

# ***Bone and Arthroscopy Science***

Editors-in-Chief

**Kenneth M.C. Cheung**

The University of Hong Kong, Hong Kong SAR, China

**Biao Wang**

*Honghui Hospital Affiliated to Xi'an Jiaotong University, China*

BIO-BYWORD SCIENTIFIC PUBLISHING PTY LTD

(619 649 400)

Level 10

50 Clarence Street

SYDNEY NSW 2000

Copyright © 2023. Bio-Byword Scientific Publishing Pty Ltd.

Complimentary Copy



## Bone and Arthroscopy Science

### Focus and Scope

*Bone and Arthroscopy Science* is a peer-reviewed articles across a wide spectrum of clinical treatise, basic research, review, frontier of orthopedics, case analysis and comment. This journal is aimed at professionals at all levels engaged in the basic and clinical work of orthopedics. Each issue is guest-edited by an acknowledged expert and focuses on a single topic or controversy.

It mainly reports new viewpoints, new achievements and new technologies in basic and clinical research of bone and joint surgery. The covered topics include, but are not limited to: sports medicine and arthroscopy, prosthetic design, biomechanics, biomaterials, metallurgy, biologic response to arthroplasty materials *in vivo* and *in vitro*.

### About Publisher

Bio-Byword Scientific Publishing is a fast-growing, peer-reviewed and open access journal publisher, which is located in Sydney, Australia. As a dependable and credible corporation, it promotes and serves a broad range of subject areas for the benefit of humanity. By informing and educating a global community of scholars, practitioners, researchers and students, it endeavors to be the world's leading independent academic and professional publisher. To realize it, it keeps creative and innovative to meet the range of the authors' needs and publish the best of their work.

By cooperating with University of Sydney, University of New South Wales and other world-famous universities, Bio-Byword Scientific Publishing has established a huge publishing system based on hundreds of academic programs, and with a variety of journals in the subjects of medicine, construction, education and electronics.

### Publisher Headquarter

BIO-BYWORD SCIENTIFIC PUBLISHING PTY LTD

Level 10

50 Clarence Street

Sydney NSW 2000

Website: [www.bbwpublisher.com](http://www.bbwpublisher.com)

Email: [info@bbwpublisher.com](mailto:info@bbwpublisher.com)

## Table of Contents

- 1 Study of the Effect of Rehabilitation Nursing on the Compliance of Patients with Hip Fracture Towards Rehabilitation Exercise and Functional Recovery**  
*Xiong Xu*
- 7 Impact of Skeletal Maturation on Bone Metabolism Biomarkers and Bone Mineral Density in Healthy Brazilian Adolescents**  
*Carla C Silva, Tamara BL Goldberg, Hong S Nga, Cilmery S Kurokawa, Renata C Capela, Altamir S Teixeira, Jose C Dalmas*
- 16 Septic Arthritis of the Hip Following Closed Acetabulum Fracture Treated Conservatively: A Case Report**  
*Marcos Raúl Latorre, Nicolas Martin Molho, María Liliana Soruco, Diaz Dilernia Fernando, Guido Sebastián Carabelli, Martín Alejandro Buttaró*
- 23 Morphological Features and Clinical Results of C2 Vertebral Body Fractures**  
*Eun-Seok Son, Hyeong-Uk Choi*
- 35 Symptomatic Lumbosacral Transitional Vertebrae (Bertolotti Syndrome) as a Cause of Low Back Pain: Classification and Imaging Findings**  
*Barış Ten, Meltem Nass Duce, Hasan Hüsnü Yüksek, Gülhan Temel, Yüksel Balcı, Kaan Esen*
- 43 3D Printing of Titanium Implants at the University of Debrecen**  
*Dóra Eszter Bodrog*
- 52 Hip Fracture Due to Osteomalacia Secondary to Celiac Disease**  
*Alberto Hernández Fernández, Cristian Pinilla-Gracia, Luis Rodríguez Nogué, Luis Rodríguez Chacón, Carlos Bejarano Lasunción*

**Call for papers – *Bone and Arthroscopy Science***

**Submission open for September - 2023**

Dear Researchers,

*Bone and Arthroscopy Science* is a peer-reviewed articles across a wide spectrum of clinical treatise, basic research, review, frontier of orthopedics, case analysis and comment. This journal is aimed at professionals at all levels engaged in the basic and clinical work of orthopedics. Each issue is guest-edited by an acknowledged expert and focuses on a single topic or controversy.

It mainly reports new viewpoints, new achievements and new technologies in basic and clinical research of bone and joint surgery. The covered topics include, but are not limited to: sports medicine and arthroscopy, prosthetic design, biomechanics, biomaterials, metallurgy, biologic response to arthroplasty materials *in vivo* and *in vitro*.

All Bio-Byword journals are free from all access barriers, allowing for the widest possible global dissemination of their manuscripts and highest possible citations. Bio-Byword publisher online submission will go through a rapid peer review and production, making the process of publishing simpler and more efficient, which benefit from its user friendly online submission system that reduces the overall time from submission to publication.

**Acceptance Notification:** Within 21 days from the date of manuscript submission

Send your manuscript to the editor at: **[info@bbwpublisher.com](mailto:info@bbwpublisher.com)**

Kind regards,  
Editorial Office  
*Bone and Arthroscopy Science*

# Study of the Effect of Rehabilitation Nursing on the Compliance of Patients with Hip Fracture Towards Rehabilitation Exercise and Functional Recovery

Xiong Xu\*

Xiamen Rehabilitation Hospital, Xiamen 362000, Fujian Province, China

\*Corresponding author: Xiong Xu, 13799270707@139.com

**Copyright:** © 2023 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

**Abstract:** *Objective:* To analyze the effect of rehabilitation nursing on the compliance of rehabilitation exercise and functional recovery in patients with hip fracture. *Methods:* 80 patients with hip fracture were selected from our hospital (Xiamen Rehabilitation Hospital) from October 2021 to December 2022 as research subjects. After being randomly divided into groups, the control group was given routine nursing, and the observation group was given rehabilitation nursing. The positive effects of different nursing programs on patients' compliance towards rehabilitation exercise, functional recovery, and quality of life were analyzed. *Results:* The rehabilitation compliance of the observation group was higher than that of the control group ( $P < 0.05$ ); the hip function recovery scores of the two groups were similar before nursing ( $P > 0.05$ ), and the scores of the observation group after nursing were significantly higher than those of the control group ( $P < 0.05$ ); The quality-of-life scores in the observation group were higher than those in the control group ( $P < 0.05$ ). *Conclusion:* Rehabilitation nursing can effectively improve the hip fracture patients' compliance towards rehabilitation exercises, which can further improve the patient's functional recovery, improve their quality of life, and the nursing effect is more ideal.

**Keywords:** Rehabilitation nursing; Hip fracture; Compliance with rehabilitation exercises; Functional recovery; Quality of life

**Online publication:** March 10, 2023

## 1. Introduction

Hip fracture mainly refers to the interruption of the continuity of the ilium in the pelvis<sup>[1]</sup>. Most of the hip fracture patients are middle-aged and elderly people<sup>[2]</sup>. Hip fractures are mostly related with age, physical condition, occupation, etc., and patients are prone to fractures caused by external force when the body function declines<sup>[4-5]</sup>. Patients with fractures often feel varying degrees of pain. If they are not treated in time, patients will not only be affected by the clinical symptoms, but their related functions could also be hindered. Surgery is often used in the treatment of hip fractures<sup>[6]</sup>. On one hand, surgery can bring more significant therapeutic effects; however, it will also cause certain damage to patients<sup>[7]</sup>. To help patients achieve better outcomes, it is important to emphasize care delivery. Focusing on the compliance of patients with rehabilitation exercises, and committed to improving functional recovery, rehabilitation nursing was implemented in our hospital while considering the patients' needs. Therefore, this study was carried out in order to demonstrate the diversified value of the application of this nursing model.

## **2. Materials and methods**

### **2.1. General information**

Patients with hip fractures admitted to our hospital from October 2021 to December 2022 were screened, and 80 patients were selected. The patients were divided into two groups of 40 with the envelope method. The male to female ratio of the patients in the control group was 22:18, aged 55–85 years old, with an average of  $68.38 \pm 3.42$  years old; the observation group had 20 males and females, aged 56–84 years old, with an average of  $68.23 \pm 3.29$  years old.

Inclusion criteria: (i) patients who were diagnosed with hip fracture by imaging examination; (ii) patient who were informed of the research content; (iii) patients with complete basic information.

Exclusion criteria: (i) patients who had mental and cognitive abnormalities; (ii) patients with complicated disorders.

### **2.2. Methods**

#### **2.2.1. Control group**

Routine care was given to the patients in the control group. The goal of nursing was to educate patients on diseases, treatment, and nursing, so as to improve their awareness and cooperation towards the treatment. The patients' psychological state was monitored to understand the patient's state of mind. Routine nursing was performed, such as posture care, diet, life guidance, medication reminders, rehabilitation exercises, etc.

#### **2.2.2. Observation group**

In the observation group, rehabilitation nursing was implemented on the basis of nursing care in the control group. (i) Upon admission, the patients' recovery was monitored, and the positions of their limbs were adjusted. The lower limbs were padded and kept abducted by  $20\text{--}30^\circ$ . The patients were asked if there was abnormality in the sensation of both lower limbs. If there was none, passive rehabilitation training was adopted, and the patients were assisted to carry out joint exercises for the lower limbs on the affected side under the leadership of the nurse. (2) At 1–2 days after admission, after the passive training, the combination of upper limb abduction, flexion and extension was carried out, and the patients' feedback were noted during the activity. The positions of the patients' lower limbs were adjusted every day, and proper posture care was provided. The knee joints of patients were evened out, and they were guided on performing voluntary muscle contraction and relaxation training. Depending on the recovery of the patient, hip-lifting training can be added at this time for patients with better recovery. (iii) At 3 to 7 days after admission, under the guidance of the nursing staff, the previous passive training was changed to active exercises. The patients were allowed to perform knee flexion and extension exercises under the guidance of the nursing staff, with the movements following being gradual and orderly. At the same time, the patients were guided to perform straight leg raising training, i.e., raising heel of the affected side from the bed, and slowly lowering it after the patient keep their legs raised at 20 cm for 5 seconds. The exercise was repeated 4 to 5 times. (iv) At 2 to 3 weeks after surgery, the hip flexion of the patients was evaluated, and patients with better recovery were guided to perform hip flexion exercises in the supine position. The exercises were performed 8 to 10 times a day, and the duration of each exercise is 10 minutes. In addition, the patient can move their upper and lower limbs up and down while sitting on the bedside. (v) At 3 to 4 weeks after surgery, the patients were taught to use crutches – getting out of bed, standing up, and walking with the help of crutches. In the initial stage, patients were instructed to get out of bed and perform repetitive exercises of standing upright and sitting down. After a while, the patient can change from standing to walking exercise. The walking time was controlled according to the patient's condition, and the walking distance and total exercise time were gradually increased. (vi) At 5 to 9 weeks after surgery, some patients who recovered better were discharged. Nursing staff kept in contact with patients through WeChat and telephone to carry out

continuous rehabilitation nursing. The patients were guided to complete the rehabilitation exercises at home over the phone or by other means, and the family members were advised to supervise the patients. The exercises that could be done at home were walking exercise, going down the stairs, and the likes. During the rehabilitation process, the family members were advised to gradually increase the amount and the type of exercises according to the functional recovery of the patient, pay attention to the exercises, and promote better rehabilitation effects.

### 2.3. Observation indicators

- (i) The patients' compliance with rehabilitation exercise were observed and they were divided into groups based on their compliance: non-compliance, partial compliance, and complete compliance.
- (ii) The recovery of hip joint function before and after nursing were scored and compared. The Harris score [8] was used to score the functional recovery. Under the 100-point system, the higher the score, the better the functional performance of the patient.
- (iii) The quality of life of patients was scored using the Brief Quality of Life Rating Scale [9], and the scores of both groups were compared.

### 2.4. Statistical methods

SPSS 24.0 software was used to analyze the measurement data (mean  $\pm$  SD) and count data (%) of patients, and *t*- and  $\chi^2$  tests were performed, in which  $P < 0.05$  was considered statistically significant.

## 3. Results

### 3.1. Comparison of rehabilitation exercise compliance

The compliance of rehabilitation exercise in the observation group was higher than that in the control group ( $P < 0.05$ ), as shown in **Table 1**.

**Table 1.** Comparison of rehabilitation exercise compliance [*n* (%)]

Group	Number of cases	Complete compliance	Partial compliance	Non-compliance	Rate of compliance
Observation group	40	27 (67.50)	12 (30.00)	1 (2.50)	39 (97.50)
Control group	40	22 (55.00)	11 (27.50)	7 (17.50)	33 (82.50)
$\chi^2$					5.000
<i>P</i>					0.025

### 3.2. Comparison of hip function scores

The Harris score of the two groups was significantly improved after nursing, and the score of the observation group after nursing was higher ( $P < 0.05$ ), see **Table 2**.

**Table 2.** Comparison of hip function scores (mean  $\pm$  SD, points)

Group	Number of cases ( <i>n</i> )	Harris score			
		Before nursing	After nursing	<i>t</i>	<i>P</i>
Observation group	40	39.64 $\pm$ 3.45	82.75 $\pm$ 4.59	47.483	0.000
Control group	40	40.02 $\pm$ 3.57	73.12 $\pm$ 3.86	39.815	0.000
<i>t</i>		0.424	10.155		
<i>P</i>		0.689	0.000		

### 3.3. Comparison of quality-of-life scores

The quality-of-life scores of the observation group were higher than those of the control group ( $P < 0.05$ ), as shown **Table 3**.

**Table 3.** Comparison of quality-of-life scores (mean  $\pm$  SD, points)

Group	Number of cases (n)	Physiological function	Psychological state	Body pain	Energy
Observation group	40	82.34 $\pm$ 5.63	83.47 $\pm$ 5.74	80.47 $\pm$ 5.78	81.44 $\pm$ 5.82
Control group	40	70.45 $\pm$ 4.22	69.27 $\pm$ 4.53	68.22 $\pm$ 4.39	70.47 $\pm$ 4.31
<i>t</i>		10.687	12.282	10.674	9.580
<i>P</i>		0.000	0.000	0.000	0.000

### 4. Discussion

If there is no effective treatment intervention for hip fractures, the function of the hip joint will be affected, and it will have a negative impact on the patient's life, work, and psychological state [10-11]. While using surgical intervention, it is necessary to emphasize the importance of nursing in order to help patients with their prognosis. On the one hand, the purpose of nursing is to meet the patients' needs during hospitalization; on the other hand, providing nursing-related services can also further improve the overall effect of surgery [12-13]. Especially in terms of patient rehabilitation exercise, a more suitable nursing model can help patients achieve better recovery [14-15]. There are many diverse nursing care plans for patients with hip fractures available [16]. Each plan has its own characteristics, and it needs to be reasonably selected according to the patient's need [17]. This study fully considered the age of patients with hip fractures and focused on the rehabilitation and functional recovery of patients. At the same time, considering the different degree of compliance among middle-aged and elderly patients, we hoped that the rehabilitation nursing can help improve patient compliance [18-19].

In this study, the effect of rehabilitation nursing on hip fracture patients was studied, and the results showed that it further helps patients improve the overall prognosis compared to routine nursing. In terms of compliance with rehabilitation exercises, the patients that underwent rehabilitation nursing showed a higher compliance under the guidance and supervision of the nursing staff. The improvement of compliance is obviously helpful to improve the exercise effect of patients and improve the prognosis [20]. As for functional recovery, there was no significant difference in the scores of the two groups of patients before nursing, indicating that the functional status of the patients before nursing was roughly the same. Although the scores of both groups improved after nursing, it can be seen that the scores of the observation group were higher, which meant that rehabilitation nursing could better improve the patients' hip function. In terms of quality of life, the scores of the observation group were better, suggesting that rehabilitation nursing can also significantly improve the quality of life of patients.

### 5. Conclusion

In short, rehabilitation nursing for patients with hip fractures can effectively improve patients' compliance towards the exercises, therefore improving functional recovery and the overall nursing effect.

### Disclosure statement

The author declares no conflict of interest.

## References

- [1] Zhang Y, Cui T, Liu T, 2022, The Effect of Rehabilitation Nursing Intervention on the Compliance of Rehabilitation Exercise and Functional Recovery of Patients with Hip Fracture. *Medical Information*, 35(16): 181–183.
- [2] Huang X, 2019, Research Status of Rehabilitation Nursing for Postoperative Limb Function Recovery in Elderly Patients with Hip Fractures. *China Disability Medicine*, 27(8): 99–100.
- [3] Shen L, 2022, The Preventive Effect of Functional Training Rehabilitation Nursing Intervention on Postoperative Knee Stiffness in Patients with Hip Fracture. *Chinese and Foreign Medicine Research*, 1(16): 103–105.
- [4] Ying W, 2022, Evaluation of the Effect of Integrated Medical and Nursing Rapid Rehabilitation Nursing on the Pain Degree of Patients after Hip Fracture Surgery. *Chinese Medicine Science*, 12(13): 151–154.
- [5] Yin F, Tang Y, 2022, Application Effect of Accelerated Rehabilitation Nursing in Patients with Hip Fracture. *Nursing of Integrated Traditional Chinese and Western Medicine (Chinese and English)*, 8(5): 109–111.
- [6] Hu Y, 2021, Early Out-of-Bed Activity Intervention for Elderly Patients with Hip Fractures Based on the Life Project Program for the Inpatient Elderly. *Chinese Contemporary Medicine*, 28(35): 220–222 + 226.
- [7] Zhang S, 2021, Research on the Nursing Effect of Upper Limb Yoga Training Combined with Breathing Exercises on Pulmonary Rehabilitation of Elderly Patients with Hip Fracture. *China Disability Medicine*, 29(19): 15–16.
- [8] Chen Q, Liu Y, Lin F, 2021, The Application of Rapid Rehabilitation Nursing Measures in Elderly Patients with Hip Fractures and the Analysis of Their Impact on Postoperative Pain and Quality of Life. *World Latest Medical Information Abstracts*, 21(88): 246–248.
- [9] Wang L, Cheng Q, Zhang X, et al., 2021, Analysis of the Application Effect of Rapid Rehabilitation Nursing in Preventing DVT Formation After Hip Fracture Surgery in the Elderly. *World Latest Medical Information Abstracts*, 21(95): 346–348.
- [10] Wu Y, Pan Y, Yu B, 2020, Analysis of the Intervention Effect of Psychological Resilience Support Combined with Rehabilitation Nursing on Elderly Patients After Hip Fracture Surgery. *Frontiers of Medicine*, 10(8): 168–169.
- [11] Yan J, Fu Y, Hou Y, et al., 2020, Effects of Psychological Assessment and Continuous Rehabilitation on Postoperative Psychology and Joint Function of Elderly Patients with Hip Fracture. *Chinese Journal of Gerontology*, 40(24): 5303–5306.
- [12] Fang S, Liu M, Yang J, 2020, The Effect of Nursing Intervention Based on Motivational Behavior Transformation on the Functional Recovery of Elderly Hip Fracture Patients. *Journal of North Sichuan Medical College*, 35(3): 531–534.
- [13] Chen J, Meng Y, Ning Y, 2020, Application Effect of Early Rehabilitation Nursing Intervention in Postoperative Lower Extremity Deep Vein Thrombosis in Elderly Patients with Hip Fracture. *Reflexology and Rehabilitation Medicine*, 29(1): 195–196.
- [14] Zhang Y, 2020, The Effect of Postoperative Intensive Rehabilitation Nursing on Constipation and Lower Extremity Venous Thrombosis in Elderly Patients with Hip Fracture. *Reflexology and Rehabilitation Medicine*, 29(10): 168–170.
- [15] Zhang J, Du J, Lu W, 2020, The Influence of Rehabilitation Nursing Based on IBM Model on

Rehabilitation Knowledge, Belief, Behavior, and Hip Joint Function of Patients with Hip Fracture. *Henan Medical Research*, 29(16): 3064–3065.

