physician to counsel individuals regarding a predicted risk of recurrence based on canal measurements.
Cervical neurapraxia in elite athletes: evaluation and surgical treatment (Joseph C. Maroon et al)	2007	Five elite football players were evaluated after experiencing episodes of neurapraxia	All patients underwent anterior cervical microdiscectomy and fusion, and cervical plates were placed in four. After aggressive rehabilitation and confirmation of fusion ranging from 9 weeks to 8 months postoperatively, the players were allowed to return to active play. Two of the players developed recurrent career-ending disc herniations, one above and the other below the fusion level. Oneplayerr equiredrepeatedspinalcorddecompression	Neurologically intact athletes with focal cord compression due to a single-level herniated disc may safely return to football after undergoing decompressive surgery and confirmation of fusion. It appears, however, that there may be an increased chance of repeated herniation above or below a fused level.

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

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Dorsal root ganglion stimulation in the treatment of complex regional pain syndrome, following a spinal cord injury

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ABSTRACT

Complex regional pain syndrome is a chronic pain condition that presents symptoms from the autonomous nervous system, as well as motor and sensory disturbances. Thus, because of the complexity of its symptoms, it becomes difficult to find the appropriate treatment for this syndrome.

The aim of this thesis, is to examine the effectiveness of dorsal root ganglion stimulation as a treatment for complex regional pain syndrome, following a spinal cord injury. The research strategy, for the identification of the relevant literature, included data retrieved from articles in English, from Greek and foreign bibliography, as well as from internet sources. The results showed great effectiveness for dorsal root ganglion stimulation, in comparison with other conventional treatments. According to several studies, significant improvement was observed in the fields of patients' pain relief and mood and quality of life, while excellent pain-paresthesia overlap was reported. Furthermore, due to the unique anatomical position of the dorsal root ganglion, no lead migrations or differences in paresthesia's intensity -due to postural changes- were reported. In addition, according to long-term outcomes, therapy habituation did not occur in patients that had dorsal root ganglion stimulation treatment and as a result, there was no loss of the therapeutic effect over time. Thus, dorsal root ganglion stimulation for complex regional pain syndrome following a spinal cord injury, is estimated to be beneficial. Nevertheless, more research is needed in order to receive more accurate results.

Key words: dorsal root ganglion stimulation, complex regional pain syndrome, spinal cord injury, spinal cord stimulation

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Introduction

Complex regional pain syndrome (CRPS) is a pain disorder that usually occurs after a surgery, an injury or a vascular accident. It is a chronic and progressive condition that involves the extremities and patients may experience vascular, sensorimotor and trophic changes [1,2]. According to the International Association for the Study of Pain (IASP), there are two types of CRPS: (a) CRPS type I (also known as Reflex Sympathetic Dystrophy or RSD) and (b) CRPS type II (also known as causalgia) [3]. The most common symptoms of this pain syndrome include hyperesthesia and allodynia, however patients can also experience changes in skin temperature and color, sweating, swelling of the affected area, muscle atrophy and decreased range of motion of the affected joints [4]. The clinical diagnostic criteria for CRPS (Budapest criteria), have recently been revised. These criteria describe CRPS as "an array of painful conditions that are characterized by a continuing regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time [5]. Establishing a treatment for CRPS that has both efficacy and long-term outcome, is difficult [6]. However, there is evidence that that early treatment may lead to improved results [7]. Therapies for both types of CRPS focus on pain relief, improvement of function of the affected extremity, decreased edema and increased range of motion of the affected joints [8].

Spinal cord stimulation (SCS) is considered to be a therapeutic option for the treatment of chronic pain, thus it is used for the treatment of CRPS when other treatments have failed. SCS has been successfully applied since 1967, for treating chronic pain in the trunk and limbs [9]. The neurostimulation system that is used, consists of stimulation leads implanted near the spinal cord and a pulse generator that produces electrical stimulation pulses [10,11]. Despite the benefits of this therapy, there are limitations and deficiencies, including changes in the intensity of stimulation due to posture related changes, lead migration and therapy habituation [12-14]. Furthermore, SCS seems not to cover completely some painful areas such as low back, groin, pelvis, buttocks and neck [15]. As a result, different neurostimulation techniques needed to be found.

Neuromodulation of the dorsal root ganglion (DRG) is an alternative treatment targeting the exact anatomical area that has been affected by CRPS and is difficult to be approached with any other traditional treatment [16]. The DRG is located within the spinal foramen in the lateral epidural space and houses the cell bodies of the primary sensory neurons, which are responsible for modulating sensory information and transferring it to the spinal cord. There are several types of DRG neurons, categorized by their size and function [17]. Recent studies have shown that DRG stimulation is safe and effective even for patients that in the past had a SCS treatment that failed [18]. In addition, DRG stimulation seems to cover in great extent the area of paresthesia and leads to pain relief, without the danger of lead migration or changes related to the intensity of stimulation because of patient's postural changes [19].

A review of the current literature was performed by using the online PUBMED, COCHRANE and PEDro database and the following keywords: dorsal root ganglion stimulation, complex regional pain syndrome, spinal cord injury, spinal cord stimulation. Inclusion criteria included: (a) date of publication, later than 2000 (b) subjects diagnosed with complex regional pain syndrome following a spinal cord injury, (c) mental state ensuring cooperation during the performance of tests.

Discussion

The search resulted in 25 studies. After checking titles and summaries, 11 articles were rejected as irrelevant to the subject. Of the 14 remaining publications, 5 were rejected due to specific reasons. After reviewing the reference lists of the included studies, 9 more studies were included. Finally, there were 18 studies included in the present review (Figure 1).

The role of dorsal root ganglion stimulation in the

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

treatment of CRPS

In a prospective study, Elliot S. Krames changed the common opinion that the DRG is not involved in the development of neuropathic pain. Instead, he proved that it is not only involved in the development of neuropathic pain, but also affects the process of chronicity, from acute to chronic pain [20]. Huygen et al., in 2019, evaluated the effects of dorsal root ganglion stimulation in 49 patients with CRPS type I or in patients with failed back surgery syndrome (FBSS) followed by CRPS type II. According to the results, patients with CRPS type II had an 43.7% average reduction of pain at 12 months post-implant, with 60% of them reporting a 50% pain relief, using the visual analog pain scale (VAS). Patients with CRPS type I, had an 46.8% average reduction of pain, with 33.3% of them reporting 50% pain relief. In addition, there was improvement in subjects' quality of life, as well as in their total mood disturbance [21]. In 2014, Long Liem et al., trialed a DRG-SCS device in 51 patients and examined its effectiveness in pain relief, using the VAS and the Brief Pain Inventory (BPI) scales and in the quality of life and mood of the subjects, using the questionnaires: EQ-5D-3L, Profile of Mood States (POMS) and the McGill Pain Questionnaire. The subjects also captured their pain and paresthesia distributions on body maps. Between baseline and the 12-month follow-up, overall pain was reduced by 56%, while pain localized to the legs, feet and back was reduced by 62%, 80% and 42%, respectively. Also, sixty per cent of patients reported more than 50% improvement in their pain. Furthermore, subjects reported high levels of satisfaction related to the results of their treatment and benefits in mood and quality of life. It is noteworthy that the coverage of pain-paresthesia area was precise and remained stable during those 12 months of the study [22].

Comparison of DRG stimulation and SCS

Timothy R. Deer et al., in 2017, directly compared the safety and efficacy of DRGS and SCS for CRPS and causalgia. At the primary end point, patients using DRG stimulation had a higher score related to treatment success (81.25%), compared to the corresponding score of traditional SCS (55.7%), while the same score at the 12-month follow-up was 74.2% for the DRG team and 53% for the SCS team. In addition, the DRG team reported a minimum change, related to the intense of paresthesia due to postural changes of the subjects, rating of 0.1±1.6, while the SCS team had a mean difference of 1.8 ± 3.0 between supine and upright intensity of paresthesia. Both groups reported improvements in SF-36 scores, but DRG patients improved even more on the physical component score, general health and social functioning, compared with SCS patients. Last but not least, at 12-month follow-up, 94.5% of the patients in DRG group, reported that they felt paresthesia only in their painful area, in contrast with 61.2% of the patients in SCS group [23]. Another comparison between DRG stimulation and SCS took place in 2019, when Robert M. Levy et al., compared therapy habituation among these two techniques, in patients with CRPS I or II. For both groups, mean percentage of pain relief (PPR) was greater at the end of the trial period than all the other follow-ups (DRG=82.2% and SCS=77.7%). After the permanent DRG system implantation, there were not significant differences on this percentage during the 12 months of the study (PPR range= 69.3-73.9%). On the other hand, PPR for SCS team at 1 month was 66.9%, while at 9 and 12 month was 58.3% and 57.9%, respectively. Furthermore, the percentage of subjects reported at least 50% pain relief from baseline, was for both teams highest after the end of the trial period (DRG=89% and SCS=86.1%). This responder rate decreased to 74% at 1 month for the DRG group, but remained stable for the rest of the study. On the contrary, for the SCS group, this percentage continues to decline, reaching 61.1% at 12 months [24].

Safety of DRG stimulation

Regarding the safety of DRG stimulation, Deer et al. in 2013, mentioned 17 events during their study. Three of them were considered as adverse events and involved pain increase after the procedure of implantation, while the other complications were related to lead migration, device inactivation and reactions to antibiotics [25]. 86 safety events were

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

reported by Liam et al. in 2014, half of them related to the device, such us lead migration and fracture or temporary motor stimulation [22]. In their study, Deer et al. compared the safety between DRG stimulation and SCS. The results showed that patients of the DRG team had a higher rate of adverse events (46.1%), than the patients of the SCS team (26.3%). This might be due to longer operative times in DRG stimulation team, than in the SCS team [23].

The results of using dorsal root ganglion stimulation as a treatment in CRPS patients are encouraging. However, evidence of long term results and effectiveness of this treatment is lacking.

Conflict of Interest

The authors declared no conflicts of interest.

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

The importance of geriatric physiotherapy in the prevention of falls and concomitant injuries of the spine

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ABSTRACT

Due to demographic issues, world population tends to age gradually. Physiological deterioration over time can lead to decreased balance capacity and increased risk of falls in old age. Frailty syndrome is therefore defined as the age-related reduction of multiple physiological processes and functions, with a negative impact on multiple areas of health such as disability, injury, various diseases, hospitalizations, falls and mortality, affecting the spine directly and indirectly.

Prevention of falls among the elderly is therefore imperative for healthcare systems. Interventions such as resistance training, balance training, endurance training, coordination training, combination exercises (ie, simultaneous strength, endurance and balance training) as well as Tai-chi, have yielded beneficial results in some functional parameters.

Recent technological developments have also led to the introduction of new virtual reality-based practice methods for performing different tasks. There is evidence that falls can be prevented by screening for risk factors and prescribing custom interventions. Determining the type of exercise intervention that is safest, most effective and most easily applicable would greatly assist clinical physiotherapists and caregivers in making informed decisions about which interventions to perform, always depending on the given clinical goals and budgets restrictions.

Key words: elderly, falls, prevention, physical therapy, spinal cord injury

Introduction

The World Health Organization identifies falls as the second leading cause of death-related injuries and prioritizes related research and development programs [1-9]. Of the elderly living in the community over the age of 64, 28–35% of them sustain a fall each year and the incidence of falls increases with age and the level of disability, up to 50% in the elderly over the age of 80 [10]. It represents a serious public health problem due to the high demands of healthcare and has a significant impact on patient's quality of life. The aging process, accompanied by mental changes in the elderly, increases the risk of falling more than 10 times, compared to young adults and middle-aged individuals

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

[11]. Almost the entire brain is involved in maintaining the right balance [12]. As a result, the effectiveness of the systems responsible for stability decreases progressively with age [13].

Furthermore, pain is an important public health issue among the elderly living in the community as it is diagnosed with a prevalence of 45-80%. It is closely linked to reduced physical function, loss of independence, psychological distress, lower quality of life and even the risk of premature death. Recent research has also found that concomitant pain in the elderly is associated with a higher risk of falls, which is another complementary health problem in the current situation [14].

Fall, by definition, occurs when a part of the human body touches the floor due to loss of balance or stability without necessarily some external stimulus in daily life or due to loss of consciousness, and this results in physical injury, reduced daily activity, loss of confidence and lifestyle changes, especially in the elderly [15]. Injury can include bruises, hematomas, fractures and even brain damage or other minor complications with reduced normal function and muscle weakness, leading to other falls in the future [16].

However, these conditions are largely preventable, with more and more evidence suggesting that exercise can be a safe and effective way to reduce falls [7]. Training techniques aim to prevent these complications in the elderly. Studies have extensively reported the effectiveness of multifactoral prevention programs that include training, exercise, environmental modification and psychological interventions [17]. Referral to a physiotherapist is one of the evidence-based interventions proposed by the CDC and the United States Preventive Disaster Management Team [18]. Physiotherapists can also help connect seniors with programs and resources provided by the community to increase physical activity, reduce the risk of falling or manage chronic diseases [19].

To optimize the plan of training and achieve these goals in the elderly with physical disability, the most effective type of exercise program should be identified taking into account the optimal combination of intensity, volume and frequency of weekly training that will promote neuromuscular cardiovascular adaptations [4]. Therefore, the overall review was

A review of the current literature was performed with the aim to create a guide to direct the physiotherapist's practice using existing programs that treat falls in older adults living in the community, using the online PUBMED database and the following keywords: elderly, falls, prevention, physical therapy, spinal cord injury. Inclusion criteria in the review comprised: (a) date of publication (2000 and later), (b) age of subjects (at least 65 years old), (c) physical condition enabling movement and performance of everyday activities, (d) mental state ensuring cooperation during the performance of tests, (e) referral for physiotherapy. Exclusion criteria comprised: (a) uncompleted studies, (b) severe comorbidities like stroke, heart attacks and other diagnosed neurological, musculoskeletal, or systemic disorders, (c) previous operations related to knee or hip joint replacement, (d) data on exercise interventions that were associated with hormonal treatments, drug therapy, or other supplements.

Discussion

The search resulted in 1472 studies. After checking titles and summaries, 1369 articles were rejected as irrelevant to the subject. Of the 103 remaining publications, 62 were rejected due to specific reasons. After reviewing the reference lists of the included studies, 2 more studies were included. Finally, 43 studies were included in the present review. (Figure 1- Flowchart).