- [16] Dong L, 2020, Effect Analysis of High-Quality Nursing Combined with Rehabilitation Nursing in the Perioperative Period of Elderly Patients with Hip Fracture. *Reflexology and Rehabilitation Medicine*, 1(20): 129–131.
- [17] Tang D, 2020, Analysis of the Application Value of Rapid Rehabilitation Nursing for Elderly Patients with Hip Fractures. *Heilongjiang Traditional Chinese Medicine*, 49(3): 330–331.
- [18] Lin X, 2020, The Effect of Rapid Rehabilitation Nursing on the Sleep Quality of Patients After Hip Fracture Surgery. *World Journal of Sleep Medicine*, 7(10): 1801–1803.
- [19] Gao Z, 2020, The effect of Continuous Rehabilitation Nursing on WeChat Platform Combined with Green's Model on Hip Joint Function and Self-Care Ability in Patients with Hip Fracture. *Chinese Medicine and Clinic*, 20(1): 148–149.
- [20] Fu Q, Jiang L, Chen X, et al., 2019, Effect of Video Rehabilitation Nursing on Postoperative Hip Joint Function and Quality of Life in Elderly Patients with Hip Fracture. *Nursing Practice and Research*, 16(14): 72–74.

**Publisher's note**

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

# Impact of Skeletal Maturation on Bone Metabolism Biomarkers and Bone Mineral Density in Healthy Brazilian Adolescents

Carla C Silva<sup>1</sup>, Tamara BL Goldberg<sup>2\*</sup>, Hong S Nga<sup>3</sup>, Cilmery S Kurokawa<sup>2</sup>, Renata C Capela<sup>2</sup>, Altamir S Teixeira<sup>4</sup>, Jose C Dalmas<sup>5</sup>

<sup>1</sup>Department of Physical Education, State University of Northern Paraná (UENP), Rio de Janeiro 86400-000, Brazil

<sup>2</sup>Department of Pediatrics, Botucatu Medical School (UNESP), Botucatu 18618-687, São Paulo, Brazil

<sup>3</sup>National Council for Scientific and Technological Development (CNPq), Brasília, Rio Grande do Norte, Brazil

<sup>4</sup>Department of Tropical Diseases and Image Diagnosis, Botucatu Medical School (UNESP), Botucatu 18618-687, São Paulo, Brazil

<sup>5</sup>Department of Applied Mathematics, State University of Londrina (UEL), Londrina 86057-970, Paraná, Brazil

\*Corresponding author: Tamara BL Goldberg, [tamara@fmb.unesp.br](mailto:tamara@fmb.unesp.br)

**Copyright:** © 2023 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

**Abstract:** This study was conducted to evaluate the behavior of biomarkers in the bone formation and resorption in Brazilian adolescents according to their biological maturation. Eighty-seven volunteers were selected and divided into three groups according to their bone age (BIA); 10-12 years (n=25), 13-15 years (n=36) and 16-18 years (n=26). Few parameters and biomarkers such as, the weight (kg), height (m), body mass index (kg/m<sup>2</sup>), 3-day calcium intake (mg/day), assessment of pubertal events by Tanner criteria, levels of the biomarkers [osteocalcin (OC) (ng/mL), bone alkaline phosphatase (FAO) (U/L), and serum carboxy-terminal telopeptide (S-CTx) (ng/mL)] and their correlation with bone mineral density (BMD) (g/cm<sup>2</sup>) were measured by dual-energy X-ray attenuation of the lumbar spine, proximal femur and total body in each volunteer. The results showed that, all the biomarkers have similar behaviors, showing a higher median value for 13 to 15 years (FAO=154.71 U/L, OC=43.0 ng/mL, S-CTx=2.09 ng/mL; p<0.01) at the pubertal stage G4, and the median is decreased with the advancing IO and sexual maturation level. Additionally, the biomarker levels showed a parallelism with a peak velocity in the stature level, and interestingly, the training biomarkers indicated a negative correlation with BMD where high BMD values correlated with the low biomarker values. In conclusion, this is the first study were conducted in Brazilian adolescents with strict, and careful inclusion and exclusion criteria to assess the correlation between the bone markers and BMD against the indicators of biological maturation. The results of this study may help to understand and monitor the bone turnover and bone metabolism respectively.

**Keywords:** Bone biomarkers; Adolescents; Bone mineral density; Bone age

**Online publication:** April 20, 2023

## 1. Introduction

The bone tissue extends throughout the body, and it is traditionally evaluated in a static and punctual way by imaging methods. As it is radiopaque, the structure can be analyzed by using qualitative techniques such as plain X-rays, and for more accurate results dual energy X-ray absorptiometry (DXA) or quantitative

tomography can be used <sup>[1]</sup>. However, metabolic, physiological, or pathological imbalances may affect the radiopaque bone structure, subsequently interfering with the detection. Therefore, the use of more dynamic methods in the detection tends to contribute to the initial stage detection of bone mass reduction more significantly, thereby helping in better understanding of mechanisms related to the prevention of this process <sup>[1]</sup>. Additionally, based on the literature search the use of bone metabolism biomarkers as a dynamic method for assessing bone turnover is a better option for this study <sup>[2-5]</sup>.

Childhood and adolescence are the only periods of longitudinal physical growth, with high rates of bone matrix undermining <sup>[6,7]</sup>, where 25% of the bone mass is incorporated in 2 years surrounding the maximum height velocity peak <sup>[1]</sup>. The development of the bone remodeling process is based on two antagonistic processes which are the bone formation and bone resorption, further, these two processes enable the bone modeling and remodeling, which are completely interconnected however, during puberty the bone formation process is more important than bone resorption.

However, the use of bone metabolism biomarkers during puberty is still limited, as it is difficult to establish normalized standards, where the results are often influenced by the intense bone growth and remodeling that occur during that period of time, and are also susceptible to variations in biomarker function that is observed in puberty <sup>[3,10]</sup>. Gordon reported that imaging method and biomarkers can be used together for monitoring the skeletal remodeling during childhood and adolescence <sup>[2]</sup>. Further, the scientific literature also suggests that biomarker levels decrease after this phase of life, although there is a continuous increase in the body size and bone mineral density (BMD) that continues for few more years <sup>[11]</sup>.

The interest in choosing the dynamic and accurate assessment of bone tissue during puberty is based on the fact that puberty is a sensitive period for increasing and reducing in the bone re-services and future bone loss respectively <sup>[3]</sup>. It is known that bone mass decreases from the age of 30 years by 1% to 2% in women, meanwhile 0.3% to 1% in men. Additionally, the bone mass is greater in men than in women, because men have larger skeletons, and the period of bone loss starts much later in men than in women, about a decade later <sup>[12]</sup>. Studies have shown that, one of the main factors in preventing chronic diseases such as, osteoporosis or subsequential bone fractures in the future, is the attempt to reach the ideal peak of bone mass during adolescence or at the end of skeletal maturation <sup>[13,14]</sup>. Although the prevalence of osteoporosis in men is reported to be lower than in women, however, the overall incident rate is still high in both genders. According to the data published in the United States of America (USA) reveal that around 1 to 2 million men was reported to have osteoporosis, while 8 to 13 million have osteopenia, and the report also showed a fracture risk of 13.5% in men aged 50 years and 25.6% in those aged 60 <sup>[15]</sup>.

The above-mentioned issues have seriously worried the public health organizations; therefore, they start to encourage the prevention of bone mineral capital loss by performing the bone mass tests, enabling the early identification of individuals presenting slightly altered BMD <sup>[16]</sup>. Additionally, follow-up of bone mass incorporation during childhood and adolescence by using DXA analysis, especially in the second decade of life when practically 95% of bone mass is incorporated, tend to be an adequate method for monitoring the bone mineral deposits, which represent a “reserve source” for bone health in future adult life.

Multiple factors are involved in the interpretation of the results of the assessment of bone biomarkers during puberty therefore, it is essential to disseminate what is known about the subject and its applicability in clinical practice as one of the tools for understanding the bone metabolism. Based on these concepts, the aim of this study was to evaluate the behavior of some bone formation and resorption biomarkers to represent the growth and skeletal maturation in a sample of healthy Brazilian male adolescents, relating biomarkers with BMD assessed by DXA of the lumbar spine, proximal femur and total body.

## 2. Casuistry and methods

Healthy white male adolescents aged between 10 and 18 years participated voluntarily in this cross-sectional study. They were students from Sao Paulo school, belongs to the high socioeconomic class. Of the 497 total students enrolled in the selected school, 87 adolescents who met the inclusion criteria were included in the study, further participated in all the evaluations. The project was approved by the Ethics Committee of the Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP), protocols nº 261/2004-CEP and 52/2007-CEP. All the participants received the informed consent form, and the form was signed by both the adolescent and his/her parents or guardian.

The inclusion criteria are stated as below <sup>[17,18]</sup>:

- (1) Adolescents between the 10th and 90th percentile weight for each age group
- (2) Adolescents between the 10th and 97.5th percentile height for each age group
- (3) Adolescents with age-appropriate body mass index (BMI)
- (4) Adolescent who consumes dairy products daily

The exclusion criteria were <sup>[19]</sup>:

- (1) Adolescents with a history of prematurity or low birth weight
- (2) Adolescents who had any of the following diseases: diabetes mellitus, acute or chronic malnutrition, congenital or acquired bone diseases, gastrointestinal diseases accompanied by malabsorption, history of nephropathy with or without chronic renal failure, endocrinopathies, early or late puberty, chronic drug abuse, cystic fibrosis, celiac disease
- (3) Adolescents who use drugs that negatively affect bone metabolism, such as anticonvulsants or antacids with aluminum
- (4) Adolescents who followed an exclusively vegetarian diet, with high intake of fibers, caffeine or soft drinks,
- (5) Adolescents who did not consume dairy products on a daily basis

The data collection is started from the school. Firstly, the adolescents were randomly selected, and those who did not present any dysfunction or disease as mentioned in the exclusion criteria were invited to have their weight and height measured subsequently, students who met the above inclusion criteria were then inquired about their smoking and alcohol consumption habits. Further, the students with secondary sexual characters were evaluated, and the results were compared with Tanner's criteria <sup>[20]</sup>. The skeletal maturation and bone age (SIA) were measured using the Greulich Pyle method <sup>[21]</sup>, subsequently, the food characterization in the selected students was determined by using a 3-day food record.

Further, blood samples were collected from the volunteers by a qualified biomedical assistant. The biological samples consisted of 5mL of blood in a dry tube to determine the bone biomarkers level in the serum. The volunteers were fasted for a minimum of 8 hours, followed by blood collection which is conducted between 7am and 9 am. The collected serum was stored and preserved in the Experimental Research Laboratory in the Department of Pediatrics at -70°C until further use. The bone formation biomarkers such as, bone alkaline phosphatase (FAO) expressed in U/L and osteocalcin (OC) expressed in ng/mL was measured by quantitative immunoassay using the monoclonal anti-FAO antibody (Metra BAP, Metra™ Biosystems) with 5% intra and 6% inter assay coefficients of variation and Metra™ competitive immunoassay kit (Metra™ Biosystems) with 8% intra and 7.6% inter assay coefficients of variation respectively. Additionally, for the resorption marker, serum carboxy-terminal telopeptide (S-CTx) expressed in ng/mL were measured by electrochemical luminescence using the commercial kit β-Cross Laps serum (Roche) and the analyzer Elecsys 1010 (Roche) with 5% inter assay coefficient of variation.

The groups were formed based on OI, according to the following limits; Group 1: 10 to 12 years, 11 months and 29 days (n=25); Group 2: 13 to 15 years, 11 months and 29 days (n=36); and Group 3: 16 to 18 years, 11 months and 29 days (n=26). In this sense, the choice of analyzing biomarkers as a function of

the skeletal growth is assessed by OI rather than pubertal stages results, from the fact that both showed a high correlation value by Spearman's linear correlation coefficient ( $R=0.93$ ) with  $p<0.01$ .

BMD assessment was performed by DXA, using a Hologic QDR 2000 device, and appropriate bone mass assessment was obtained by using the pediatric software, with the BMD results expressed in  $g/cm^2$ . Evaluations were performed in the lumbar spine between L1-L4, in the total proximal femur (collofemoral, trochanteric and intertrochanteric regions, and Ward's area) and total body.

The data were further analyzed using the Statistica Version 6 software. The evaluation values obtained from the descriptive statistics (mean  $\pm$  standard deviation) were included in the analysis of variance and the Scheffe test. Additionally, Kruskal-Wallis variance analysis were performed for comparing the OIs and bone biomarkers, and Shapiro-Wilk test were used to verified that the total variables is not presented in the normal data distribution. Spearman's correlation coefficients were calculated between bone biomarkers and BMD results at the assessed region, lastly a minimum statistical difference of 5% was considered significant.

### 3. Results

The general characteristics of the 87 adolescents are presented in **Table 1**, which shows the anthropometric indicators (body weight, height, and BMI), the average daily intake of calcium, and the osseous mineralization indicators (BMD in the lumbar spine region between L1–L4, in the proximal femur and in the whole body) in relation to the OIs.

**Table 1.** Mean and standard deviation of anthropometric indicators, calcium intake and indicators of bone mineralization in relation to the groups classified according to OI (n=87)

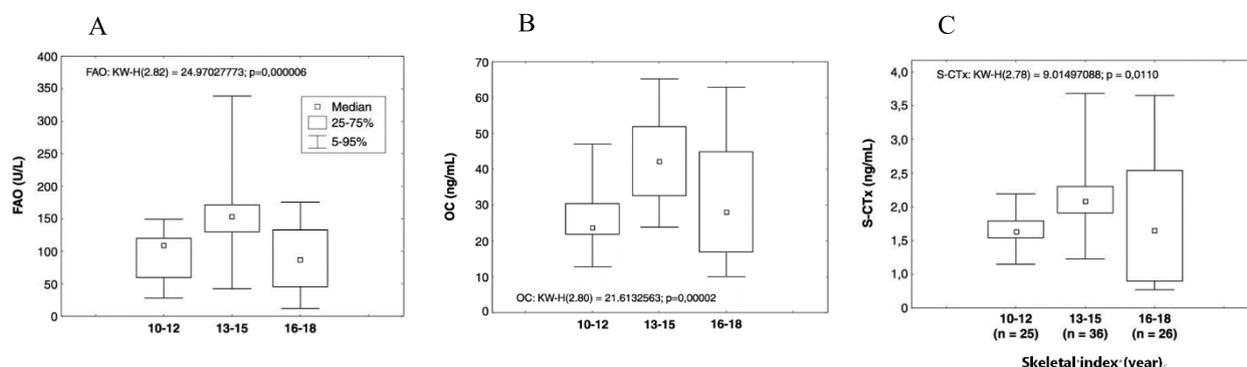
Variables	IO (years)		
	IO 1 (10–12) (n = 25)	IO 2 (13–15) (n = 36)	IO 3 (16–18) (n = 26)
Weight (kg)	38.4 $\pm$ 7.9*	52.1 $\pm$ 8.2*	62.9 $\pm$ 8.6*
Height (m)	1.48 $\pm$ 0.08*	1.64 $\pm$ 0.08*	1.74 $\pm$ 0.06*
IMC ( $kg/m^2$ )	17.3 $\pm$ 2.09*	19.1 $\pm$ 1.88*	20.6 $\pm$ 2.51*
Calcium intake (mg/day)	802.1 $\pm$ 202.0	747.1 $\pm$ 255.0	911.0 $\pm$ 264.2
BMD ( $g/cm^2$ )–column	0.63 $\pm$ 0.08*	0.78 $\pm$ 0.15*	0.94 $\pm$ 0.10*
BMD ( $g/cm^2$ )–femur	0.78 $\pm$ 0.04*	0.90 $\pm$ 0.13*	1.03 $\pm$ 0.11*
BMD ( $g/cm^2$ )–whole body	0.84 $\pm$ 0.03*	0.92 $\pm$ 0.09*	1.06 $\pm$ 0.07*

Note: BMD = bone mineral density; BMI=body mass index; OI = bone age; Scheffe test for localization of differences between IOs ( $p<0.01$ ); \*IO 1<IO 2<IO 3.