Combination exercise - key to prevent falls in the elderly

Combination interventions are known to prevent falls among the elderly, but the relative importance between different strategies is unknown [20]. Balance is a variable that can be effectively increased by different means of exercise. Therefore, it is essential to promote physical activity in old age. There is evidence that some types of exercise programs have long-term benefits and results can be maintained for up to two years after intervention [21]. These programs should provide gradual increases in their frequency, intensity and complexity to be the best strategy to improve gait, balance and strength, as well as to maintain functional capacity during aging [4]. Exercise interventions, especially the combination of strength training and balance, immediately show their effectiveness in preventing falls [22]. Most of the studies showing improvements in gait, balance and risk of falling have used this combi-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

nation [4]. However, due to the physical characteristics of the elderly, the exercises should not pose a risk of injury and should be easy to apply, even at home [16]. The aim of this study, therefore, was to determine the results of such a program in the measurements related to this risk. Preventive screening for instability factors can lead to the creation of a personalized intervention, parts of which will be applied directly by the physiotherapist in consultation with other health professionals. Exercise, including structured physiotherapy, is an effective component of a fall prevention program and physiotherapists can always provide additional advice on both the modification of the environmental space as well as the footwear and other aids which are part of the general education about risk of fall [6].

International education and fall prevention programs for the elderly

Referral for appropriate interventions is a necessary follow-up after the screening. In the USA, the majority of physiotherapists who report to assess the elderly for risk of falls in the community are aware that the National Council on Aging (NCOA) recommends institutionalized and implemented programs for the elderly [18]. The most common references are in the Otago, A Matter of Balance, Tai Chi and YMCA Moving for Better Balance exercise programs. More specifically, performing Otago-based exercises can additionally reduce pain, both in the short and long term, making it a valuable tool for both pain management and fall prevention, in the higher-risk target population [14].

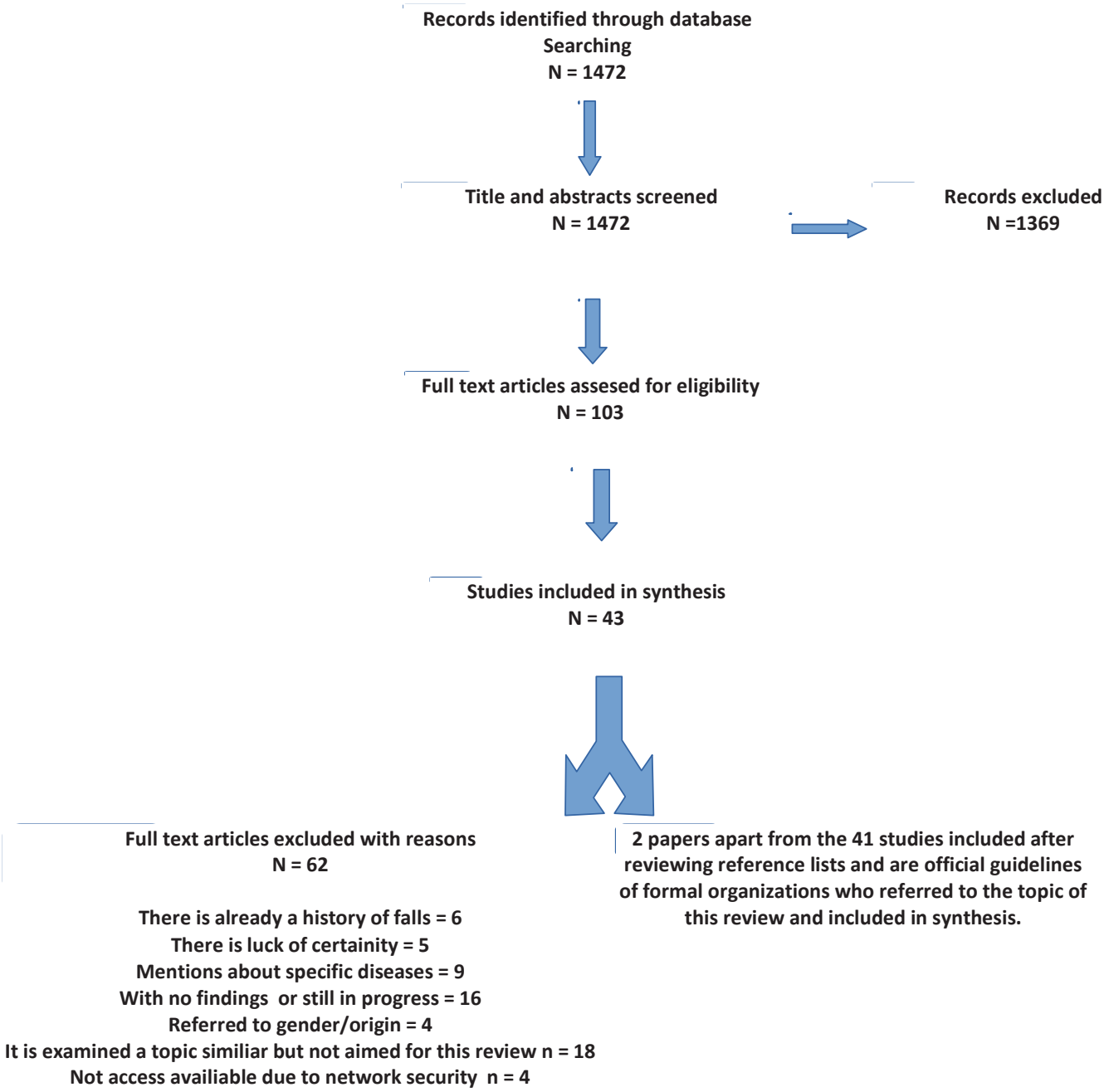
However, there are other proven programs that, depending on their clinical goal, further cover the range of prevention in old age. In an effort to assess the fear that is directly related to the functional isolation of the elderly, the program "Activity, Balance, Learning and Exposure" (ABLE) has been developed. The application of ABLE, which integrates cognitive-behavioral therapy and exercise, reduces the fear and avoidance of activities in the elderly with disproportionate fear of falls during the intervention period of 8 weeks [23]. Decreased risk and fall rates have also been observed in the HOP-UP-PT (Home-based Older Persons Upstreaming Prevention-Physical Therapy) program. The HOP-UP-PT also uses a multifactorial approach with the unique element that referrals in the program do not originate from health professionals, but directly from the local rehabilitation centers for the elderly [24].

The LiFE program provides an alternative to traditional exercise as well, with functional exercise and the daily background of the elderly being the focus of interventions, so as to protect against falls and to improve and maintain functional capacity [25]. Reference is additionally made to the Multisystemic Exercise Program (MPE), which is designed based on the components of fall risk assessment, using the Physiological Profile Assessment (PPA). MPE, in accordance with the above, consists of four parts: susceptibility training, muscle strengthening training, reaction time training with acoustic signals and rational balance training with the results indicating that MPE is a tolerable and sustainable method, which leads to reducing the fear of falls and depression and increasing the quality of life [2].

Technological interventions in the field of prevention

The findings of this work suggest that both visual training and cognitive training enhance physical performance, reaction time, executive functions, obstacle avoidance, and significantly reduce the rate and fear of falling. More specifically, visual biofeedback training is believed to help improve balance through sensory integration, because it creates reflex reactions through visual information against body movement [15]. Center of gravity improves following virtual reality training, indicating that the balance ability of the elderly is gradually ameliorated. Participating in such programs makes the elderly understand the importance of orthostatic control by observing their dummy on a screen. Indicatively, in a special assessment of balance with the eyes open or closed, virtual reality training has equally improved the ability to balance, both with and without visual information [5]. The observed improvements in distraction as well as in gait with simultaneous execution of various tests underline the condition that an exercise program should include at least one element of cognitive-virtual challenge [26]. The benefits of these interventions are found in exercise programs such as EMAT, a 2-hour workout in which participants complete a ladder-type, mesh-type and circular-type exercise-game, weekly, for a total of 3 months, effec-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023



(Fig.1). Flowchart of the present review.

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

tively reducing the risk of falling and increasing gait for multiple tasks. Other study findings show that unsupervised Interactive Cognitive-Motor Step Training (ICMT) in which participants perform four gait games that require attention span, inhibition of irrelevant stimuli, toggle between tasks, rotation of objects, and rapid decision-making has led to improvements with regard to certain cognitive functions associated with falls in old age. Also, the widespread Wii, has now the potential to serve as a useful training tool for vulnerable populations at home or even during hospital stay. Training can be achieved with the safety of a fixed device that can be equipped with balance rods or straps [27].

Similar adaptive improvements could be gained by perturbation training that improves reactive balance and the frequency of falls after slips and vibrations, caused by special machines on a treadmill [28]. Given the positive findings after a single session, such a slip-training is strongly suggested as a complement to conventional training or in combination with other similar approaches [28]. The combination of a low-cost balance plate or disc and a workout-exercise seems to be an ideal approach to the risk of falls in the elderly based on improvements in orthostatic oscillation [29]. Slip and Trip training is an emerging field, which has been shown to have significant benefits in laboratory clinical trials. However, these exercises, applied in open ground of different type and quality, can have a synergistic effect, reflecting a great advantage for the elderly to maintain their independence with a simple and easy activity in their daily lives and providing evidence to facilitate the transfer of clinical practice trials from indoor to outdoor activities [30].

These results provide a new benchmark for fall prevention protocols, suggesting that similar to the "fall-learning" seen in early childhood, through the experience of slipping and falling, the elderly can utilize the experience provided by these programs and novel technologies.

Conflicts of interest

The authors declared no conflicts of interest.

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The role of adapted/therapeutic exercise for paraplegic patients

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ABSTRACT

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

Key words: adapted exercise, physical activity, paraplegia, Spinal Cord Injury

Introduction

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

Thousands of people suffer every year SCI. It is es-

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

timated that there are 15-40 new cases per million of population every year [3,10]. The estimated global incidence rate is 23 per million, resulting in almost 18.000 new cases every year, mainly young people [1,11]. Although SCI remains an incurable condition, the survival has increased over the last years due to successful therapies for life threatening complications, early intervention and rehabilitation processes following SCI [12].

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

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

Health risks and consequences after SCI

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

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

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

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

The musculoskeletal system is also highly affected. The paralyzed muscles and muscle fibers below the

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

lesion loose gradually their properties, distribution and volume and undergo morphological and contractile changes [24,25]. Lack of activity and loading result in deteriorating muscle atrophy below the lesion [21]. Bone and joint deterioration are often experienced, even by young individuals [3]. Bone demineralization and osteoporosis manifests rapidly after the injury and continues to climax some years after [14,33]. Bone fractures are common, particularly after falls [34,35]. Other complications are spasticity, affecting approximately 70% of the individuals [36], and fatigue, a physical tiredness, hindering mobility and function [37].

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

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

Adapted exercise - Barriers and facilitators

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

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

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

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

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

The beneficial role of exercise intervention in health and physical fitness

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

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

Systematic training has a direct effect on AC, by increasing peak oxygen consumption (VO2peak)[14-15, 61-62]. It is associated with cardiovascular and cardiorespiratory health, endurance and functioning

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

[8,16,20,26]. There is credible evidence that systematic aerobic or circuit training has positive cardiorespiratory responses, even if restricted in the upper part of the body [2,15,63]. The same result is observed with resistance training in paraplegics [64]. Moreover, exercise targeting at the accessory respiratory muscles, leads to ventilation efficiency [61] and improved fatigue resistance [15].

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

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

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

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

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

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

Another mode for training paralyzed limbs is passive exercise, as passive leg cycling. A systematic review examining the musculoskeletal, cardiovascular

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

and neurological outcome of this method, concluded that multiple sessions have indeed positive impact on reflex excitability, spasticity, blood flow in the lower extremities, and range of motion [83].

Not only the physical but also the psychological and social well-being improved significantly from systematic training programs [84-85]. The beneficial effect is linked with psychological balance, achieved through the promotion of functional independence, perceived health status, reduced stress and pain levels [7,53-56]. Psychological health is closely related to autonomy. Every intervention that improves fitness, strength and physical capacity, enhances the individual's functional performance, the ability to be socially active and personally autonomous, and thus has a critical impact on psychosocial status [86-87].

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

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

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

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

Exercise prescription

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

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

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

Orthostatic or exercise-induced hypotension, due to circulation dysfunctions, may lead in nausea or syncope and need blood pressure monitoring, slow position alteration and progressive exercise introduction [2,20,55]. The same manipulation decreases the possibility of painful spasticity incidents. Sensory impairments may lead to ulcers and professionals should monitor skin areas frequently, adapt material and equipment and relief pressure regularly [2,63]. There

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

is also increased hazard of bone fractures after falls or stretching of paralyzed limbs, especially in team sport, due to osteoporosis and lack of sensation, leading in delayed detection [2]. Musculoskeletal injuries must be prevented, mainly by gradual exercise introduction and pain self-report [42]. Thermoregulation and sweating dysfunctions may cause overheating and need cooling strategies [2,63]. Nevertheless, there is no doubt that beneficial outcomes outweigh the dangers and the adverse incidents are rare and usually not severe [2,68].

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

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

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

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

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

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

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

A multidisciplinary panel developed in 2011 the first SCI-specific, evidence-based Physical Activity Guidelines [55]. The goal of it was to improve fitness and determine elements of exercise in a feasible way. The recommended frequency was 2 times/week of aerobic and strength training in a moderate-vigorous intensity for at least 20min, but 30min would elicit better results. An update of 2018, emphasizing on cardiometabolic health, recommended aerobic exercise, performed 3 times/week for at least 30min in a moderate-intense mode [95].

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

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

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

Conclusion

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

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

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Gait Rehabilitation Techniques In Incomplete Cervical Spinal Cord Injuries

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ABSTRACT

Incomplete cervical spinal cord injuries can lead to severe functional loss, with mobility deficits of the lower limbs and motor control. Contemporary gait rehabilitation techniques focus on the motor reprogramming of neuronic circuits. This systematic review aims to compare the results of different rehabilitation techniques, ranging from robotic exoskeleton systems, to new and improves weight- bearing systems, and other methods including virtual reality, on their ability to achieve measurable therapeutic goals.

Three electronic databases (MEDLINE, PEDro and Google Scholar) were systematically searched for clinical trials, up until May 2022. The following search terms were used: "Incomplete Cervical Spinal Cord Injury" AND "Gait Training" OR "Rehabilitation" OR "Exoskeletal assisted walking" OR "Lokomat" OR "Robot- assisted gait training".