The results show that the values increase with age and present significant differences when the means are compared by variance analysis and the differences are identified by the Scheffe test. The significant level increases in body weight, height, and BMI are observed with age, a typical event consistent with the natural process of intense physical growth that occurs at puberty. Further, BMD also shows a tendency to increase significantly with advancing skeletal maturation in all the analyzed sites. Calcium intake assessed by 3-day dietary report show similarity in the different age groups. This finding is in accordance with the inclusion criteria of the study, which emphasize the daily consumption of dairy products.

**Figure 1** shows the medians of FAO, OC and S–CTx bone biomarkers in relation to the OIs. Kruskal–Wallis analysis of the variance revealed a significant ( $p<0.01$ ) value for all the tested biomarkers. Although the non-parametric statistical analysis did not identify differences between OIs, it also can be observed that the group with OI between 13 and 15 years presents a higher medians value than the other OIs for all the

tested bone biomarkers, for bone formation (FAO and OC) and bone resorption (S-CTx). Importantly, the last OI (16–18 years) presents a considerably lower medians value compared to the younger groups.



**Figure 1.** A: Median FAO, B: OC and C: S-CTx according to groups classified by bone age (n=87).

FAO=bone alkaline phosphatase; KW-H=Kruskal-Wallis analysis; OC=osteocalcin; S-CTx=serum carboxy-terminal telopeptide.

Finally, Spearman’s correlation coefficients were analyzed between bone markers and BMD in the lumbar spine, proximal femur and whole body.

The **Table 2** showed that the bone formation biomarkers (FAO and OC) were significantly correlated, however, the bone resorption biomarker (S-CTx) showed very low correlation scores, indicating that there was no association between S-CTx and bone mass acquisition in the adolescents analyzed. An interesting finding is that, the bone formation biomarkers indicated negative values; in other words, lower values of formation biomarkers correlated with higher bone densities in the respective sites (**Table 2**).

**Table 2.** Correlation coefficients between bone biomarkers and indicators of bone mineralisation in the lumbar spine (L1–L4), proximal femur and whole body (n=87)

	S-CTx (ng/mL)	OC (ng/mL)	FAO (U/L)
BMD-column (g/cm <sup>2</sup> )	-0.22 (p=0.28)	-0.13 (p=0.51)	-0.37 (p=0.04)*
BMD-femur (g/cm <sup>2</sup> )	-0.02 (p=0.93)	-0.45 (p=0.02)*	-0.57 (p=0.00)*
BMD-whole body (g/cm <sup>2</sup> )	-0.02 (p=0.91)	-0.47 (p=0.00)*	-0.69 (p=0.00)*

BMD=bone mineral density; FAO=bone alkaline phosphatase; OC=osteocalcin; S-CTx=serum carboxy-terminal telopeptide;

\*Significant correlations.

#### 4. Discussion

Studies on adolescence and bone health is an important aspect in the international research scenario. Understand the mechanisms which are involved in bone mineralization, especially occurring during the puberty, may be a response to the development of a good quality bone mass, which may result in an active life during aging, through the achievement of a dignified life, from the standpoint of autonomy, independence, and physical capacity [8,22].

Several researchers have highlighted the importance of understanding BMD in children and adolescents, demonstrating that BMD values increase with age [2,7,8,14], however, this growth does not present a linear distribution, which is greater during adolescence. The same observations were reported in Brazil by Silva et al., demonstrated that the critical period for a bone mass increase in healthy male adolescents was between 13 and 15 years of age, during the G4 pubertal development stage [23,24].

Additionally, the literature has reported that the adolescent period is marked by a significant rate of bone formation, as bones are characterized by the metabolically active tissue that is subject to a continuous process of true remodeling.

The results of this study as presented in **Table 1** are similar to the report presented in the specialized literature. In our sample of adolescent males, there is a significant increase in bone mass in the analyzed regions with the advancing skeletal age, especially from 14 years onwards, with the highest averages between the ages of 16 and 18 years, similar results were demonstrated in previous studies [7,10,23]. Box plots showed the medians of biomarkers of the groups classified according to skeletal age, is from 10 to 18 years of age. Statistical treatment by Kruskal-Wallis analysis of variance indicates  $p < 0.01$  for the biomarkers of bone formation (FAO and OC) and bone resorption (S-CTx). The graphs showed that the medians of the group between 13 and 15 years were considerably higher and then decreased in the group between 16 and 18 years. The lowest biomarker concentrations were observed at the end of puberty, a similar behavior pattern already highlighted by other authors, who reported the values in 18-year-old individuals similar to those found in adults [12].

Additionally, Tuchman et al., found a strong correlation between bone biomarkers and the peak height velocity (PVE), indicating that there is a parallel correlation between the elevated levels of markers and an increase in growth velocity [25]. Moreover, although BMD continues to increase with age until reach a peak bone mass, a reduction in growth velocity was observed as adolescents approach their final height, which is in line with the behavior of bone markers, a fact that reinforces the relationship between the two events.

From this perspective, Van Coeverden et al., assessed the magnitude of the relationship between bone turnover, indicated by the level of bone biomarkers, and EWP by measuring the level of sex steroids, insulin-like growth factor 1 (IGF-1), and insulin-like growth factor binding protein 3 (IGF-BP-3) [7]. The authors also conducted a semi longitudinal study in 155 boys and 141 girls aged between 8.2 to 15.7 years. The results showed that the rapid growth in height was concomitant with the incorporation of bone mass, but not with bone turnover. At the end of puberty, a decrease in estradiol levels was observed, which inhibits chondrocyte proliferation. As a consequence, the authors observed a decrease in the growth rate and in the levels of bone biomarkers. However, bone mass subsequently increased, which was probably influenced by sex steroids, IGF-1 and IGF-BP-3 [7].

The data found in our study (**Table 2**) revealed a significant and negative correlation between the biomarkers OC, FAO, and S-CTx on BMD in the lumbar spine, proximal femur and whole body among all the adolescents. These results differ from those presented for males in the study by van Coeverden et al., who found no significant differences in the values of bone markers between youths in pubertal stages G4 and G5. This is probably due to the fact that the sample consisted of individuals with a maximum age limit of 15.7 years, and because adolescents who were in the G5 stage had a mean age of  $13.8 \pm 0.9$  years. In addition, the authors correlated the results with bone mass content, not with BMD data, and observed a significant correlation, but not a negative correlation as demonstrated in our study. This is probably influenced by the age which is used as a cutoff point, which did not include the entire age range encompassing adolescence, thus not presenting the lower values of bone markers found at the end of this phase of life, as observed in our study.

This research is the first Brazilian study to analyze healthy white male adolescents using a strict inclusion and exclusion criteria, similar to those reported by Yilmaz et al., who showed a reduction in the concentration of biomarkers at the end of puberty only in female adolescents, while BMD continued to increase, revealing a negative correlation between the bone turnover and BMD [26]. In the same study, the authors did not observe a negative correlation between BMD and bone formation markers in male adolescents. However, they evaluated only boys between the age of 10 to 15 years, leading to the decrease in the sensitivity of the test, besides not being able to analyze the complete evolutionary process, because

markers of bone formation and bone turnover show a reduction in the years after the maximum age limit analyzed, as observed in our study, which evaluated adolescents with OIs compatible with the age of 16, 17 and 18 years.

Regarding the relationship between the biomarkers of bone formation and resorption with the secondary sexual characters, our data reveal that biomarkers showed higher medians when the analyzed adolescents reached the G4 pubertal stage (FAO 148, 51 U/L, OC 43.58 ng/mL, S-CTx 2.10 ng/mL), a moment coinciding with the maximum peak of stature velocity, and when they had OI between 13 and 15 years (FAO=154.71U/L, OC=43.0ng/mL, S-CTx=2.09ng/mL;  $p<0,01$ ). During the G5 stage, the lowest medians were observed for the analyzed biomarkers (FAO 62.21U/L, OC 20.45ng/mL, S-CTX 1.21ng/mL). A statistically significant association was observed between the biomarkers and secondary sexual characters, based on the study of correlation coefficients (data not shown).

Other researchers compared biomarkers of bone formation and bone resorption in children ( $n=86$ ), with a mean age of 10 years, and adults ( $n=30$ ), with a mean age of 28 years, in both the genders. Results showed higher levels of FAO and N telopeptide cross-linking (NTx), a marker of bone resorption, in the children group (FAO=170.1±131.4 ng/mL and NTx=89.8±38.9 ng/mL) compared to adults (FAO=20.2±7.5 ng/mL and NTx=15.3±2.5 ng/mL;  $p<0.01$ ). The authors stated that their results were consistent with the specialized literature, which highlights a considerable increase in the bone metabolic activity in children and adolescents during physical growth. The results also indicated that after the long period of growth, FAO and NTx values showed a considerable decrease [9].

The clinical importance of bone metabolism biomarkers is due to their rapid production during bone remodeling, compared to resulting BMD assessments by traditional methods. The scientific literature has given a specific importance to biomarkers, especially in relation to osteoporosis, which is considered one of the main causes of fragility fractures. Bone markers are proven to be dynamic and effective tool for the evaluation of patients with osteoporosis, and for the follow-up of the effects of medications used for the treatment in these patients, however, the use of biomarkers for diagnosis purposes are not recommended. In prospective studies with postmenopausal women, the increase in resorption markers doubled the risk of fractures was reported. However, it is important to note that the marker responses related to the skeleton as a whole and not only to specific sites, thus the results obtained reveal a risk of probable fracture but not in a specific site [27].

Therefore, tests with biochemical markers of bone remodeling provide an important information for understanding the dynamics of bone metabolism, and can be repeated in short periods of time. However, the great individual variability in the concentration of biomarkers and their release in various anabolic and catabolic processes prevents them from being used alone for diagnosis. Therefore, despite the importance, bone biomarkers are still used in a limited way in the clinical practice and considered as a complementary method to bone densitometry [28], in situations involving the evaluation and follow-up of osteoporosis. The data presented in this study confirm that the assessment of bone mass should be performed using bone biomarkers as a complement to the assessment of BMD. The study and follow-up of biomarkers favor a qualitative evaluation of bone formation and resorption, resulting from the high anabolism observed during puberty. However, the analysis of biomarkers should be complemented by the study of bone densitometry, translation of the timing and pattern of the formation and resorption indexes [29,30]. The combination resulting from the evaluation of various biomarkers of bone formation and resorption is useful for understanding and investigating bone turnover both in healthy children and adolescents and in those with some disease, and also for monitoring the effects resulting from the treatment of diseases that affect bone metabolism.

## Disclosure statement

The authors declare no conflict of interest.

## References

- [1] Gilsanz V, Wren T, 2007, Assessment of Bone Acquisition in Childhood and Adolescence, *Pediatrics*, 119(Suppl 2): S145-9.
- [2] Gordon CM, 2005, Evaluation of Bone Density in Children. *Curr Opin Endocrinol Diabetes*, 2005(12): 444-51.
- [3] Lacativa PG, Farias ML, 2006, Office Practice of Osteoporosis Evaluation. *Arq Bras Endocrinol Metabol*, 2006(50): 674-84.
- [4] Jurimae J, 2010, Interpretation and Application of Bone Turnover Markers in Children and Adolescents. *Curr Opin Pediatr*, 2010(22): 494-500.
- [5] Lenora J, Ivaska KK, Gerdhem P, 2010, Use of Bone Turnover Markers in Osteoporosis. *Clinic Rev Bone Miner Metab*, 2010(8): 1-14.
- [6] Gafni RI, Baron J, 2007, Childhood Bone Mass Acquisition and Peak Bone Mass May not Be Important Determinants of Bone Mass in Late Adulthood. *Pediatrics*, 119: S131-6.
- [7] Van Coeverden SC, Netelenbos JC, De Ridder CM, et al., 2002, Bone Metabolism Markers and Bone Mass in Healthy Pubertal Boys and Girls. *Clin Endocrinol (Oxf)*, 2002(57): 107-16.
- [8] Ward KA, Adams JE, Mughal MZ, 2005, Bone Status during Adolescence, Pregnancy and Lactation. *Curr Opin Obstet Gynecol*, 2005(17): 435-9.
- [9] Van-Summeren M, Braam L, Noirt F, et al., 2007, Pronounced Elevation of Undercarboxylated Osteocalcin in Healthy Children. *Pediatr Res*, 2007(61): 366-70.
- [10] Vargas DM, Audi L, Carrascosa A, 1997, Peptídeos Derivados do Colágeno: Novos Marcadores Bioquímicos do Metabolismo Osseo [Collagen-Derived Peptides: New Biochemical Markers of Bone Metabolism]. *Rev Assoc Med Bras*, 1997(43): 367-70.
- [11] Crawford PB, Wang MC, Sabry ZI, et al., 2002, Adolescent Diet is Predictive of Peak Bone Mass. *Am J Clin Nutr*, 2002(75): S356.
- [12] Naliato EC, Farias ML, Violante AH, 2005, Prolactinomas e Densidade Mineral Ossea em Homens [Prolactinomas and Bone Mineral Density in Men]. *Arq Bras Endocrinol Metabol*, 2005(49): 183-95.
- [13] Goldberg TB, Silva CC, 2004, Osteoporose e Uma Doença que Afeta Crianças e Adolescentes? [Is Osteoporosis a Disease that Affects Children and Adolescents?]. *J Pediatr (Rio J)*, 2004(80): 165-6.
- [14] Walsh JS, Henry YM, Fatayerji D, et al., 2009, Lumbar Spine Peak Bone Mass and Bone Turnover in Men and Women: A Longitudinal Study. *Osteoporos Int*, 2009(20): 355-82.
- [15] Bilezikian JP, 1999, Osteoporosis in Men. *J Clin Endocrinol Metab*, 84: 3431-4.
- [16] Brandao CMA, Camargos BM, Zerbini CA, et al., 2009, Posições Oficiais 2008 da Sociedade Brasileira de Densitometria Clínica (SBDens) [Official 2008 Positions of Brazilian Society of Clinical Densitometry (SBDens)]. *Arq Bras Endocrinol Metab*, 2008(53): 107-12.
- [17] Hamill PV, Drizd TA, Johnson CL, et al., 1979, Physical Growth: National Center for Health Statistics Percentiles. *Am J Clin Nutr*, 1979(32): 607-29.
- [18] Centers for Disease Control and Prevention (CDC), Prevalence of Overweight among Adolescents-United States, 1988-91, *MMWR Morb Mortal Wkly Rep*, 1994(43): 818-21.

- [19] Thornton MJ, Sedlak CA, Doheny MO, 2004, Height Change and Bone Mineral Density: Revisited. *Orthop Nurs*, 2004(23): 315-20.
- [20] Marshall WA, Tanner JM, 1970, Variations in the Pattern of Pubertal Changes in Boy. *Arch Dis Child*, 1970(45): 13-23.
- [21] Greulich WW, Pyle SL, 1959, *Radiographic Atlas of Skeletal Development of the Hand and Wrist*, Palo Alto: Stanford University Press.
- [22] Goldberg TB, 2006, Modelacao E Remodelacao Ossea E Suas Relações Com Os Eventos Pubertarios [Tese Livre Docencia] [Bone Modelling and Remodelling and Their Relationship with Pubertal Events [Phd Thesis]], Sao Paulo, SP: Universidade Estadual Paulista, Faculdade de Medicina de Botucatu.
- [23] Silva CC, Goldberg TB, Teixeira AS, et al., 2004, Mineralizacao Ossea Em Adolescentes do Sexo Masculino: Anos Criticos Para Aquisicao De Massa Ossea [Bone Mineralisation in Adolescent Males: Critical Years for Bone Mass Acquisition]. *J Pediatr (Rio J)*, 2004(80): 461-7.
- [24] Silva CC, Goldberg TB, Teixeira AS, et al., 2007, Bone Mineralization in Brazilian Adolescents: The Years of Maximum Bone Mass Incorporation. *Arch Latinoam Nutr*, 2007(57): 118-24.
- [25] Tuchman S, Thayu M, Shults J, et al., 2008, Interpretation of Biomarkers of Bone Metabolism in Children: Impact of Growth Velocity and Body Size in Healthy Children and Chronic Disease. *J Pediatr*, 2008(153): 484-90.
- [26] Yilmaz D, Ersoy B, Bilgin E, et al., 2005, Bone Mineral Density in Girls and Boys at Different Pubertal Stages: Relation with Gonadal Steroids, Bone Formation Markers and Growth Parameters. *J Bone Miner Metab*, 2005(23): 476-82.
- [27] Brown JP, Albert C, Nassar BA, et al., 2009, Bone Turnover Markers in the Management of Postmenopausal Osteoporosis. *Clin Biochem*, 2009(42): 929-42.
- [28] Avgeri M, Papadopoulou A, Platokouki H, et al., 2008, Assessment of Bone Mineral Density and Markers of Bone Turnover in Children under Long-term Oral Anticoagulant Therapy. *J Pediatr Hematol Oncol*, 2008(30): 592-7.
- [29] Federico G, Baroncelli GI, Vanacore T, et al., 2003, Pubertal Changes in Biochemical Markers of Growth. *Horm Res*, 2003(60): 46-51.
- [30] Holm IA, 2006, Challenges in Clinical Assessment of Bone Density and Quality in Children. *Curr Opin Endocrinol Diabetes*, 2006(13): 15-20.

**Publisher's note**

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

# Septic Arthritis of the Hip Following Closed Acetabulum Fracture Treated Conservatively: A Case Report

Marcos Raúl Latorre\*, Nicolas Martín Molho, María Liliana Soruco, Diaz Dilernia Fernando, Guido Sebastián Carabelli, Martín Alejandro Buttaro

Italian Hospital of Buenos Aires, Institute of Orthopedics Dr. Prof. Carlos E. Ottolenghi, Buenos Aires, Argentina

\**Corresponding author:* Marcos Raúl Latorre, marcosraul.latorre@gmail.com

**Copyright:** © 2023 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

**Abstract:** Nowadays, fractures of the acetabulum associated with low energy trauma are common in older adults. The indication for surgical or conservative treatment depends on multiple factors, such as patient age and comorbidities, type and location of the fracture, and socioeconomic environment. Regardless of the treatment chosen, none is free of complications. A patient with a conservatively treated acetabular fracture that resulted in septic arthritis of the quadrilateral joint is described below.