Of the initial 2.411 papers, 54 were selected to be review for eligibility to this systematic review, leading to the final 20 that were included. The most common evaluation tools were 6MWT, 10MWT, TUG, LEMS and WISCI-II. In all 20 papers significant or very significant changes were noted between the time of the first assessment and the last. 13 of them noted statistically significant differences between the control groups and the intervention groups at the end of the trial period, regardless of the method used. In this systematic review, 409 patients were recruited for trials on robotic exoskeletons, 70 participated in Weight- Bearing trials, and another 55 completed trials on interventions including WBV, OLT and GRAIL. In regards to the use of a robotic exoskeleton system, 10 out of 13 trials noted statistical significant differences between groups, a result shared by 2 out of 3 trials on weight-bearing systems. Contemporary interventions using the latest technological advances, whether they be robotic exoskeletons, advanced weight-bearing systems or enhanced virtual reality, may contribute to a faster and more efficient gait rehabilitation of patients suffering from incomplete cervical spinal cord injuries.

Key words: Incomplete Spinal Cord Injury, Gait Training, Rehabilitation, Exoskeleton

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

Introduction

The incidence of spinal cord injuries is estimated to range between 40-80 new cases per million, with traumatic injuries accounting for about 90% [1-3]. The extrapolation of the prevalence to the global population shows that up to 500,000 patients per year face the consequences of spinal cord injuries. Traumatic spinal cord injuries overwhelmingly predominate over non-traumatic ones, the latter taking up to 10% of all spinal cord injuries [3]. In Greece, the epidemiological recording effort was carried out by KAT General Hospital, studying 1489 files of patients who came to the outpatient clinic of the hospital between 1987 and 1999. Their mean age was 33 years and the male/ female ratio was 4:1 (78,8% and 21,2% respectively)[4].

Incomplete cervical spinal injuries (cervical iSCI) account for 59% of all cervical spinal cord injuries [5]. These patients present deficits in balance, gait, sensation, as well as abnormal muscle tone, coordination and co-contractions [6]. Spinal cord injury occurs when a cause inflicts damage to one level of the spinal cord. The spinal level indicates the point at which the function of the nerves below is reduced or even suspended, depending on the extent of the damage. Spinal cord injury prevents information from being transmitted through nerve cells in both directions (motor and sensory pathways). Impaired information transfer can result in transient or permanent loss of mobility and sensation [7].

Spinal cord injuries, at the cervical level, are usually incomplete but, at the same time, due to the topography of the lesion, are amongst the most severe. Depending on the level of severity, these patients may experience difficulties with breathing, loss of mobility of upper and lower limbs, generalized weakness, loss of control of urination and defecation and muscle tone disorders [8]. A cervical iSCI, with the exception of injuries of the last myelotomy, leads to tetraplegia, i.e. the presence of neurological symptoms in the upper and lower limbs, and involvement of the trunk muscles, and usually falls under the AIS categories D to B [9,10].

Research in recent year has focused on the plasticity of neural tissue and its ability to form new connections and adapt post injury. Advances in rehabilitation, such as gait retraining using weight-bearing suspension treadmills, robotic exoskeletons and Functional Electric Stimulation (FES) are some of the new possibilities of technology used in therapeutic protocols, which mainly aim to reorganize, but also regenerate, neural circuits in order to improve patients' motor ability. Rehabilitation is focusing not only on compensating for any deficits, but more importantly on maximizing the potential for motor recovery [11, 12]. Current rehabilitation methods direct the processes of plasticity to create and enhance those synapses that serve the patients' functionality, and gait is capital to daily tasks and quality of life [13, 14].

Discussion

The negative consequences of a spinal cord injury do not result solely from damage to the grey and white matter. Neurons that are dead or in the process of necrosis activate the immune system, which sends macrophages and microglia to remove dead cells, thus triggering a series of inflammatory reactions, which in turn are responsible for the secondary damage that occurs after an injury [15, 16]. In an attempt to limit secondary damage, the body activates reactive astrocytes, which reduce inflammation and thus limit the area of damage by forming neuroglia [17]. This barrier, however, created by neuroglia can simultaneously limit neuronal regeneration, preventing neuronal growth, oligodendrocyte maturation and re-myelination attempts [15, 17].

Spinal cord injuries bring about structural changes, which cause the body to react, first by trying to regenerate and then by reorganizing the synapses and neural circuits that have survived. If the damage is such that there is a gap between the two ends of the nerve, then there is the possibility of axonal sprouting. A single axis may result in multiple collateral sprouting, of which few will be able to penetrate the zone of injury. The body's automatic response to damage can lead to both functional adaptations and maladaptation, examples of which are spasticity, dysreflexia and neuropathic pain. In some other cases, however, spontaneous reorganization can restore functionality following incomplete spinal cord injury, as in the case of Brown-Séquard syndrome (unilateral hemiparesis) despite the permanent loss of centrifugal nerve fibers [18].

Neuroplasticity is defined as the capacity for change,

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

both at the functional and anatomical level of the nervous system, in response to training/retraining stimuli or in response to damage [15]. The process of neuroplasticity roughly involves the creation or rejection of synapses so as to maximize synaptic efficiency, and is the driving force behind learning, memory, and qualitative improvement in motor control. Until recently, the prevailing view was that synapses only change during the neurodevelopmental process, assuming that adult neural circuits are stable and do not change. Now, research has demonstrated that the CNS also makes modifications in adults, especially after injury [19].

Neuroplasticity is related to the strengthening and weakening of synapses, which occurs in response to incoming stimuli, but also to the timing of these changes. Thus, it is now known that the capacity for neuroplasticity depends on the composition of pre- and post-synaptic regions [19]. New synapses that contribute to the transient gratification of a stimulus, if proven functional, are further strengthened to require less stimulus to carry the energy potential, thus contributing to what is called longer-lasting plasticity [20] (Figure 1).

As can be understood, the smaller the extent of the damage, the greater the effects of plasticity can be expected through restoration. Therefore, after an incomplete spinal cord injury, better results are expected through rehabilitation than after a complete injury at a corresponding spinal level.

Therapeutic strategies for gait rehabilitation after Incomplete Cervical Spinal Cord Injury

The plasticity of the CNS is a remarkable feature, since it allows for relearning and recovery after injury. However, without the guidance of plasticity from rehabilitation, the likelihood of functional recovery is clearly reduced [15]. Rehabilitation interventions are studied for their effect on functionality and therefore the structural changes they can bring about in the spine following injury. These changes do not simply occur through movement, but are directly dependent on functional activity, i.e. muscle contraction is not sufficient, but a combination of functional movements are required to achieve a specific action, such as walking or Activities of Daily Living (ADLs) to make a record in the CNS [21]. By moving the body to achieve motor activities, the spine receives stimuli about the quality of movement from sensory neurons in the skin, muscles and joints. The neurons of the posterior horn receive these impulses from the periphery and promote or reject new synapses. In addition, the process is controlled through feedback from centres higher up in the spinal cord, which are co-responsible for the quality of movement (cerebellum, basal ganglia, motor cortex, etc.) [15, 22].

The main therapeutic strategies, so far, in the field functional rehabilitation of incomplete cervical spinal cord injuries are therapeutic exercise - with the use of suspensions or exoskeletons, electrical stimulation and the recently emerging field of the use of Brain-Computer Interface (BCI) technology. Exercise can improve the functionality of spinal motor neurons and remodel the cerebral cortex by increasing the neural activity of specific neurons, leading to the strengthening of specific neural pathways [12, 23]. Electrical stimulation can regulate the excitability of spinal circuits, aid muscle strengthening and promote the process of plasticity [4=24, 25]. Finally, the brain-computer interface is under investigation for the potential it may provide in translating brain activity into movement [22].

Therapeutic Exercise: Therapeutic exercise can reduce apoptosis rates, promote neuronal regeneration, reduce inflammation and increase those spinal functions that have not been affected by the injury [26]. In addition, exercise can reduce the size of a potential syringomyelia and the surface area of the glial fossa, thereby increasing the potential for axonal growth, synapse remodeling, and the axonal myelination process [27]. Exercise can affect unaffected spinal cord parts and muscles and promote remodeling of neural circuits to achieve functional movement [28]. In fact, it is thought that maintaining skeletal muscle function may regulate the normal metabolic function of spinal neurons and have a positive centripetal effect on the cerebral cortex [29].

Intervention techniques begin immediately after admission to hospital and in the acute phase are mainly aimed at preventing seizures, maintaining range of motion and preserving respiratory capacity. Research has shown that early mobilization, including stretch-

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

ing, passive and active exercises (depending on the level of injury), has a positive effect on pulmonary function as well as muscle strengthening. For this reason, in the acute phase, exercise should be performed close to the patient's strength levels for maximum results [30]. In the subacute and chronic phase, effort is focused on moving as independently as possible. For patients with an incomplete C4-C8 injury, even independent transfer from bed to wheelchair is a challenge, so retraining gait requires sophisticated equipment. Even the use of this equipment, however, requires the patient to maintain weight at normal levels, increase aerobic capacity and increase muscle mass [30].

Alternatives to traditional strengthening methods are also being explored, such as the use of vibration to improve spasticity (In et al, 2018), and the use of therapeutic water pools, in which buoyancy helps to significantly reduce the load on the lower limbs [31].

Advances in technology have paved the way for new applications in the field of gait rehabilitation for patients with cervical spinal cord injury, with the aim of achieving safe and independent mobility without a wheelchair. For these patients, simple orthotic means are not sufficient and the use of robotic technology is therefore required. The robotic devices currently in use can be categorized into exoskeletons that attach to a fixed point, over a walking treadmill and exoskeletons that can be worn and assist walking anywhere. Fixed exoskeletons, such as the Lokomat, are programmed for walking on a treadmill, where robotic limbs facilitate hip and knee movement and part of the patient's weight is held in place by suspension. In contrast, mobile exoskeletons support patients in retraining upright positioning, weight transfers and gait on different surfaces, even stairs. The choice of the most appropriate exoskeleton is related to the level of impairment and the implied treatment goals that the rehabilitation team has for the patient. In patients with incomplete cervical spinal cord injury, the use of fixed robotic systems is predominantly preferred [9,10,32,33].

Electrical stimulation: Electrical stimulation can contribute to axon growth and myelin formation [34] and stimulate neurons to induce muscle contraction [2]. The stimulation pathway of neuronal circuits is regulated by electrical stimulation, such as Epidural Electrical Stimulation (EES), Functional Electrical Stimulation (FSE) and Transcutaneous Spinal Cord Stimulation (tSCS) [35]. One clinical study reported that EES can promote recovery of the spinal kinesthetic network after spinal cord injury by producing coordinated and sufficiently strong electrical activity in the muscles involved in posture and gait [36]. In another clinical study, EES was able to reactivate voluntary movement control in patients with a severe clinical picture after spinal cord injury [25]. Finally, tSCS is a novel therapeutic approach that can stimulate the spinal cord through the skin. In a recent study, it was reported that using this method to obtain mobility and sensation in the upper limb of a geriatric patient with incomplete spinal cord injury, which gives hope for its use in promoting neuroplasticity, even in the geriatric population [37].

Brain-computer interface: With the advancement of technology in recent years, the field of research has opened up to the use of advanced computers. The operation of these systems is based on the recording of brain waves (via an encephalogram) and their decoding by a computer, which makes the algorithm matching the movement that the patient would like to make. The computer then sends the appropriate signal either to robotic systems or to the muscles themselves, via electrodes, to induce the desired movement [38,39].

Although, to the best of our knowledge, no research has been published on the use of this technology for gait retraining in people who have suffered spinal cord injury, there are several literature reports on patients with stroke. Their results are encouraging, which may mean that the scope of application of this technology will be extended to other categories of patients with CNS lesions.

Virtual Reality and Gait Rehabilitation: Recent technological advances have allowed rehabilitation specialists to utilize innovative methods in their therapeutic protocols. One such method is the use of virtual environments [40]. The concept behind it is that technology simulates real- life environments (walking in the city or on an uneven terrain such as a hill or a forest) for the brain. At the same time the actual training takes place in a completely controlled, and

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

therefore, safe environment, and patients are not at risk of fall and/ or injury. Virtual environments can help train gait and balance safely and, at the same time, push the patient to explore the extent of their capabilities and even improve them, while practicing in a diverse and motivating way [41]. Different modules of training allow the patient to learn how to avoid stable and moving obstacles, step with more precision and react to possible every- day situations that may occur in a normal surrounding (i.e. crowded city places). More importantly, adapting ones gait to the environmental conditions that are out of control, increases functionality in Activities of Daily Living and reduces the risk of fall [41, 42]. In patients with iSCI, precision stepping has been proven to improve gait by improving walking variables such as speed and balance [43].

Conclusions

Technological advances can provide new alternatives for gait rehabilitation after iSCI. Robotic exoskeletons, advanced weight-bearing systems, FES, brain-computer interface and virtual reality are all employed and screened to offer more efficient recoveries, and a better Quality of Life. More research is needed to determine what could be an optimal protocol for gait rehabilitation after cervical iSCI, given the complexity of the clinical implications the lesions' topography presents, but the current the recent research findings are encouraging. A

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

The effect of acupuncture on the inflammatory response and spasticity following spinal cord injury

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ABSTRACT

Spinal cord injury (SCI) is a serious pathological condition, which causes significant morbidity and mortality in patients who are suffering from it. Acupuncture is an important and integral part of traditional Chinese Medicine, which has been practiced in Asian countries for more than 5,200 years. The present narrative literature review aims to present recent research data in relation to the therapeutic effect of acupuncture on patients with SCI, and more specifically on the reduction of the inflammatory response and the spasticity after an injury of the spinal cord.

It seems that acupuncture, through its anti-inflammatory effect, is effective in patients with SCI. This therapeutic effect is multifactorial, including the regulation of the activity of various endogenic biological mediators, the regeneration of nerve fibres and stem cells and the inhibition of inflammation, neural apoptosis and oxidative stress in the injured spinal cord.

Since there is evidence that inflammation plays an important role in the spasticity seen in patients with SCI, there is necessity for future research, both at the experimental and also at the clinical level, in order to test the hypothesis of a close correlation between the anti-inflammatory effect of acupuncture and the successful treatment of spasticity in patients with SCI.

Key words: Spinal cord injury, Inflammation, Spasticity

Introduction

Spinal cord injury (SCI) is a particularly serious pathological condition, which causes significant morbidity and mortality in patients who are suffering from it, the incidence of the condition, on an annual basis, is estimated to be in the range between 8 and 246 cases / 1,000,000 people, with the total number of patients worldwide, estimated to be between 236 – 1,298 / 1,000,000 people [1]. In the U.S.A. alone, for the year 2012, the number of patients with SCI is estimated in the range of 25,000 – 1,275,000, with the relative trend showing a continuous increasing prevalence rate [2]. Since SCI can cause transient to permanent dysfunction of the nervous, urinary and musculoskeletal system leading to enormous psychological, economic and social burden, its successful treatment and rehabilita-

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

tion strategy is mandatory [3].