**Keywords:** Acetabulum; Hematoma; Infectious arthritis

**Online publication:** June 9, 2023

## 1. Key concepts

### 1.1. What is known about the subject

It is uncommon to develop septic hip arthritis after a conservatively treated closed acetabulum fracture. Infections are more likely after an open fracture than after a closed fracture. Although there are reports of arthritis following hip fracture, the literature following acetabular fracture is sparse.

### 1.2. What this work contributes

When an infectious condition in the event of a torpid evolution of a hematoma is suspected, such as erythema, pain, increase in local temperature, aggressive surgical toileting should be performed, and correct cultures with corresponding antibiograms are essential for adequate antibiotic treatment.

Septic arthritis of any joint is a serious condition, with a significant increase in morbidity and mortality. Failure to detect such conditions early can lead to catastrophic consequences for the joint involved and the patient's life. In general, infection following an open fracture is more common than a closed fracture, and the latter is presented in this case study. We consider the rare presentation of this case to be important, because its rapid diagnosis and aggressive treatment is fundamental to therapeutic success.

## 2. Introduction

The incidence of acetabular fractures has increased 2.4-fold in those over 60 years of age in recent decades [1], and their annual mortality varies between 8% and 25% [2]. The treatment of these fractures depends on numerous factors, such as the type and location of fracture, the duration of fracture, and the general

condition of the patient. Both open reduction and internal fixation and total hip arthroplasty are valid options for surgical treatment [3]. However, the possibility of conservative treatment has been proposed for elderly patients with numerous comorbidities or poor general condition [4]. The development of a joint infection following conservative treatment of an acetabular fracture is an extremely rare complication. We present here a patient who developed an infected hematoma at her hip after conservative treatment of a closed, non-displaced acetabular fracture, which led to septic arthritis of the coxofemoral joint.

### 3. Case report

A 73-year-old woman, with no relevant medical history, consulted our emergency department for left coxalgia and inability to bear weight, which had persisted for 20 days. Anteroposterior radiograph of the pelvis (**Figure 1**) and computed axial tomography showed a fracture of the left acetabulum. Using the algorithm described by Mauffrey [5], the fracture was classified as a combined anterior column and posterior hemitransverse pattern, according to Judet and Letournel [6]. As the fracture had persisted for 20 days and did not have a displacement of more than 2 mm, conservative treatment was the primary option.

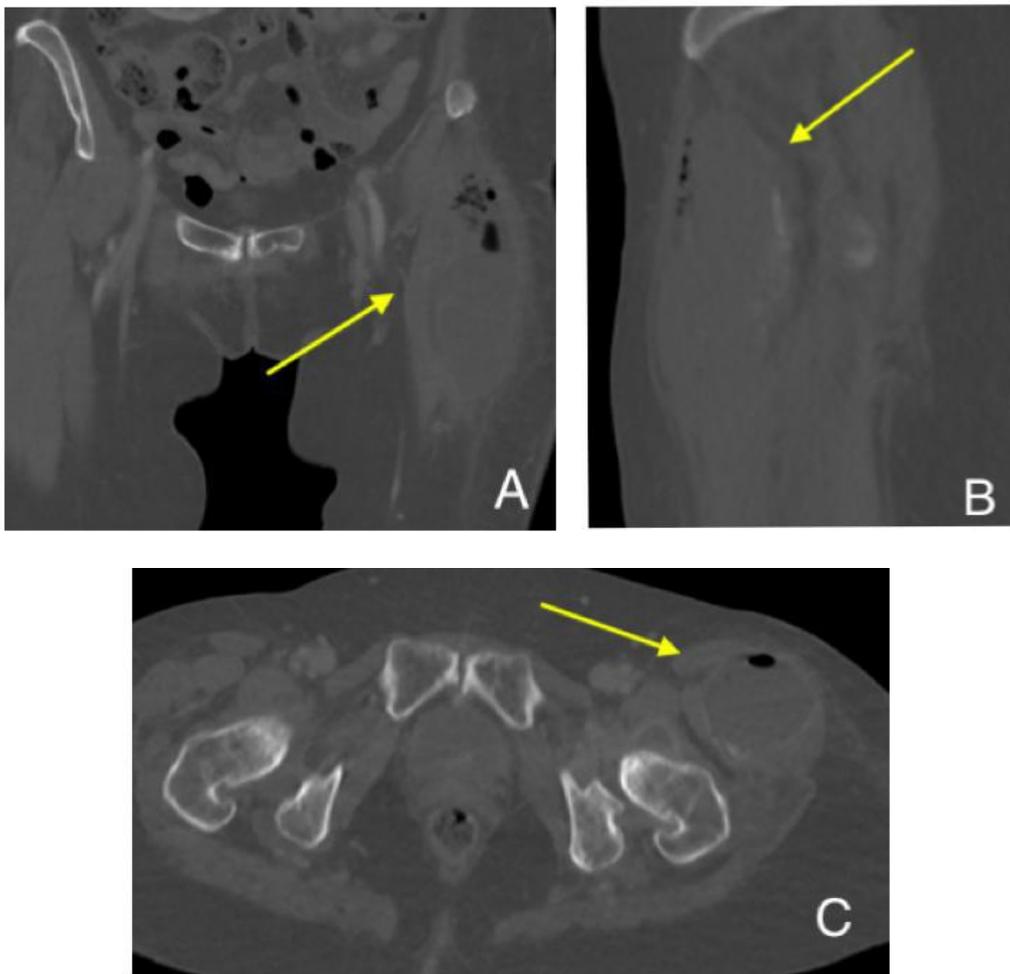


**Figure 1.** Anteroposterior (AP) X-ray of the pelvis showing fracture of the left acetabulum

Two weeks later, he presented with pain at the level of his left hip associated with oedema and local erythema (**Figure 2**). Laboratory tests showed increased inflammatory parameters (White blood cells [WBC]: 20125, C-reactive protein [CRP]: 405 mg/L, and ESD: 65 mm). A CT-angiography showed a 70 x 50 mm collection in his left thigh (**Figure 3A, B and C**), so surgical toileting was performed, and abundant purulent material was obtained. *Staphylococcus aureus* was isolated from the cultures obtained from the surgery. The patient was treated with oral antibiotics – cefazolin for 2 weeks.

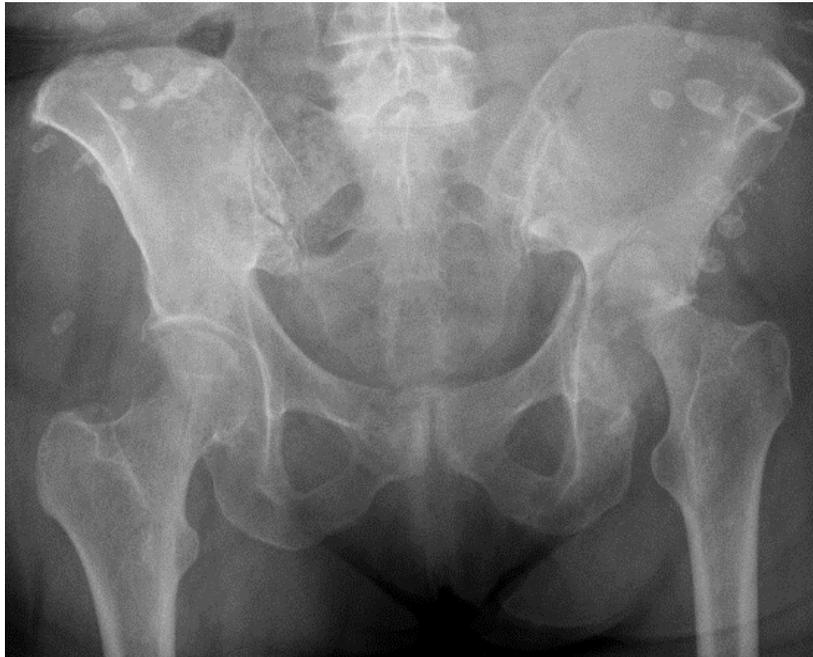


**Figure 2.** Soft tissue involvement of the supero-lateral aspect of the left thigh



**Figure 3.** CT scan showing soft tissue collection at the level of the left hip. (A) Coronal, (B) sagittal, and (C) axial slices

At the 45-day follow-up, the patient reported episodes of fever. A new pelvis X-ray showed large erosive changes at the level of the left coxofemoral joint (**Figure 4**).



**Figure 4.** AP X-ray of the pelvis showing erosive changes at the level of the left coxofemoral joint

A new CT scan showed persistence of the collection at the same level, so a sample of the collection was extracted, and *Staphylococcus aureus* was isolated again. Due to the persistence of the infection, resection arthroplasty (Girdlestone) was performed, along with placement of an antibiotic-loaded cement spacer (**Figure 5**). The patient underwent antibiotic treatment, which was intravenous ceftriaxone and oral rifampicin for 65 days.



**Figure 5:** AP radiograph of pelvis with cement spacer in left hip

After an improvement was seen in the inflammatory laboratory parameters, with considerable decreases in CRP and ESD, a hybrid left total hip arthroplasty (THA) was performed. A 56 mm uncemented tantalum cup was inserted due to Paprosky type IIC acetabular bone defect [7], with a 36 mm polyethylene insert, a 36 mm + 0 metal head, and a size 0 vancomycin cemented stem (**Figure 6**).



**Figure 6.** AP X-ray of the pelvis showing left CTA

Sample cultures taken at the last procedure were tested negative. The patient completed another 30-day antibiotic treatment with ceftriaxone and rifampicin and showed good postoperative progress. At the annual follow-up, the patient was asymptomatic and was able to ambulate without assistance, with a Harris score of 80.

#### **4. Discussion**

Acetabulum fractures in older patients are common in emergency rooms. The multidisciplinary approach to this type of pathology is the key to successful treatment [2]. Individualization of each patient by taking into account the patient's age, medical history, functionality, and bone quality, is essential to formulate an appropriate therapy. Different strategies can be used to address this pathology, such as open reduction internal fixation (ORIF), CTA, or conservative treatment. Regardless of the treatment chosen, the goal is to achieve an acceptable mobility, relieve pain and reduce immobilization time.

Septic arthritis of the hip is a rare complication of acetabulum fracture, with little literature available. In our case, this condition developed after an acetabulum fracture was treated conservatively. We believe that the hematoma produced by the fracture predisposed the terrain for a possible accumulation of germs, which later led to the infectious condition.

Cases have been reported in the literature of patients with hip fractures who developed infectious arthritis while awaiting surgery. Chewakidakarn *et al.* [8] described a case of a patient with a pathological fracture of the femoral neck, diagnosed 15 days after the initial trauma. The patient had no signs of local inflammation but had pain and was unable to walk, associated with increased inflammatory parameters in the laboratory. The patient was diagnosed with infectious arthritis intraoperatively due to the large amount of purulent material in the joint, and a two-stage surgical treatment was carried out.

In addition, Hearth *et al.* [9] reported two cases of septic arthritis secondary to fractures of the proximal femur in patients awaiting surgery. Both patients were elderly and had multiple clinical comorbidities. The germ isolates were *Staphylococcus aureus* in one case and *Proteus* in the other. Both patients died in the immediate postoperative period.

There are different risk factors for triggering a joint infection. Conditions that interfere with the patient's immunity such as diabetes mellitus, cirrhosis, oncological diseases, hypogammaglobulinemia, or intravenous drug use may increase the incidence of septic arthritis. Joint degeneration and diseases such as rheumatoid arthritis with prolonged corticosteroid treatment may also lead to infection [10]. In our case, the patient had no previous disease, only coxofemoral joint degeneration.

A joint infection is challenging for an orthopedic surgeon, and it is necessary for the surgeon to know a few treatment methods for it. Chen *et al.* [11] described 28 patients with septic arthritis who received treatment in two stages: resection arthroplasty followed by prosthetic implantation. 14 % of the patients were reported to have recurrent infections, and up to 36% experienced complications, demonstrating the complexity of completely eradicating a joint infection. The most frequently isolated germ in the series was oxacycline-resistant *Staphylococcus aureus*. Bauer *et al.* [12] also described two-stage treatment for hip and knee infections. They recorded an 87% success rate with this therapy, with *Staphylococcus aureus* also being the most prevalent germ.

Another treatment alternative is two-stage surgery, which is the placement of an antibiotic-loaded cement spacer. This option allows the specific germ to be identified, the antibiotic treatment can be adjusted according to the antibiogram, and then the implant can be placed. Success rates of up to 89% have been reported for this method [13]. Failure of this treatment may be due to old age, high preoperative CRP levels, and bacterial resistance [13]. Our patient had a preoperative CRP of 2 mg/L, and no highly resistant germs were evident in the cultures.

In our case, although the origin was a fracture of the acetabulum and not a fracture of the femoral neck, the latter alternative was chosen. The first surgical toileting performed was not sufficient, as 45 days later, the patient intercurrent with pain and fever showing a large erosive involvement of the coxofemoral joint in imaging studies. The isolated germ was *Staphylococcus aureus*, coinciding with existing reports in the literature.

The two-stage surgical treatment with antibiotic-loaded cement spacer and subsequent CTA, in addition to intravenous antibiotic treatment, was successful in this case. However, the results should be interpreted with caution and more reports like this one are needed to standardize appropriate routine therapeutics.

## 5. Conclusion

Septic hip arthritis following an infected hematoma from a closed acetabulum fracture is a rare complication. We found no reports in the literature showing hip joint infection associated with a hematoma from a conservatively treated acetabulum fracture. It is essential to consider this complication in the presence of a torpid course with groin pain, fever, and signs of local inflammation. Rapid identification and accurate diagnosis are necessary for successful treatment. *Staphylococcus aureus* was the isolated germ, and an adequate antibiogram is useful to avoid resistance to antibiotic treatment. Two-stage treatment using an antibiotics-loaded cement spacer is a valid option to combat the infection. Finally, it is worth stressing the importance of performing aggressive surgical toileting to eradicate the infection to the biggest extent and avoid future complications.

## Disclosure statement

The authors declare no conflict of interest.

## References

- [1] Ferguson TA, Patel R, Bhandari M, et al., 2010, Fractures of the Acetabulum in Patients Aged 60 Years and Older: An Epidemiological and Radiological Study. *J Bone Joint Surg Br.*, 92(2): 250–257. <https://doi.org/10.1302/0301-620X.92B2.22488>
- [2] Antell NB, Switzer JA, Schmidt AH, 2017, Management of Acetabular Fractures in the Elderly. *J Am Acad Orthop Surg*, 25(8): 577–585. <https://doi.org/10.5435/JAAOS-D-15-00510>
- [3] Ranawat A, Zelken J, Helfet D, et al., 2009, Total Hip Arthroplasty for Post Traumatic Arthritis After Acetabular Fracture. *J Arthroplasty*, 24(5): 759–767. <https://doi.org/10.1016/j.arth.2008.04.004>
- [4] Walley KC, Appleton PT, Rodriguez EK, 2017, Comparison of Outcomes of Operative Versus Non-Operative Treatment of Acetabular Fractures in the Elderly and Severely Comorbid Patient. *Eur J Orthop Surg Traumatol*, 27(5): 689–694. <https://doi.org/10.1007/s00590-017-1949-1>
- [5] Mauffrey C, Stacey S, York PJ, et al., 2018, Radiographic Evaluation of Acetabular Fractures: Review and Update on Methodology. *J Am Acad Orthop Surg*, 26(3): 83–93. <https://doi.org/10.5435/JAAOS-D-15-00666>
- [6] Judet R, Judet J, Letournel E, 1964, Fractures of the Acetabulum: Classification and Surgical Approaches for Open Reduction – Preliminary Report. *J Bone Joint Surg Am*, 46: 1615–1646.
- [7] Sheth NP, Nelson CL, Springer BD, et al., 2013, Acetabular Bone Loss in Revision Total Hip Arthroplasty: Evaluation and Management. *J Am Acad Orthop Surg*, 21(3): 128–139. <https://doi.org/10.5435/JAAOS-21-03-128>
- [8] Chewakidakarn C, Nawatthakul A, Suksintharanon M, et al., 2019, Septic Arthritis Following Femoral Neck Fracture: A Case Report. *Int J Surg Case Rep*, 57: 167–169.
- [9] Hearth M, Compson JP, Phillips S, 2002, Unrecognised Septic Arthritis Following Fracture of the Proximal Femur in Patients Awaiting Surgery. *Injury*, 33(5): 457–459. [https://doi.org/10.1016/s0020-1383\(02\)00027-x](https://doi.org/10.1016/s0020-1383(02)00027-x)
- [10] Mader JT, Shirliff M, Calhoun JH, 1999, The Host and the Skeletal Infection: Classification and Pathogenesis of Acute Bacterial Bone and Joint Sepsis. *Baillieres Best Pract Res Clin Rheumatol*. 13(1): 1–20. <https://doi.org/10.1053/berh.1999.0003>
- [11] Chen C-E, Wang J-W, Juhn R-J, 2008, Total Hip Arthroplasty for Primary Septic Arthritis of the Hip in Adults. *Int Orthop*, 32(5): 573–580. <https://doi.org/10.1007/s00264-007-0366-1>
- [12] Bauer T, Lacoste S, Lhotellier L, et al., 2010, Arthroplasty Following A Septic Arthritis History: A 53 Cases Series. *Orthop Traumatol Surg Res*, 96(8): 840–843. <https://doi.org/10.1016/j.otsr.2010.06.009>
- [13] Xu C, Kuo F-C, Kheir M, et al., 2019, Outcomes and Predictors of Treatment Failure Following Two-Stage Total Joint Arthroplasty with Articulating Spacers for Evolutive Septic Arthritis. *BMC MusculoskeletDisord*, 20(1): 272. <https://doi.org/10.1186/s12891-019-2652-7>

### Publisher's note

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

# Morphological Features and Clinical Results of C2 Vertebral Body Fractures

Eun-Seok Son, Hyeong-Uk Choi\*

Department of Orthopedic Surgery, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu 41931, Korea

\*Corresponding author: Hyeong-Uk Choi, [neozy0525@dsmc.or.kr](mailto:neozy0525@dsmc.or.kr)

**Copyright:** © 2023 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

**Abstract:** *Type of study:* Retrospective study. *Objectives:* To classify and analyze the morphological patterns of vertebral body fractures and report the clinical results. *Summary of literature review:* There have not been many reports on the classification of vertebral body fractures and treatment results, and it remains a matter of debate. *Materials and methods:* Among 107 patients diagnosed with an axis fracture from 2005 to 2019, 53 patients with fracture involving the vertebral body were selected. After the exclusion of 9 patients with a history of cervical spine surgery or who were lost to follow-up, 44 consecutive patients were enrolled in this retrospective study. Patients were classified into 5 groups (coronal, sagittal, transverse, avulsion, and complex) according to the main fracture line. The demographic data, injury mechanism, discoligamentous injury, combined injury, neurological symptoms, and clinical treatment results were analyzed. *Results:* Patients' average age was 61.7 years (range, 25–81 years). 24 patients were male and 20 were female. The average follow-up period was 14.2 months (range, 7–33 months). The coronal, sagittal, transverse, avulsion, and complex groups contained 5, 5, 8, 7, and 19 patients, respectively. Six patients were injured by slip-down accidents, 12 patients by falling height, and 26 patients by traffic accidents. Eighteen patients were presented with a discoligamentous injury. Twenty-five patients showed a combination of fractures of cervical vertebrae and bones. Thirteen patients presented neurological symptoms. 16 patients were treated with a neck collar and 28 patients were treated with a halo-vest. Two patients eventually required surgical fusion because union was not achieved with conservative management. In the final follow-up, all neurological symptoms were resolved; however, 4 patients still complained of a mild tingling sensation in the upper extremity. Pin site infection occurred in 3 patients who were treated with a halo-vest, but it was controlled after antibiotic administration. *Conclusion:* Vertebral body fractures accounted for almost 50% of axis fractures in this study. Vertebral body fractures can be classified into 5 groups (coronal, sagittal, transverse, avulsion, and complex) according to the morphological pattern. Non-operative management can be a reasonable treatment option with good clinical results and bone union.