There are two main stages following acute SCI: (i) the primary phase, immediately following injury, where destruction of the neural parenchyma, disruption of the neuraxonal network, bleeding in the injured area, and disruption and disorganization of the neuroglial membrane occur and (ii) the secondary phase which reflects a series of complex pathophysiological processes, occur immediately after the primary lesion, and evolve over the following several weeks triggering a "cascade" of inflammatory processes, with immediate activation of innate immune responses, demyelination, apoptosis of the oligodendrocytes, degeneration of the axons and finally apoptosis (death of the neurons) [4-10].

One of the most frequently occurring complications of SCI that significantly impairs patients' clinical condition and function is spasticity [11], which is estimated to occur in up to 70% of patients surviving after a serious SCI [12]. Spasticity can be either localized, regional or general and according to the European working group EUSPAM is defined as the "disordered sensorimotor control resulting from an upper motor neuron lesion and presenting as intermittent or sustained involuntary muscle activation [13,14]. Scientific research in recent years has also focused on inflammation as one of the causes of persistent spasticity in patients after severe SCI [15]. After all, there is already evidence that the combination of inflammation and neuronal destruction plays an important role in the development of spasticity in pathologic conditions such as multiple sclerosis, transverse myelitis or even in rarer diseases characterised by significant spasticity, such as the HTLV-1-associated myelopathy / tropical spastic paraparesis [16-23].

Acupuncture is an important and integral part of traditional Chinese medicine, [24], with a continuous increasing popularity on the treatment and management of painful pathological conditions [25-32].

The present narrative literature review provides recent research data in relation to the therapeutic effect of acupuncture on patients with SCI and on the reduction of the inflammatory response and spasticity following spinal cord injury. An extensive literature research was conducted in PubMed/NCBI, Cochrane Library and Goggle Scholar online databases. The mesh-terms used were: *Spinal cord injury, Acupuncture, Spasticity, and Inflammation* in various combinations and using the disjunctive terms AND and OR. The inclusion criteria were: original studies (both clinical and experimental) in humans and animals, published since 2005. Figure 1 presents the flow-chart of the review, according to the principles of PRISMA

Discussion

Of the 611 studies originally screened, 29 were finally included for further analysis. Literature data supports that acupuncture may improve patients' sensory and motor dysfunction, decrease the level of pain, improve bowel function, alleviate the neurogenic bladder symptoms, improve pressure ulcers outcomes, demonstrate a positive effect on post-injury osteoporosis and finally improve SCI-induced myospasms and spasticity [33-37]. The above mentioned therapeutic actions of acupuncture are multifactorial and include: (i) regulation of the activity and expression of various endogenic biological mediators, (ii) promotion of the regeneration of nerve fibers and stem cells, thus improving the neuroplasticity and (iii) combination of inhibition of inflammation, inhibition of neural apoptosis and decrease of the oxidative stress in the affected area of the spinal cord [33].

Furthermore, Cai and Shen [38] directly correlated the antiapoptotic mechanism of action of acupuncture in various neurologic diseases with the anti-inflammatory action of the therapeutic method, for example through the inhibition of the activation of the MAPK/ERK and P13K/Akt, the down-regulation of caspase-3 and cytochrome c expression on the spinal cord, along with the down-regulation of the serum TNF-αcontent [39-41]. Finally, in another more recently published literature review, Tang et al. (2020) [42] presented a direct correlation between the anti-inflammatory effect of acupuncture after SCI and the therapeutic effect noticed on post-injury nerve recovery after mesenchymal stem cells transplantation.

The therapeutic effect of acupuncture on inflammation following spinal cord injury

Regarding the therapeutic effect of acupuncture on the inflammatory processes that follow SCI, a number of experimental studies published in the last decade

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

have shown very promising findings. Choi et al. published the first proof of the neuroprotective effect of acupuncture after SCI in an experimental rat model. The authors reported statistically significant reduction in the activity of microglia, p38 MAPK and 3 pro-inflammatory factors, including TNF-α, IL1-β, IL-6, matrix-metalloprotease-9 and cycloxygenase-2 [43]. Three years later, Lee et al. showed in a rat experimental model, that acupuncture after a SCI produces significant anti-inflammatory activity in both astrocytes and activated microglia, primarily through the inhibition of the activation of JNK (Jun-N—terminal kinase) [44]. Renfu et al., in an experimental trial on New Zealand rabbits, showed that the effectiveness of acupuncture in the treatment of SCI is most probable due to the regulation of the Pl3-K/Akt and MARK signaling pathways, which are directly related to the cell survival and apoptosis in the first stages of an acute SCI [45]. In another experimental rat model, after severe spinal cord compression, Nascimento de Souza et al., showed that bee venom acupuncture, applied at acupoints GV3 and ST 36, increased the anti-inflammatory expression of IL-10 just six hours after treatment and decreased the pro-inflammatory expression of IL-6 to the treatment group, in comparison to the control group. The final clinical outcome of the study was that the participants in the treatment group showed a statistically significant improvement in their locomotor performance and a reduction in the final extent of SCI compared to participants in the control group [46].

Spinal cord ischemia reperfusion injury (also referred as "white cord syndrome") is a rare pathological condition whose exact pathophysiology is not yet fully understood and which is characterized by acute SCI (paraplegia or quadriplegia), after surgical procedures of spinal decompression [47]. Fang et al. showed that the application of electroacupuncture, either before or after the procedure could alleviate the ischemia of the spinal cord, mainly due to the neuro-anti-inflammatory effect of the method (mainly due to the decreased expression of TNF-αand IL-1β) [48]. Another experimental model involving rats with SCI showed that yellow laser stimulation at GV2 acupoint resulted in an enhanced recovery of the injured spinal cord, mainly due to the down-regulation of a number of pro-inflammatory factors and cells, including the polymorphonuclear leucocytes, the COX-2, the BAX and the Caspase-3 [49]. The effect of acupuncture on the pathophysiological mechanism of Caspase-3 in various tissues, has been already shown by Du et al. (2013) [50] on rabbits, through the Fas-Caspase-3 cascade pathway. On the other hand, Shi et al. (2016), presented the role of apoptosis-regulator BAX protein (also known as bcl-2-like protein 4) in rats with moderate degree of SCI. The authors showed that animals treated with needle therapy at ST28 and BL54 acupoints presented recovery from acute SCI through a neuroptotective and anti-inflammatory effect [40].

The anti-inflammatory effect of acupuncture in SCI was recently demonstrated in another experimental study by Dai et al. (2021), showing that electroacupuncture treatment after SCI in mice, protected myelinated axons and neurons through a complex mechanism which down-regulated the pro-inflammatory cytokines, while it up-regulated anti-inflammatory cytokines. The most probable pathway of this anti-inflammatory effect was mediated through an apolipoprotein-E (apo-E) dependent mechanism [51]. Jiang et al. summarized the anti-inflammatory effect of acupuncture after severe SCI. The researchers applied three different modalities of acupuncture (transcutaneous acupoint electrical stimulation, manual acupuncture and electoacupuncture) at DU26 and DU16 acupoints, in 110 rats in order to study the neuroprotective effects of the methods. The researchers found a statistically significant reduction of a number of inflammatory cytokines, including IL1-β, IL-6 and TNF-α. In addition, the antioxidant action of acupuncture was confirmed by the reduction of the activity of both superoxide dismutase (SOD) and malondialdehyde (MDA) immediately after the injury. They concluded that therapeutic intervention with acupuncture at DU26 and DU16 acupoints immediately after SCI, offers significant neuroprotective action and increased neuronal recovery, through a complex antioxidative, anti-inflammatory and anti-apoptotic mechanism [52].

The non-inflammatory therapeutic effect of acupuncture following SCI

During the last few years, a number of experimental animal studies have been published demonstrating the efficacy of acupuncture on SCI, by mechanisms

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

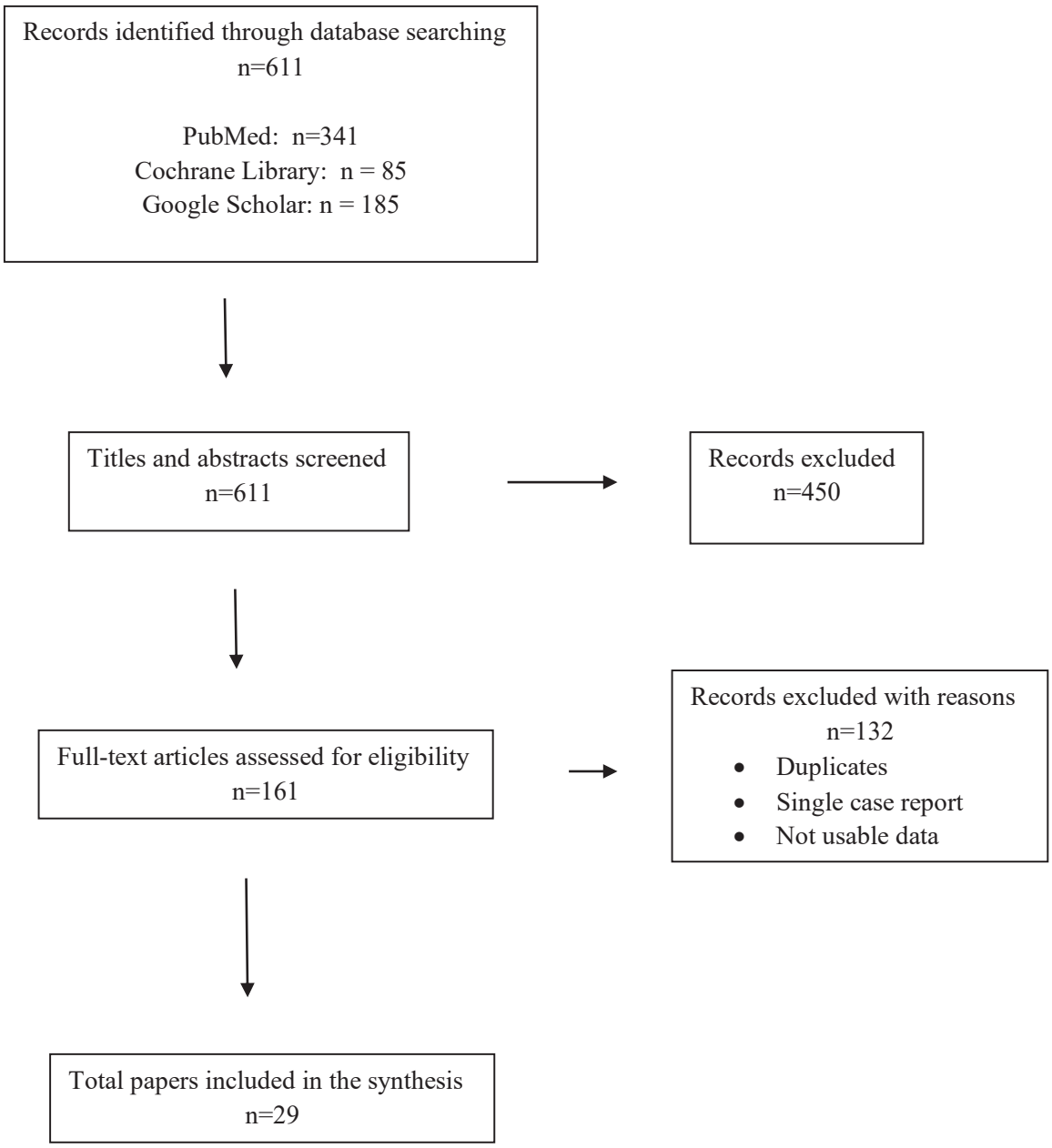

Figure 1: The PRISMA flow-diagram of the present literature review.

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

other than the direct anti-inflammatory action.

Huang et al., in an experimental model of c SCI injury in rats, showed that just 14 days of electoacupuncture treatment at Kl3 and ST36 acupoints produced both locomotor improvement and improvement of the ultrastructural features of the myelin sheath in the affected area of the spinal cord, through the inhibition of the death and the promotion of the proliferation of the oligonedrocytes [53].

Zhou et al. (2020) studying the effect of acupuncture on the abnormal microRNA (miRNA) expression on 6 rats, showed that in the treatment group (elecroacupuncture) the apoptotic indices were lower in comparison to the control group [54]. Yang et al. reported that electoacupuncture on SCI rats increased the acetylcholinesterase (AChE) activity, upregulated of glial cell line-derived neurotrophic factor mRNA (GDNF mRNA) expression, with the end result being the functional recovery of the anterior horn motor neurons [55].

In the last decade, the effect of acupuncture on the regeneration of nerve fibers and differentiation of mesenchymal stem cells has been studied. Yan et al. showed that electoacupuntcure treatment, seven days after SCI induction on rats, produced an increase of the endogenous neutrophin-3 (NT-3) at the injured area, promoting mesenchymal stem cells differentiation into oligodendrocyte-like cells and neuronal-like cells [56]. Similar findings were also presented by an experimental study published two years earlier, showing that acupuncture promotes both the differentiation and the survival of bone marrow mesenchymal cells of rats after induced SCI [57]. The most likely mechanism of this action is an increase in the levels of cAMP and neurotrophin-3 (NT-3), with the final result being the stimulation of the axonal growth in the area of the SCI and the improvement of the rat's hind limb locomotion.

Finally, Liu and Wu demonstrated the anti-apoptotic action of electroacupuncture through a combination of : (i) down-regulation of a number of pro-apoptotic proteins, including cleaved-caspase-3, cleaved caspase-9 and cleaved PARP, (ii) up-regulation of the anti-apoptotic protein Bcl-2, (iii) up-regulation of a large set of miRNAs, from which the most significant was the miR-214, and finally, (iv) up-regulation of BAX protein (bcl-2-like protein and Nav 1.3 voltage-gated sodium channels [58]. These combined mechanisms, involving both inflammatory and non-inflammatory pathways, were also presented in the study of Li et al. where the researchers found that among 15 proteins whose levels changed after acupuncture, two of them (annexin A5 and collapsin response mediator protein 2) might be the most important neural specific factors concerning the therapeutic effects of electroacupuncture after SCI, in an number of pathways, including inflammation, migration and adhesion of neural cells, and apoptotic and signal transduction processes [59].

Conclusion

Acupuncture is an alternative therapeutic method that has been applied for thousands of years to a large number of patients and a variety of pathological conditions. Through its anti-inflammatory effect, it appears to be effective in patients with SCI. As there is evidence that inflammation plays an important role in the development of spasticity in patients with SCI, it is necessary for future research, both at the experimental (in vitro) and clinical (in vivo) level, to test the hypothesis of a close correlation between the anti-inflammatory effect of acupuncture and the successful treatment of spasticity.

Conflict of Interest

"The authors declared no conflicts of interest".

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

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