**Keywords:** Cervical trauma; Axis body fracture; Classification

**Online publication:** June 9, 2023

## 1. Introduction

Cervical spine trauma accounts for 5% of all trauma patients, and among them, fractures of the axial spine are known to be the most common at 32%<sup>[1,2]</sup>. As the population ages, the number of patients diagnosed and treated for axial spine fractures is increasing, reaching 600 per year according to statistics<sup>[3,4]</sup>. Due to its anatomical specificity, the axial fractures appear in various forms such as odontoid fractures, hangman fractures, lateral body fractures, and vertebral body fractures, and the classification and treatment of fractures other than vertebral body have already been reported in several papers<sup>[5-8]</sup>. Fujimura and Benzel

*et al.* proposed a morphologic classification of fractures for vertebral body fractures of the axial spine, but it has limitations when applied to various types of fractures seen in clinical practice<sup>[9,10]</sup>. Therefore, we aim to report the morphologic classification of vertebral body fractures of the axial spine, their frequency, and treatment outcomes using plain radiographs and three-dimensional computed tomography (3D CT).

## 2. Materials and methods

Among 107 patients diagnosed with vertebral body fractures from 2005 to 2019, we excluded 12 patients with hangman fractures and 10 patients with fractures outside the vertebral body, such as the posterior arch and spinous process. Of the 3 types of spinous process fractures, those involving more than 1/2 of the spinous process bilaterally were classified as vertebral body fractures, and those involving less than 1/2 were classified as spinous process fractures, and 32 patients were excluded. Among the 53 patients with vertebral body fractures, 9 patients with history of cervical spine surgery or showed no bone union after 6 months of treatment were excluded. At last, 44 patients were retrospectively analyzed.

Radiographs and 3D CT of the cervical spine were performed to analyze the appearance of the fracture line. The fracture lines were classified as coronal, sagittal, transverse, avulsion, and complex according to their morphology, and complex was defined as a combination of two or more different fracture lines. The mean age at presentation, gender ratio, mechanism of injury, intervertebral ligament injury, comorbidity, neurological symptoms, and clinical outcomes of each group were compared and analyzed.

The mechanism of injury was categorized into slip, fall, and traffic accident. Intervertebral ligament injuries were assessed based on magnetic resonance imaging, and fractures in other parts of the spine were considered as comorbidities. Neurologic symptoms included radiating pain, tingling, and placebo sensation that occurred immediately after the injury. All patients were initially treated conservatively with a neck brace if the fracture was stable, and a halo-vest if unstable. Stability of the fracture was determined by a combination of the degree of dislocation of the fracture fragment, the presence of intervertebral ligament damage, the presence of fractures in adjacent vertebrae, and the presence of neurologic symptoms. If fracture instability persisted despite conservative treatment or if there was no evidence of bone union for more than 6 months, surgical treatment was carried out. Clinical outcomes included the evaluation of persistence of neurologic symptoms, fracture union, and local infection at the pin insertion site. Fractures were considered united when there was no pain at the fracture site and radiographic and 3D CT findings demonstrated trabecular union in at least one cortical bone<sup>[11]</sup>

This study was approved by the Institutional Review Board (IRB No. 2020-09-064).

## 3. Results

The study subjects included 24 men and 20 women. The average age at the time of hospitalization was 61.7 years old (25–81 years old). The average follow-up period was 14.2 months (7–33 months). The mechanism of injury was slip and fall in 5 cases, fall from height in 13 cases, and motor vehicle accident in 26 cases. Intervertebral ligament injury was observed in 18 cases. In 25 cases, fractures were present in areas other than the axial spine. Neurological symptoms at the time of presentation included radiating pain and tingling in the upper extremities in 10 cases and mild to moderate muscle weakness in 3 cases, totaling up to 13 cases. Conservative treatment was performed using a neck brace in 16 cases and a halo-vest in 28 cases, and surgical treatment was performed in 2 cases that was treated with a halo-vest due to no evidence of union.

At final follow-up, neurologic symptoms had resolved in all but four cases of mild upper extremity tingling. Osteosynthesis was achieved in all cases, including the 2 cases that underwent surgical treatment, and 4 cases showed evidence of malunion but no complaints of discomfort. The mean duration of union was 7.7 months (5–19 months). Of the 28 cases treated with a halo-vest, localized infection at the pin

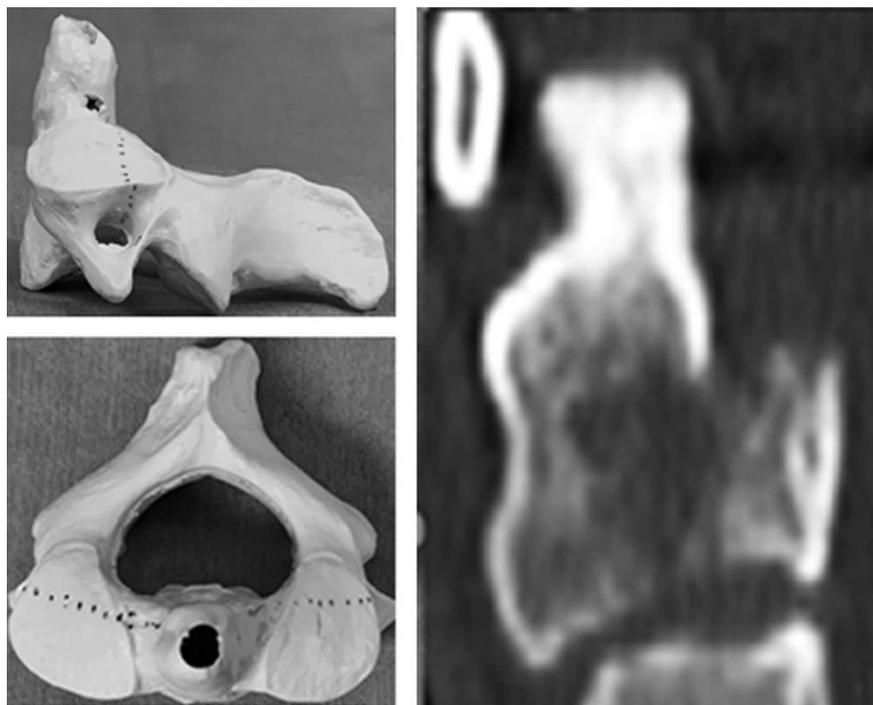
insertion site occurred in 3 cases, but were all resolved with antibiotics, and there was no evidence of infection at final follow-up.

#### 4. Fracture classification

Fractures can be classified into five categories according to the morphologic shape of the fracture line: coronal, sagittal, axial, diaphyseal, and combined. Coronal, axial, sagittal, and sagittal images from radiographs and 3D CTs taken at the time of presentation, as well as 3D reconstruction images, were considered.

##### 4.1. Coronal type

The fracture line of coronal type fracture is at the vertebral body parallel to the coronal plane, in which five cases were included in this study. The fracture lines were mainly located in the posterior part of the vertebral body, starting from the area of the intervertebral transition between the spinous process and the spinal canal, extending to the inferior part of the vertebral body (**Figure 1**). It is thought that compressive and shear forces acted from the posterior superior to the anterior inferior in the extensor position. The patients were injured in two cases by falls and in three cases by automobile accidents. Two cases had concomitant intervertebral ligament injuries the other four had concomitant non-vertebral fractures. Conservative treatment included a neck brace in three cases and a halo-vest in two cases. As for neurological damage, two patients complained of right-hand numbness and mild placebo sensation at the time of presentation, but there were no symptoms at final follow-up.

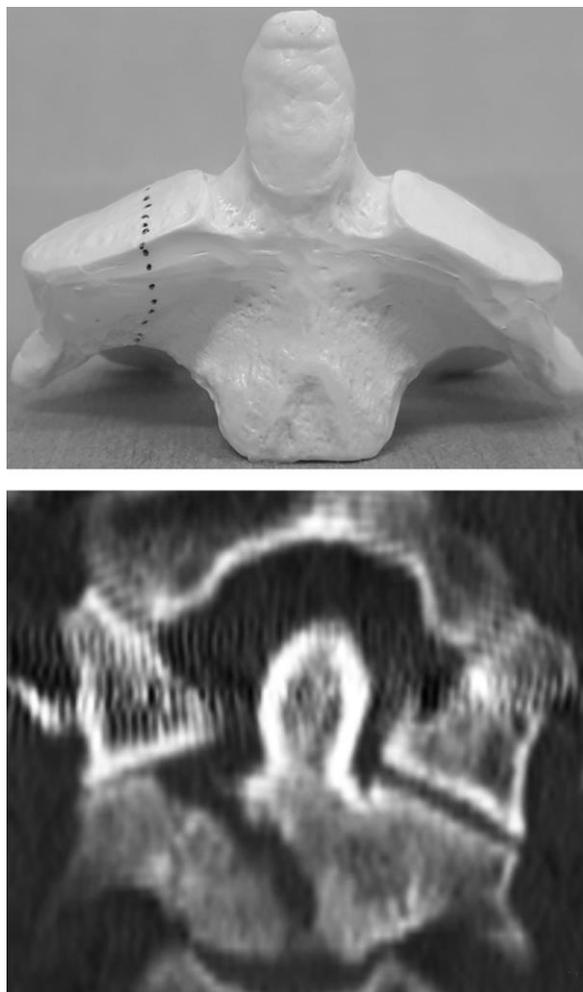


**Figure 1.** Coronal-type C2 vertebral body fracture depicted on an anatomical skeleton model and CT scan. The purple dotted line is the fracture line, located mainly in the posterior aspect of the vertebral body. It originates from the transitional zone of the odontoid process, moves to the vertebral body, which is connected to the spinal canal, and exits to the base of the C2 vertebral body (A-C).

##### 4.2. Sagittal type

The fracture line of sagittal-type fracture is located at the vertebral body parallel to the sagittal plane, in which five cases were included in this study. The fracture line ran from the upper articular process to the

transverse process or the lower articular process (**Figure 2**). The fracture line was unilateral and was thought to have been subjected to lateral pressure above flexion. The patients were all motor vehicle accident victims. Conservative treatment was performed with a neck brace in 3 cases and a halo-vest in 2 cases. Neurological injuries included mild placebo sensation in the unilateral hand in 1 case at presentation and mild tingling at the final follow-up.

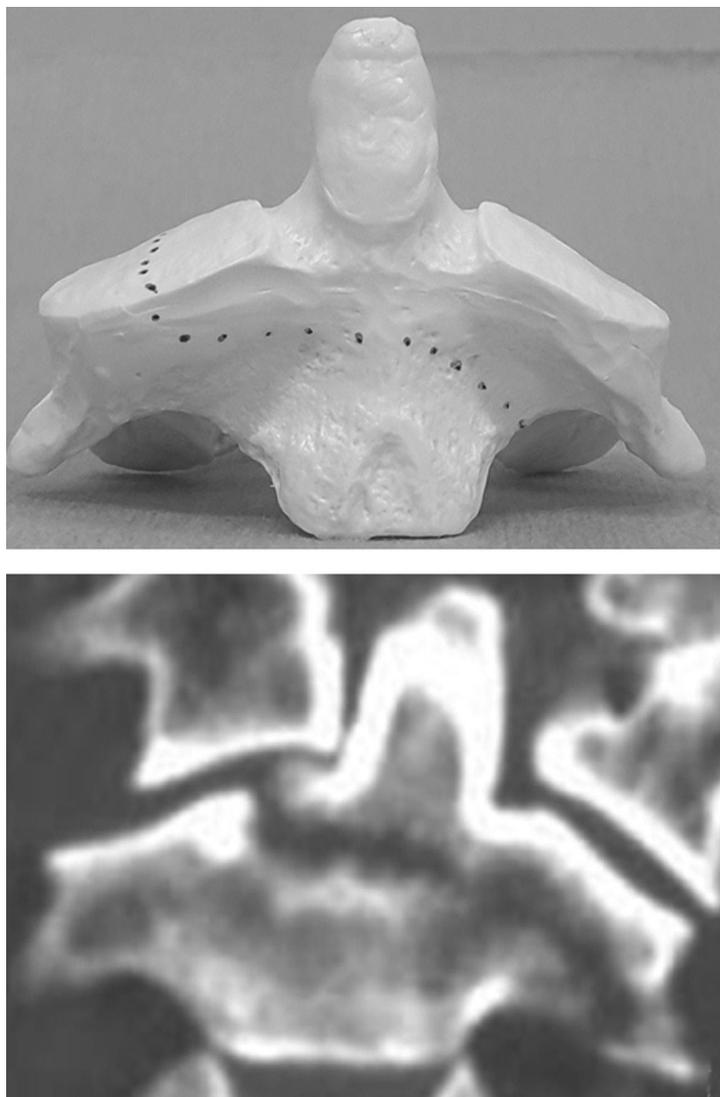


**Figure 2.** Sagittal-type C2 vertebral body fracture depicted on an anatomical skeleton model and CT scan. The purple dotted line is the fracture line, originating from the superior articular process and extending to the ipsilateral side of the transverse foramen or inferior articular process (A-B).

#### 4.3. Transverse type

The fracture line of transverse-type fractures is located at the vertebral body parallel to the axial plane, in which eight cases were included in this study. The fracture line included the supra-articular process or started from the outer side of the spinous process and continued to the contralateral transverse process or vertebral body lateralization, and the upper fragment included the spinous process (**Figure 3**), which are most likely caused by compressive and rotational forces. In 2 cases, the injury was caused by a slip and fall, 1 case by a falling from a height, and 5 cases by a motor vehicle accident. 4 cases were accompanied by intervertebral ligament injuries, and 2 cases were accompanied by fractures other than axial vertebrae. Conservative treatment was performed with a neck brace in two cases and a halo-vest in six cases. In 1 case treated with a halo-vest, pain persisted and there was no evidence of fusion even after 6 months of treatment, so a 1-2 cervical interbody fusion was proposed using the posterior reach method, but the patient did not

consent. Therefore, the patient was monitored, and surgical treatment was performed 1 year later. Due to neurological damage, 1 patient complained of right upper extremity pain and numbness at the time of presentation, 1 patient complained of mild placebo sensation, and 1 patient complained of mild numbness at the time of final follow-up. One case treated with a halo-vest had a localized infection that required additional antibiotics, and there was no evidence of infection at final follow-up.

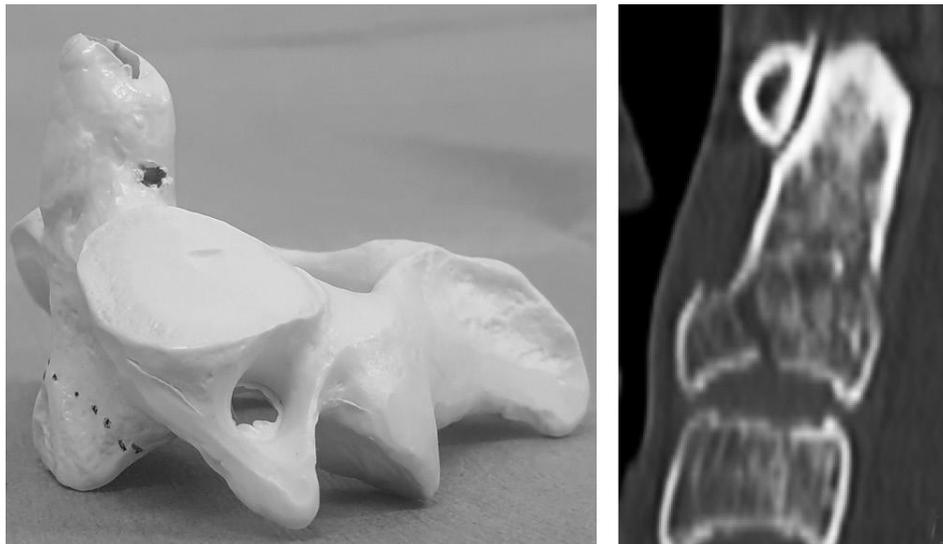


**Figure 3.** Transverse-type C2 vertebral body fracture depicted on an anatomical skeleton model and CT scan. The purple dotted line is the fracture line, originating from the medial side or the middle of the superior articular process and extending to the contralateral side of the vertebral body (A-B).

#### **4.4. Avulsion type**

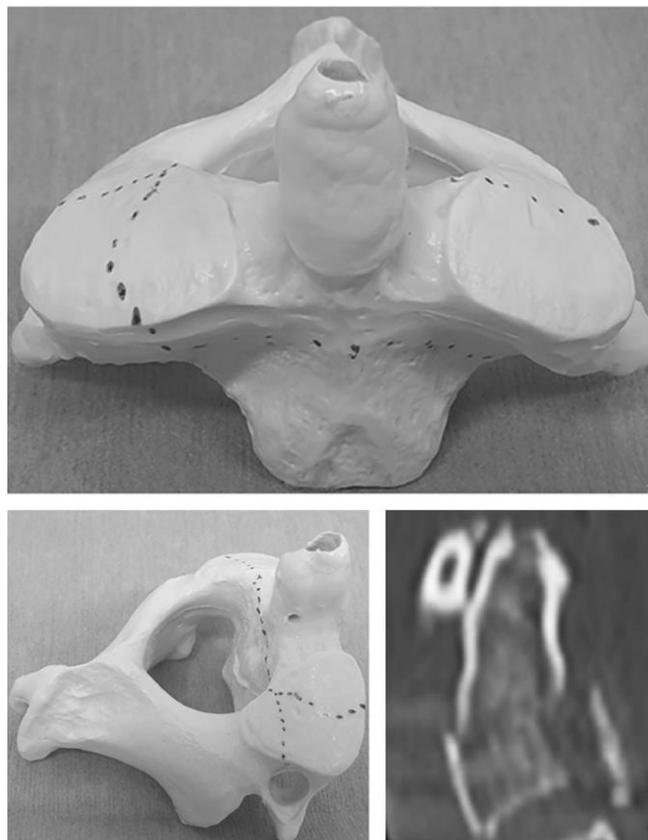
The fracture line of avulsion-type fractures runs from the anterior superior to the posterior inferior of the vertebral body (**Figure 4**), in which seven cases were included in this study. The fractures were all fractures of the anterior longitudinal ligament and were thought to have been caused by extensor forces. The injury was caused by a slip and fall in 1 case, a fall from a height in 2 cases, and a motor vehicle accident in 4 cases. Two cases were accompanied with intervertebral ligament injuries, and five cases were accompanied with fractures other than the axial spine. Four cases were treated conservatively with a rigid brace and three cases with a Yoon vest brace. Neurologic injury included upper extremity numbness at presentation in 5 cases and mild numbness at final follow-up in 1 case. Malunion was noted in 1 case, but there was no

discomfort at final follow-up.



**Figure 4.** Avulsion-type C2 vertebral body fracture depicted on an anatomical skeleton model and CT scan. The purple dotted line is the fracture line, lying on the anterior-inferior side of the vertebral body, which corresponds to the insertion site of the anterior longitudinal ligament (A-B).

#### 4.5. Complex type

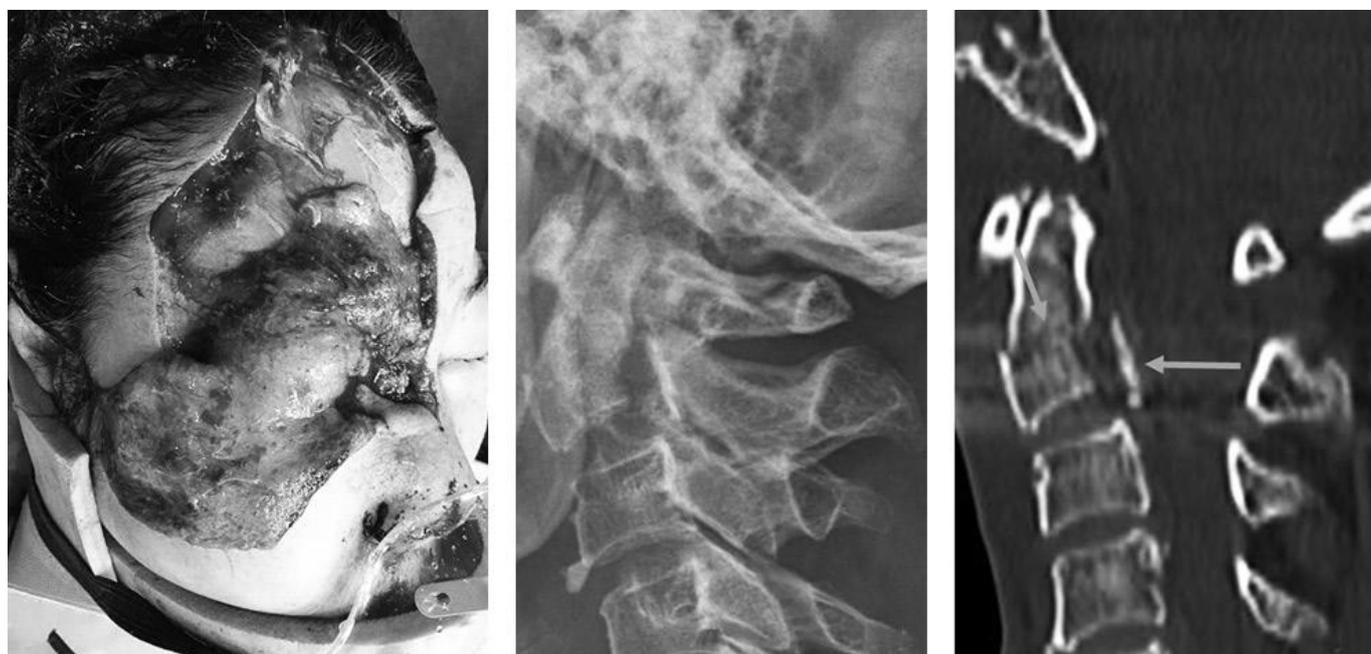


**Figure 5.** Complex-type C2 vertebral body fracture, corresponding to a combination of more than one fracture line, depicted on a CT scan and an anatomical skeleton model. The purple dotted line is the fracture line, which is a combination of coronal and transverse fracture lines (A-C).

This group consisted of cases involving two or more fracture lines in the vertebral body (**Figure 5**), in which 19 cases were included in this study. The injury was caused by a slip and fall in 2 cases, a fall from a height in 8 cases, and a traffic accident in 9 cases. Five cases involved intervertebral ligament injuries, and 9 cases involved fractures other than the axial spine. Conservative treatment was performed with a neck brace in 4 cases and a halo-vest in 15 cases. In 1 case, the patient was treated with the halo-vest, but the patient did not cooperate with the medical staff, and despite multiple adjustments, there was still instability of subluxation and subjugation and worsening pain. Seven weeks after the treatment, a 2-3-4 level cervical interbody fusion was performed using the posterior approach. Neurological damage: Upper or lower extremity numbness was present in 3 cases upon presentation, and mild upper extremity numbness was present in 1 case at final follow-up. Malunion occurred in 3 cases, but there were no complaints of discomfort at final follow-up. Of the 15 cases treated with the halo-vest, 2 cases showed localized infection at the pin insertion site, which required additional antibiotics, and no infection was found at final follow-up.

### 5. Case analysis

A 60-year-old female patient presents after falling from a height of 4 meters. She had a history of steroid use for rheumatoid arthritis, and on physical examination, she had a degloving injury on her face. Cervical spine radiographs showed fracture lines along the axial and sagittal planes of the vertebral bodies, with multiple rib fractures and orbital fractures as comorbidities (**Figure 6**). Interbody fusion of the 1st-2nd-3rd cervical vertebrae using the posterior approach could be considered for surgical treatment but considering the clinical outcome of the patient's comorbidities and limited postoperative range of motion, conservative treatment with a halo-vest was performed. Twelve weeks later, the osteosynthesis was and halo-vest were removed, and there was no evidence of osteosynthesis or instability on the final follow-up radiographs, and good clinical outcome (**Figure 7**).



**Figure 6.** A 60-year-old woman with a degloving injury on the forehead. (A) A lateral view of a plain radiograph of the cervical spine shows a complex fracture line. A coronal-type fracture line on the posterior aspect of the axis body and a transverse-type fracture line at the base of the odontoid process. (B) A sagittal image of a CT scan clearly demonstrates the radiographic findings. (C) The blue arrow indicates the fracture line.



**Figure 7.** Final follow-up of the same patient at post-traumatic 9 months. Plain radiography and computed tomography show formation of a callus and trabeculae across the fracture site (A-B). The flexion-extension view shows no evidence of instability (C).

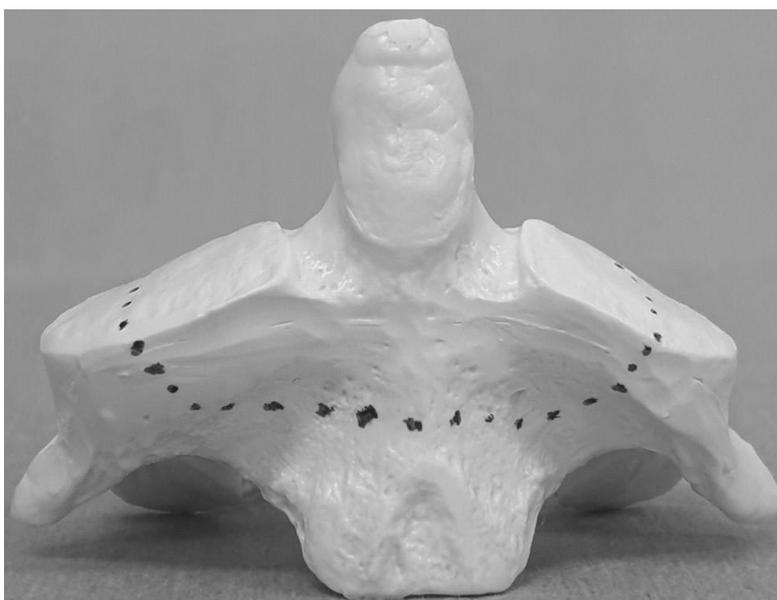
## 6. Literature review

As the elderly population increases and diagnostic techniques become more common, fractures of the axial spine are on the rise [4]. Axial spine fractures are classified according to the anatomical location of the fracture line. The frequency, classification, treatment, and outcomes of odontoid fractures, hangman fractures, and lateral mass fractures have been reported in literature, but there are not many reports on vertebral body fractures [12].

In the United States, there are approximately 50,000 cases of cervical spine fractures per year, of which fractures of the axial spine are the most common, accounting for 32% [1,2]. The most common form of axial spine fracture is odontoid fracture, which is reported to be 58–75%, and the frequency of vertebral body fractures is reported to be about 10% of upper axial spine fractures. The proportion of vertebral body fractures varies widely, with Greene *et al.* reporting 67 of 340 vertebral body fractures (20%), Burke *et al.* reporting 31 of 165 (18%), Lomoschitz *et al.* reporting 7 of 90 (8%), and Bakhsh *et al.* reporting 11 of 26 (42%) [12-16]. The reason for this variation in reported rates of vertebral body fractures is likely due to the lack of a clear definition and confusion in distinguishing vertebral body fractures from vertebral body fracture type 3. Spinous process fracture type 3 is generally defined as a fracture involving the spinous process on the unilateral side and the fracture line involving the cancellous bone portion of the vertebral body, but the clinical presentation, treatment policy, and prognosis are different from types 1 and 2 [14]. There are various disagreements on the classification of spinous process fracture type 3 as a vertebral body fracture, and in this study, cases involving more than 1/2 of the bilateral gastrocnemius process were classified as vertebral body fractures, which were included; and cases involving less than 1/2 were classified as spinous process fractures, which were excluded (**Figure 8**) [2]. Atypical hangman fractures were excluded from vertebral body fractures in this study because the main anatomical location of the fracture is the isthmus of the axial spine [8,17].

German *et al.* reported the morphologic classification and treatment results of 21 patients with

vertebral body fractures [18] and classified the fractures into two groups: vertical-coronal oriented and vertical-sagittal oriented. Benzel *et al.* reported fracture morphology, classification, and treatment results according to cervical spine posture and external force direction at the time of injury in 15 patients with vertebral body fractures and classified them into three groups: coronal, sagittal, and horizontal [9]. Fujimura *et al.* reported morphological classification and treatment results in 31 patients with vertebral body fractures, and classified them into four groups: avulsion, transverse, burst, and sagittal [10]. However, each study has limitations such as insufficient number of patients and inability to classify all types of vertebral body fractures seen in clinical practice. In this study, we analyzed the radiographic images of patients who visited our clinic and classified them into five morphological types: coronal, sagittal, transverse, avulsion, and combined.



**Figure 8.** Example of a transverse-type C2 vertebral body fracture depicted on an anatomical skeleton model. The purple dotted line is the fracture line. It was classified as a transverse-type C2 vertebral body fracture because more than half of both superior articular processes was involved. It is difficult to distinguish from a type III dens fracture.

Some studies have shown good results with conservative treatment for vertebral body fractures [18–19]. In this study, conservative treatment was performed first, which is using a neck brace or halo-vest depending on the stability of the fracture. Although there was no statistical significance due to the small number of cases, the rate of treatment with the halo-vest was high in the transverse and complex types (75% in the transverse type and 79% in the complex type), as shown in **Table 1**. Conservative treatment resulted in bone union in 42 of 44 cases (95%) with good clinical outcomes at final follow-up, which was similar to previous studies. This may be due to the fact that the vertebral body of the axial spine is composed of cancellous bone, has a good blood supply, and a large cross-sectional area of the fracture.

A few articles have reported the outcomes of surgical treatment in vertebral body fractures. In a study of 28 patients, Zhang *et al.* performed conservative treatment when the fracture was stable and surgical treatment when there was adjacent joint instability or when the supraspinatus fracture fragment could not be treated [20]. Both groups reported good results in terms of osseointegration, but since cervical spine fusion causes movement restriction, surgical treatment should be decided with caution and the indications should be discussed further. In our institution, we performed surgical treatment in 1 case with no evidence of fusion despite conservative treatment and 1 case with persistent instability, which were transverse and complex types, respectively, and both cases achieved bone union at final follow-up.

**Table 1.** Demographics and complications of C2 vertebral body fracture

	Classification					Total
	Coronal	Sagittal	Transverse	Avulsion	Complex	
Number of cases]	5	5	8	7	19	44
Demographics						
Male: Female	3 : 2	2 : 3	5 : 3	3 : 4	11 : 8	24 : 20
Age	64.0	48.4	64.0	61.6	63.7	61.7
Injury mechanism						
Slip down	0	0	2	1	2	6
Fall from height	2	0	1	2	8	12
Traffic accident	3	5	5	4	9	26
Discoligamentous injury	2	5	4	2	5	18
Combined injury	4	5	2	5	9	25
Neurologic symptom						
Radiating pain & tingling sensation	1	0	1	5	3	10
Weakness	1	1	1	0	0	3
Treatment						
Neck collar	3	3	2	4	4	16
Halovest	2	2	5	3	14	26
Fusion	0	0	1	0	1	2
Complications						
Persistent neurologic symptoms	0	1	1	1	1	4
Mal-union	0	0	0	1	3	4
Pin site infection	0	0	1	0	2	3

This study is limited by the small number of cases. Other limitations include the difficulty in determining the exact direction of the external force at the time of injury. Although some biomechanical experiments have been conducted on the external forces acting on the vertebral body and fracture patterns, studies that consider the combined effects of fractures on anatomical structures such as ligaments and muscles around the vertebral body are lacking, and further research is needed <sup>[21]</sup>.

## 7. Conclusion.

Vertebral body fractures of the axial spine accounted for approximately 50% of axial spine fractures. The fractures could be categorized into five types according to their morphology: coronal, sagittal, transverse, and complex. Conservative treatment resulted in bone union without significant complications and good clinical outcomes. We believe that conservative treatment can be used as a first-line treatment.

## Disclosure statement

The authors declare no conflict of interest.

## References

- [1] Passias PG, Poorman GW, Segreto FA, et al., 2018, Traumatic Fractures of the Cervical Spine: Analysis of Changes in Incidence, Cause, Concurrent Injuries, and Complications Among 488,262 Patients from 2005 to 2013. *World Neurosurg*, 110: e427–e37. <https://www.doi.org/10.1016/j.wneu.2017.11.011>
- [2] Pryputniewicz DM, Hadley MN, 2010, Axis Fractures. *Neurosurgery*, 66(3 Suppl): 68–82. <https://www.doi.org/10.1227/01.Neu.0000366118.21964.A8>
- [3] Hirschmann MT, Konala P, Amsler F, et al., 2011, The Position and Orientation of Total Knee Replacement Components: A Comparison of Conventional Radiographs, Transverse 2D-CT Slices and 3D-CT Reconstruction. *J Bone Joint Surg Br*, 93(5): 629–633. <https://www.doi.org/10.1302/0301-620x.93b5.25893>
- [4] Pearson AM, Martin BI, Lindsey M, et al., 2016, C2 Vertebral Fractures in the Medicare Population: Incidence, Outcomes, and Costs. *J Bone Joint Surg Am*, 98(6): 449–456. <https://www.doi.org/10.2106/JBJS.O.00468>
- [5] Seybold EA, Bayley JC, 1998, Functional Outcome of Surgically and Conservatively Managed Dens Fractures. *Spine (Phila Pa 1976)*, 23(17): 1837–1845. <https://www.doi.org/10.1097/00007632-199809010-00006>
- [6] Girardo M, Rava A, Gargiulo G, et al., 2018, Clinical and Radiological Union Rate Evaluation of Type 2 Odontoid Fractures: A Comparison Between Anterior Screw Fixation and Halo Vest in Elderly Patients. *J Craniovertebr Junction Spine*, 9(4): 254–259. [https://www.doi.org/10.4103/jcvjs.JCVJS\\_93\\_18](https://www.doi.org/10.4103/jcvjs.JCVJS_93_18)
- [7] Murphy H, Schroeder GD, Shi WJ, et al., 2017, Management of Hangman’s Fractures: A Systematic Review. *J Orthop Trauma*. 31(Suppl 4): S90–S95. <https://www.doi.org/10.1097/BOT.0000000000000952>
- [8] Anderson LD, D’Alonzo RT, 1974, Fractures of the Odontoid Process of the Axis. *J Bone Joint Surg Am*. 56(8): 1663–1674.
- [9] Benzel EC, Hart BL, Ball PA, et al., 1994, Fractures of the C-2 vertebral body. *J Neurosurg*, 81(2): 206–212. <https://www.doi.org/10.3171/jns.1994.81.2.0206>
- [10] Fujimura Y, Nishi Y, Kobayashi K, 1996, Classification and Treatment of Axis Body Fractures. *J Orthop Trauma*, 10(8): 536–540. <https://www.doi.org/10.1097/00005131-199611000-00005>
- [11] Koller H, Acosta F, Forstner R, et al., 2009, C2-Fractures: Part II. A Morphometrical Analysis of Computerized Atlantoaxial Motion, Anatomical Alignment and Related Clinical Outcomes. *Eur Spine J*, 18(8): 1135–1153. <https://www.doi.org/10.1007/s00586-009-0901-4>
- [12] Radovanovic I, Urquhart JC, Rasoulinejad P, et al., 2017, Patterns of C-2 Fracture in the Elderly: Comparison of Etiology, Treatment, and Mortality Among Specific Fracture Types. *J Neurosurg Spine*. 27(5): 494–500. <https://www.doi.org/10.3171/2017.3.SPINE161176>
- [13] Bakhsh A, Alzahrani A, Aljuzair AH, et al., 2020, Fractures of C2 (Axis) Vertebra: Clinical Presentation and Management. *Int J Spine Surg*. 14(6): 908-15. <https://www.doi.org/10.14444/7139>
- [14] Greene KA, Dickman CA, Marciano FF, et al., 1997, Acute Axis Fractures. Analysis of Management and Outcome in 340 Consecutive Cases. *Spine (Phila Pa 1976)*, 22(16): 1843–1852. <https://www.doi.org/10.1097/00007632-199708150-00009>
- [15] Kepler CK, Vaccaro AR, Fleischman AN, et al., 2017, Treatment of Axis Body Fractures: A Systematic Review. *Clin Spine Surg*. 30(10): 442–456. <https://www.doi.org/10.1097/BSD.0000000000000309>
- [16] Lomoschitz FM, Blackmore CC, Mirza SK, et al., 2002, Cervical Spine Injuries in Patients 65 Years

Old and Older. *AJR Am J Roentgenol.* 178(3): 573–577.  
<https://www.doi.org/10.2214/ajr.178.3.1780573>

- [17] Burke JT, Harris JH Jr, 1989, Acute Injuries of the Axis Vertebra. *Skeletal Radiol*, 18(5): 335–346. <https://www.doi.org/10.1007/bf00361422>
- [18] German JW, Hart BL, Benzel EC, 2005, Nonoperative management of vertical C2 body fractures. *Neurosurgery*, 56(3): 516–521. <https://www.doi.org/10.1227/01.neu.0000153908.53579.e4>
- [19] Motiei-Langroudi R, Sadeghian H, 2016, C2 Body Fracture: Report of Cases Managed Conservatively by Philadelphia Collar. *Asian Spine J*, 10(5): 920–924. <https://www.doi.org/10.4184/asj.2016.10.5.920>
- [20] Zhang YS, Zhang JX, Yang QG, et al., 2014, Surgical Management of the Fractures of Axis Body: Indications and Surgical Strategy. *Eur Spine J*, 23(8): 1633–1640. <https://www.doi.org/10.1007/s00586-013-3158-x>
- [21] Teo EC, Paul JP, Evans JH, et al., 2001, Experimental Investigation of Failure Load and Fracture Patterns of C2 (Axis). *J Biomech*, 34(8): 1005–1010. [https://www.doi.org/10.1016/s0021-9290\(01\)00071-9](https://www.doi.org/10.1016/s0021-9290(01)00071-9)

**Publisher's note**

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

# Symptomatic Lumbosacral Transitional Vertebrae (Bertolotti Syndrome) as a Cause of Low Back Pain: Classification and Imaging Findings

Barış Ten<sup>1\*</sup>, Meltem Nass Duce<sup>1</sup>, Hasan Hüsnü Yüksek<sup>1</sup>, Gülhan Temel<sup>2</sup>, Yüksel Balcı<sup>1</sup>, Kaan Esen<sup>1</sup>

<sup>1</sup>Department of Radiology, Faculty of Medicine, Mersin University, Mersin 33342, Turkey

<sup>2</sup>Department of Biostatistics and Medical Informatics, Faculty of Medicine, Mersin University, Mersin 33342, Turkey

\*Corresponding author: Barış Ten, drbaristen@hotmail.com

**Copyright:** © 2023 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

**Abstract:** *Objective:* To determine the most common pathologies of lower back pain and the proportion of Bertolotti syndrome (BS) among these pathologies and to reveal possible gender-age differences, and to group the lumbosacral transitional vertebrae (LSTV) according to Castellvi classification and find their prevalence rates. *Method:* The images and reports of 357 patients who underwent magnetic resonance imaging (MRI) of the sacroiliac joint between March 2020 and October 2021, mostly due to low back pain, were evaluated by a radiologist specialized in musculoskeletal radiology. *Results:* The mean ages of patients with and without BS were 43.9 years old and 44 years old, respectively, and there was no correlation between BS and patient age ( $P = 0.976$ ). The age range of patients with BS was 15–77 years old. Twenty per cent of the patients with BS were younger than 30 years old and 50% were younger than 40 years old. No gender difference was observed among patients with BS ( $P = 0.572$ ). The prevalence rates of LSTVs according to Castellvi classification, were 10% in Type 1a, 11.4% in Type 1b, 35.7% in Type 2a, 17.1% in Type 2b, 4.3% in Type 3a, 12.9% in Type 3b and 8.6% in Type 4. The main pathologies causing lower lumbar pain were active-chronic sacroiliitis, vertebral and disc degenerations, and facet joint arthrosis, while BS comes after, with 2.8%. In BS, the pain originated from the lumbosacral transitional vertebrae. *Conclusion:* According to our results, BS starts to be seen below the age of 30 years, but there is no significant relationship with age or gender. BS is one of the most common causes of lower lumbar pain after sacroiliitis, vertebral degeneration, and discopathy. There are different hypotheses in the literature about the etiology of BS and there is no common opinion. Therefore, there is a need for multicenter studies with large sample sizes.

**Keywords:** Bertolotti syndrome; Lumbosacral transitional vertebrae; Sacroiliac joint MRI

**Online publication:** June 9, 2023

## 1. Introduction

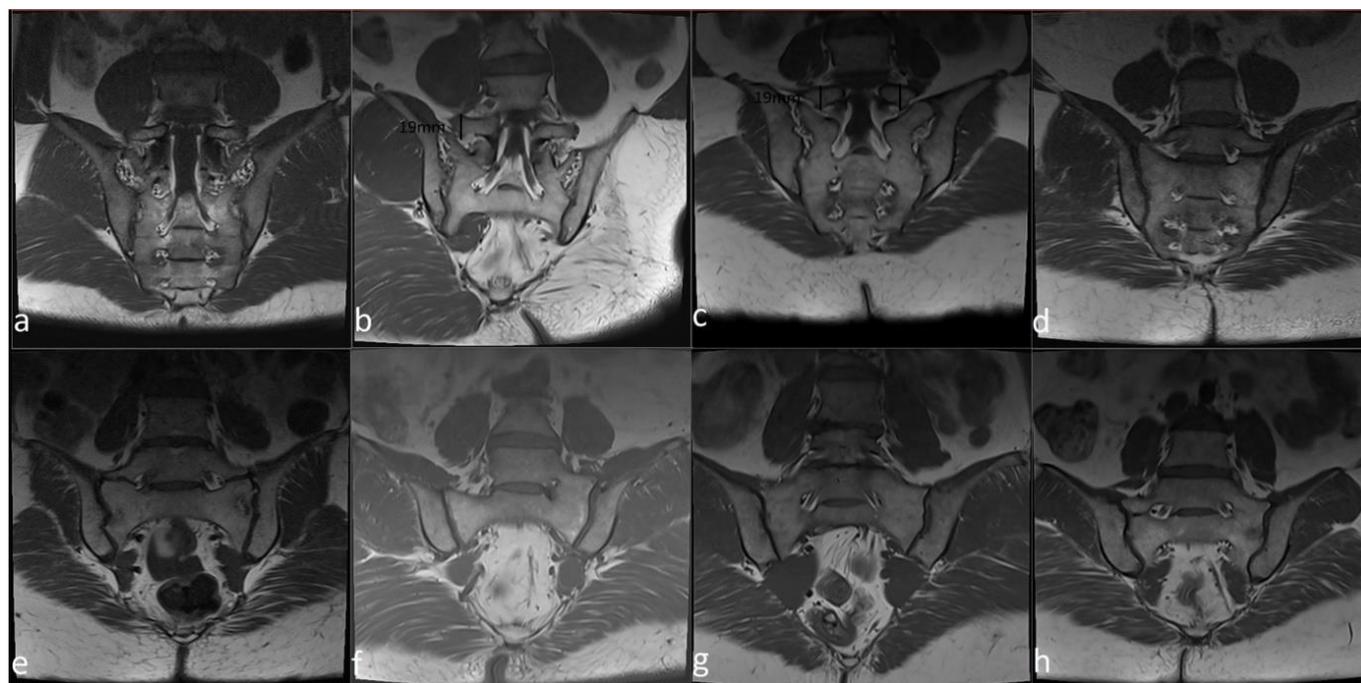
The lumbosacral transitional vertebra (LSTV) is a congenital vertebral anomaly consisting of the fusion of the transverse process of the last lumbar vertebra with the first sacral vertebral segment <sup>[1]</sup>. The LSTV encompasses a wide spectrum of morphological variations ranging from partial or complete sacralization of the L5 vertebra to partial or complete lumbarization of the S1 vertebra <sup>[2]</sup>. Bertolotti associated this anomaly with low back pain in 1917. Bertolotti Syndrome (BS) is a clinical and radiological diagnosis given to patients who experience pain due to LSTV <sup>[3]</sup>. This syndrome is said to affect 4–8% of the population <sup>[4]</sup>. Given the social and economic impact of lower back pain on young people, BS should be

included in the differential diagnosis list of low back pain. Magnetic resonance imaging (MRI) of the sacroiliac joint is usually performed for the diagnosis of sacroiliitis, which is one of the causes of low back pain. In addition to sacroiliac joint MRI, facet joint arthrosis, lower lumbar vertebral disc degeneration, osteodegenerative changes in the end plates of the lower lumbar vertebrae, spondylodiscitis, strain/tear/myositis in the erector spinae, scoliosis, metastasis, fracture, and BS can also be evaluated.

The aim of our study is to determine the most common pathologies of lower back pain, to reveal the rate of BS in these pathologies and to investigate the age-gender tendency of BS by compiling the results of sacroiliac joint MRI images and reports.

## 2. Materials and methods

In this study, the images and reports of 357 patients who underwent MRI of the sacroiliac joint for any indication, mostly low back pain, at the Department of Radiology, Mersin University Faculty of Medicine, between March 2020 and October 2021 were retrospectively evaluated. All reports were reviewed by a radiologist specialized in musculoskeletal radiology with 10 years of experience in radiology. Approval was obtained from the ethics committee of the university (number: 2022/192) before the study was carried out. All sacroiliac joint MRI scans were performed on a 1.5 T Siemens Magnetom Area scanner (Erlangen, Germany) using unilateral/bilateral, phased-array abdominal/cardiac or special hip coils. In sacroiliac joint MRI, the axial slice thickness was set as 3.5 mm and coronal slice thickness was set as 4 mm. Images were obtained with T1A, fat-suppressed T1A with and without contrast, followed by fat-suppressed T2A in the axial plane. In the coronal plane, images were obtained with T1A, T1A with and without fat-suppressed contrast, followed by STIR. LSTV evaluation was performed according to the Castellvi classification on coronal T1A images (**Figure 1**).



**Figure 1.** LSTV Types according to Castellvi classification. (a) Normal coronal T1A sacroiliac joint MRI image without lumbosacral transitional vertebrae, (b) triangular dysplastic unilateral transverse process at least 19 mm wide [Type 1a], (c) triangular dysplastic bilateral transverse process at least 19 mm wide [Type 1b], (d) unilateral diarthrodial joint between the transverse process and sacrum [Type 2a], (e) bilateral diarthrodial joint between the transverse process and sacrum [Type 2b], (f) unilateral bone fusion between transverse process and sacrum [Type 3a], (g) bilateral bone fusion between transverse process and sacrum [Type 3b], (h) unilateral diarthrodial joint and unilateral bone fusion [Type 4].

According to the Castellvi classification, Type 1 is characterized by a triangular dysplastic transverse process of at least 19 mm wide. Dysplastic transverse process is classified as 1a if it is unilateral and 1b if it is bilateral. In Type 2, a diarthrodial joint is observed between the transverse process and the sacrum and is considered incomplete lumbarization/sacralization. Type 3 is characterized by a bony fusion between the transverse process and sacrum, considered as complete lumbarization/sacralization. In Type 2 and Type 3, lumbarization/sacralization is classified as “a” if unilateral and “b” if bilateral. If diarthrodial joint is observed on one side and bone fusion is observed on the other side of the same patient, it is considered as Type 4 [5]. Appearances suggestive of acute inflammation and/or chronic degeneration in localizations with diarthrodial joint/bone fusion between the transverse process and sacrum were radiologically evaluated as BS. Areas that were hypointense on T1A images, hyperintense on T2A images, and showed contrast uptake on fat-suppressed postcontrast images were considered as acute inflammation. Areas that were hyperintense on T1A images and suppressed on fat-suppressed sequences were considered as fatty bone marrow infiltration due to hematopoietic red bone marrow ischemia, and areas that were hypointense on T1A and T2A images were considered as increased sclerosis and indicative of chronic degeneration (**Figure 2**). The described pathologies were categorized according to the results of MRI reports.



**Figure 2.** Appearances suggestive of acute inflammation and chronic degeneration in the diarthrodial joint between the L5TV and sacrum, consistent with Bertolotti syndrome. Acute inflammation: Hyperintense areas on STIR images (a) and contrast enhancement on fat-suppressed postcontrast images (d) compared to fat-suppressed non-contrast images (c). Chronic degeneration: Hyperintense areas on T1A images (b) and suppressed areas on fat-suppressed sequences (a, c, d). Fatty bone marrow infiltration due to hematopoietic red bone marrow ischemia.

Shapiro-Wilk test was used to check whether the measurements were normally distributed in the groups. The continuous variables obtained in the study were found to have normal distribution. Mean and standard deviation were used for descriptive statistics and numbers and percentage were used for categorical variables. A student *t*-test was performed to check whether there was a difference between the averages of two groups. Chi-square test was performed to identify the relationships between the categorical variables.  $P < 0.05$  was taken as statistical significance.

### 3. Results

Of the 357 patients who underwent sacroiliac joint MRI, 244 (68.35%) were female and 113 (31.65%) were male. The age range of the women was 13–76 years old, and the mean age was  $45.1 \pm 12.84$  years old. The age range of males was 10–82 years old, and the mean age was  $45.1 \pm 12.84$  years old.

The pathologies that may cause lower lumbar pain in 357 patients who underwent sacroiliac joint MRI were grouped (**Table 1**). The main pathologies causing lower lumbar pain were active-chronic sacroiliitis, vertebral degeneration, discopathy, and facet joint arthrosis. After these main pathologies, the most common pathology with a prevalence of 2.8% was BS, which was the cause of pain originating from the LSTV.

**Table 1.** Number and percentages of pathologies that may cause low back pain in patients with sacroiliac joint MRI

	Number	Percentage
Sacroileitis (active sacroileitis + chronic sacroileitis + chronically active sacroileitis)	108	30.2
Normal (no radiological pathology)	103	28.9
LSTV	70	19.6
*1a	7	2
*1b	8	2.2
*2a	25	7
*2b	12	3.4
*3a	3	0.8
*3b	9	2.5
*4	6	1.7
Vertebral degeneration and discopathy (vertebral degeneration + facet joint Arthrosis + disc degeneration)	56	15.7
Other causes (degenerative cystic changes + scoliosis + benign cystic bone lesions + erector spinae strain + fracture + metastasis + spondylodiscitis+ iliac wing osteomyelitis + posterior ligamentous injury + piriformis strain)	20	5.7
Total patients	357	100
# Bertolotti syndrome (radiological evidence)	10	2.8

\*Subtypes of the LSTV

# Bertolotti syndrome is symptomatic LSTV

In our study, the prevalence of LSTVs according to the Castellvi classification was 10% for Type 1a, 11.4% for Type 1b, 35.7% for Type 2a, 17.1% for Type 2b, 4.3% for Type 3a, 12.9% for Type 3b, and 8.6% for Type 4. The ratios of LSTV groups to all patients undergoing sacroiliac joint MRI are also shown (**Table 1**).

In our study, no gender preference was observed in LSTV ( $P = 0.597$ ). Six of 10 patients with BS in our study were female and four were male. When the gender distribution of patients with and without Bertolotti syndrome was analyzed, no gender preference was observed in BS ( $P = 0.572$ ). In our study, the mean age of patients with LSTV was 47.2 years old and the mean age of patients without LSTV was 43.3 years old. In our study, the mean age of patients with BS was 43.9 years old and the mean age of patients without BS was 44 years old, and no correlation was found between BS and patient age ( $P = 0.976$ ). The age range of patients with BS was 15–77 years. Twenty per cent of the patients with BS were younger than 30 years old and 50% were younger than 40 years old (**Table 2**).

**Table 2.** Distribution pattern of patients with and without LSTV, BS according to gender and age

	LSTV (+)	LSTV (-)	<i>P</i>	BS (+)	BS (-)	<i>P</i>
Percentage of female patients	46 (65.7)	198 (69)	0.597	6 (60)	238 (68.6)	0.572
Percentage of male patients	24 (34.3)	89 (31)		4(40)	109 (31.4)	
Average age	47.2	43.3	0.03	43.9	44	0.976

Abbreviations: LSTV, Lumbosacral transitional vertebra; BS, Bertolotti syndrome

#### 4. Discussion

Lower lumbar pain may radiate unilaterally or bilaterally to the hip and lower extremities. Clinicians may request lumbosacral spinal MRI and sacroiliac joint MRI examinations after physical examination and anamnesis to investigate the etiology of lower lumbar pain [6]. Although the main task of radiologists in sacroiliac joint MRI examination is to diagnose possible active or chronic sacroiliitis, they are obliged to convey the pathologies in all areas included in the examination to clinicians by placing them in order of importance. Many pathologies that may or may not be related to each other can be detected by sacroiliac joint MRI examination alone.

In the study by Tini *et al.* 37 (47.4%) of 78 patients with LSTV experienced lower back pain, while 41 (52.6%) did not experience lower back pain. Therefore, they concluded that there was no relationship between LSTV and lower back pain [7]. Since the 1970s, studies have focused on the fact that LSTV does not cause lower back pain in the early period and that BS may be due to degeneration in the LSTV itself or in the structures surrounding the LSTV over time. Therefore, many publications have been made on the etiologies of lower lumbar pain in BS arising from many different localizations. Louma *et al.* stated that disc, spinal canal, and posterior element pathologies above the level of the transitional vertebrae are responsible for the etiology of BS [8]. Mahato *et al.* showed facet joint arthrosis contralateral to the unilateral fusiform or diarthrodial articulating LSTV as the etiology of BS [9]. Ravikanth *et al.* reported extraforaminal stenosis due to the presence of an enlarged transverse process in the etiology of BS [11]. Elster *et al.* found no significant difference in the rate of disc protrusion, stenosis in the neural foramen and spinal canal, spondylolysis, facet joint degeneration, tumor, trauma, and infection between the groups with and without LSTV. However, they found a statistically significant difference in the presence of disc protrusion and neural foraminal stenosis at the level immediately above the LSTV compared to other levels in patients with LSTV ( $P < 0.00001$ ) [10]. Hence, the results of Elster *et al.* contradict the results of Mahato *et al.* and Ravikanth *et al.*, but support the conclusions of Louma *et al.*

Connolly *et al.* reported that degeneration in the abnormal articulation between the LSTV and the sacrum is responsible for the etiology of BS [11]. In our study, appearances suggestive of acute inflammation and/or chronic degeneration in the locations where diarthrodial joint/bone fusion between the LSTV and

the sacrum was observed were evaluated as BS, similar to Connolly *et al.* This syndrome have been reported to affect 4–8% of the population [4]. The prevalence of BS, which we found as 2.8% in our study, is similar to those reported in literature. According to the Castellvi classification, 8 of the 10 cases with BS were Type 2a, one was Type 2b and one was Type 3b. Therefore, it can be said that BS tends to involve the diarthrodial joint rather than the fused joint.

There have been many studies on the rate of LSTV with different imaging modalities. Elster *et al.* identified LSTV in 140 patients (7%) in a study of 2000 patients with 1500 CT scans and 500 MRI scans [10]. In studies using lumbosacral radiographs, Ravikanth *et al.* [11] identified LSTV in 134 of 500 patients (26.8%), Tini *et al.* [7] identified LSTV 78 of 798 patients (9.7%), Castellvi *et al.* [5] identified LSTV in 60 of 200 patients (30%), and Apazidis *et al.* [12] identified LSTV in 75 of 211 patients (35.6%). LSTV was observed in 70 (19.6%) of 357 patients with sacroiliac joint MRI. There are very few articles that grouped LSTVs according to the Castellvi classification and compared their rates among all subgroups.

The numbers and percentages of LSTV groups of studies done by Castellvi *et al.* [5] and Apazidis *et al.* [12] were compared (Table 3). According to the these two studies, the total percentage of Type 1 groups was lower, and the total percentages of Type 2, Type 3 and Type 4 groups were higher. The reason for this difference may be that these two studies were based on lumbosacral radiographs, whereas our study was based on MRI examinations of the sacroiliac joint. According to the Castellvi classification, Type 1 is characterized by a triangular dysplastic transverse process of at least 19 mm wide. Transverse process thickness measurements below 19 mm are considered normal. Differences can be observed in length measurements made on direct radiographs and MRI images. The main reason for the differences in these length measurements may be due to magnification (the image reflected is larger than the size of the object) or distortion (the image reflected is different from the object in terms of shape), which are geometric factors of direct radiography [13].

**Table 3.** Comparison of the number and percentage of LSTV types according to Castellvi classification

Type of LSTV according to Castellvi classification	Number (percentage) of LSTV patients (Castellvi <i>et al.</i> )	Number (percentage) of LSTV patients (Apazidis <i>et al.</i> )	Number (percentage) of LSTV patients in our study (percentage)
1a	9 (15)	31 (41.3)	7 (10)
1b	16 (26.6)	18 (24)	8 (11.4)
2a	12 (20)	9 (12)	25 (35.7)
2b	11 (18.3)	8 (10.6)	12 (17.1)
3a	1 (1.6)	4 (5.3)	3 (4.3)
3b	4 (6.6)	3 (4)	9 (12.9)
4	3 (5)	2 (2.6)	6 (8.6)
Number of patients with LSTV	60 (100)	75 (100)	70 (100)
Total number of patients	200	211	357
LSTV/percentage of total patients	30	35.6	19.6

Apazidis *et al.* found that 35 (46.7%) of 75 patients with LSTV were female and 40 (53.3%) were male [12]. Castellvi *et al.* observed 60 patients with LSTV, of whom 28.5% were female and 71.5% were male. Castellvi *et al.* mentioned that LSTV tends to be more common in males [5]. McGrath *et al.* stated in their review that LSTV is more common in males than females [3]. Ravikanth *et al.* did not find a relationship

between LSTV and the gender of the patients <sup>[1]</sup>. The results of our study were in agreement with Ravikanth *et al.* that no relationship was found between BS and the gender of the patients (**Table 2**).

Ravikanth *et al.* also found no correlation between LSTV and the age of the patients <sup>[1]</sup>. In our study, patients with LSTV were older than patients without LSTV ( $P = 0.03$ ) (**Table 2**). Quinlan *et al.* reported that the age of patients with BS was between 15 and 60 years old and the mean age was 32.7 years old <sup>[4]</sup>. Kapetanakas *et al.* reported that 18.5% of patients with BS were under 30 years of age <sup>[14]</sup>. Although the results of our study are consistent with Kapetanakas *et al.*, there was no significant relationship between age and BS.

## 5. Conclusion

According to our study results, Bertolotti syndrome starts manifesting below the age of 30 years, but there is no significant relationship with age or gender. Bertolotti syndrome is one of the most common causes of lower lumbar pain after sacroiliitis, osteodegeneration, and discopathy.

There have been different hypotheses about the etiology of Bertolotti but no consensus has been achieved. Therefore, multicenter studies with a large number of patients are needed.

## 6. Limitations of the study

The main limitation of the study is that the study was performed retrospectively, and the diagnosis of BS was made radiologically in patients with lower lumbar pain. There is no confirmation of the diagnosis with treatment results after radiological diagnosis.

## Disclosure statement

The authors declares no conflict of interest.

## Author contributions

*Conceptualization:* B.T., K.E., and M.N.D.

*Resources:* B.T., H.H.Y., Y.B.,

*Supervision:* B.T., K.E., G.T.,

*Writing – original draft:* B.T., G.T., Y.B.,

*Writing- review & editing:* B.T., G.T., M.N.D.

## References

- [1] Ravikanth R, Majumdar P, 2019, Bertolotti's Syndrome in Low-Backache Population: Classification and Imaging Findings. *Ci Ji Yi Xue Za Zhi*, 31(2): 90–95.
- [2] Mahato NK, 2013, Redefining Lumbosacral Transitional Vertebrae (LSTV) Classification: Integrating the Full Spectrum of Morphological Alterations in a Biomechanical Continuum. *Med Hypotheses*, 81: 76–81.
- [3] McGrath K, Schmidt E, Rabah N, et al., 2021, Clinical Assessment and Management of Bertolotti Syndrome: A Review of the Literature. *Spine J*, 21(8): 1286–1296.
- [4] Quinlan JF, Duke D, Eustace S, 2006, Bertolotti's Syndrome. A Cause of Back Pain in Young People. *J Bone Joint Surg Br*, 88(9): 1183–1186.
- [5] Castellvi AE, Goldstein LA, Chan DP, 1984, Lumbosacral Transitional Vertebrae and Their Relationship with Lumbar Extradural Defects. *Spine (Phila Pa1976)*, 9: 493–495.

- [6] Bernard SA, Kransdorf MJ, et al., 2017, ACR Appropriateness Criteria Chronic Back Pain Suspected Sacroiliitis-Spondyloarthritis. *J Am Coll Radiol*, 14(5S): S62–S70.
- [7] Tini PG, Wieser C, Zinn WM, 1977, The Transitional Vertebra of the Lumbosacral Spine: Its Radiological Classification, Incidence, Prevalence, and Clinical Significance. *Rheumatol Rehabil*, 16(3): 180–185.
- [8] Luoma K, Vehmas T, Raininko R, et al., 2004, Lumbosacral Transitional Vertebra: Relation to Disc Degeneration and Low Back Pain. *Spine (Phila Pa 1976)*, 29: 200–205.
- [9] Mahato NK, 2011, Facet Dimensions, Orientation, and Symmetry at L5-S1 Junction in Lumbosacral Transitional States. *Spine (Phila Pa 1976)*, 36: E569–E573.
- [10] Elster AD, 1989, Bertolotti's Syndrome Revisited: Transitional Vertebrae of the Lumbar Spine. *Spine (Phila Pa 1976)*.14:1373-1377.11.
- [11] Connolly LP, d'Hemecourt PA, Connolly SA, et al., 2003, Skeletal Scintigraphy of Young Patients with Low-Back Pain and a Lumbosacral Transitional Vertebra. *J Nucl Med*, 44(6): 909–914.
- [12] Apazidis A, Ricart PA, Diefenbach CM, et al., 2011, The Prevalence of Transitional Vertebrae in the Lumbar Spine. *Spine J*, 11: 858–862.
- [13] Kaya T, 2017, Basic Principles of Radiography and Basic Principles of Radiographic Interpretation. *Trd Sem*, 5: 1–22.
- [14] Kapetanakis S, Chaniotakis C, Paraskevopoulos C, Pavlidis P, 2017, An Unusual Case Report of Bertolotti's Syndrome: Extraforaminal Stenosis and L5 Unilateral Root Compression (Castellvi Type III an LSTV). *J Orthopaed Case Rep*, 7(3): 9–12.

**Publisher's note**

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

# 3D Printing of Titanium Implants at the University of Debrecen

Dóra Eszter Bodrog\*

Faculty of Technology, University of Debrecen, Debrecen 4032, Hungary

\*Corresponding author: Dóra Eszter Bodrog, bodrogd@gmail.com

**Copyright:** © 2023 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

**Abstract:** Additive manufacturing technologies are becoming increasingly popular in the field of medicine. Advances in laser-based techniques, which can also be used to print metals, have made it possible to produce fully customized, biocompatible implants, which are a major breakthrough in the treatment of bone defects. The University of Debrecen is involved in the production of such implants. On the basis of the available literature and preliminary experience, the individualization of implants, the implantability and material requirements, and the novelties offered by the technology are summarized in this paper.

**Keywords:** Additive manufacturing; Bone grafting; Direct Metal Laser Sintering; Implant; Reverse engineering; Titanium

**Online publication:** June 9, 2023

## 1. Introduction

The advancement of technology has opened more and more avenues for innovation in all areas of life, including medicine. The emergence of various metal printing techniques has allowed the production of biocompatible implants that can be fully customized.

However, this is not possible with traditional material forming processes although customization benefits both patients and doctors. Therefore, the University of Debrecen started a research project on the design and 3D printing of unique titanium implants, in which the first phases involved the collection and evaluation of existing knowledge, the development and preparation of the project, and the study and deployment of the technologies to be used.

The additive manufacturing of medical implants is a complex subject that requires practical application of engineering skills. However, it is essential to carry out thorough research, to systematize and summarize previous experience and to draw conclusions, and if possible, to propose further alternatives before starting the project. The aim of this research is to make the knowledge base as comprehensive as possible, with emphasis on the engineering aspects.

## 2. Basic information

The basic principle of additive manufacturing technologies is that the workpiece is built directly from a pre-designed three-dimensional computer model by depositing material bottom up, layer by layer. The model can be based on the digitization of an existing object (laser scanning, CT, MRI) or created directly through a three-dimensional design software, which is quick and cost-effective. These benefits are also being exploited in many areas of medicine.

- (i) Manufacturing custom hearing aid housings and designing of specialized medical devices;
- (ii) The production of anatomical models for surgical planning
- (iii) Printing tissue for research purposes
- (iv) Creating dental crowns, bridges, custom-made braces, and prostheses
- (v) Cost-effective production of prostheses for limb replacement
- (vi) Printing orthopedic implants <sup>[1]</sup>

### **3. About orthopedic implants in general**

Implants are devices that can be implanted in the body to maintain, or in some cases improve or restore the functions of the human body, or for aesthetic purposes. The primary function of orthopedic implants is to correct defects in the musculoskeletal system, such as damaged or deficient bones or damaged joints.

The most commonly used prostheses are for replacing hip and knee joints. Usually, these prostheses are made in units of a certain size range. The components that best fit the patient's physical characteristics are selected from a range of mass-produced products and then implanted. The advantage of this method is that the components can be produced relatively quickly in large numbers according to a certain pattern, and they usually meet the implantability requirements. However, there are special cases where, for example, the patient's bone structure or geometry does not allow the placement of conventionally manufactured implants. In such cases, individual solutions are required, with particular attention to individual specificity and special needs, without neglecting the basic implantology requirements.

### **4. Implantability requirements**

The two main requirements for implants are biocompatibility and biofunctionality. In the case of the latter, the emphasis is on ensuring performance, i.e., the implanted device must be able to perform a predefined function with a given set of properties, or in simple terms, the expected lifetime of the implants. This functionality is influenced by the prosthetic loads, the resulting stress distribution, the main mechanical properties of the materials, the degree of friction, and the resistance to wear and corrosion <sup>[2,3]</sup>.

Biocompatibility is the ability of a device to maintain its expected properties while performing a predefined function, and to affect the tissues of the body only to a certain extent. The degree of compatibility may be influenced by, the chemical and physical properties of the material used, the geometry, the size and mechanical properties of the device, the types of tissue present at the implantation site and their relationship to the tissues, and the way the surgery is performed <sup>[2,3]</sup>. Another important factor is the compatibility of different materials, as the formation of an upper electrode element must be avoided.

From an engineering point of view, the selection of the right materials and the correct design and manufacture of the implant play the most important role in ensuring biocompatibility and thus performance.

### **5. Material requirements**

In the case of devices implanted in the body, the compatibility of the materials used with the original functionality of the device is particularly important. Biocompatible materials that are biologically, chemically, and physically best suited to the task would be preferable. In all cases, it is important that the devices do not release particles that cause toxic reactions or interact with the body's tissues in undesirable ways. Examples of biocompatible materials are gold, titanium, Co-Cr-Mo and Ti-6Al-4V alloys, porcelain, or acrylate <sup>[2]</sup>.

The position of the implants varies from place to place and individual to individual, and the material properties should not be determined based on the location of the implant alone. In the case of bone replacements, the first priority apart from biocompatibility is to ensure load transfer, so adequate mechanical strength is important. In addition, the material should be wear-resistant and have a similar

weight to the bone structure and a modulus of elasticity as close as possible to that of natural bones [4-6].

The importance of similar mechanical properties lies in avoiding the so-called “stress shielding” phenomenon, whereby implants with a higher strength than natural bone increasingly transfers the load to the surrounding bone over time. Bone tissues have a special structure that can change under the influence of stress, so in this case they gradually lose their function, as they have to bear the mechanical stresses that they are subjected to. As a result, bone resorption occurs, the implant starts to loosen out of place, and in the worst case, the bone itself can break [7,8].

## 6. Titanium implants

One of the most commonly used materials for implantation today is titanium and its alloys. Pure titanium is a bioinert non-ferrous metal, i.e., it does not react or reacts only slightly with the body’s tissues. The effects caused have not been associated with negative consequences, so titanium is considered to be biocompatible [4-6].

Titanium, which has a solid hexagonal crystal lattice structure in the  $\alpha$ -phase, undergoes an allotropic transformation at about 882.5 °C, i.e., its lattice structure is modified without any change of state: above this temperature, the metal is characterized by a central cubic lattice structure in the space, which is now in the  $\beta$ -phase [4,5,7] (Figure 1).

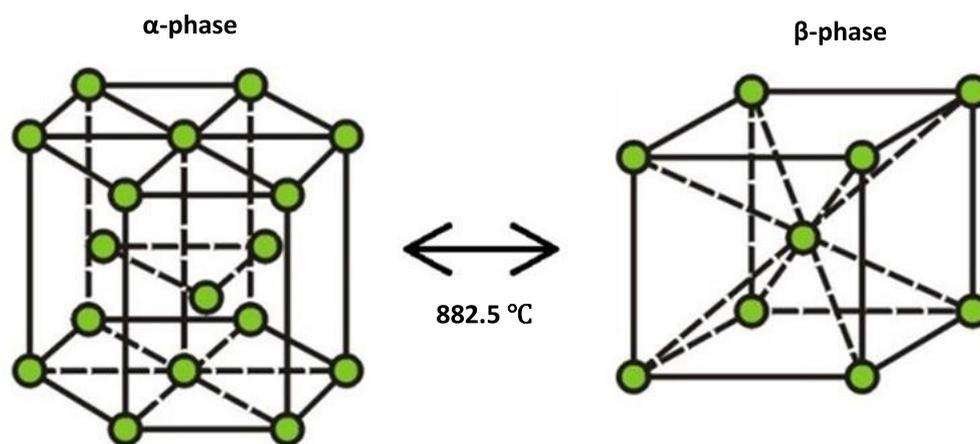


Figure 1. Phase transformation of titanium allotope [9]

Metals are alloyed so that certain physical, chemical, and mechanical properties can be achieved according to the desired application. Depending on the alloying materials, titanium alloys can be  $\alpha$ -,  $(\alpha+\beta)$ - or  $\beta$ -phase. The main materials used for orthopedic implants are titanium alloys of the  $(\alpha+\beta)$ -type, such as Ti-6Al-4V alloyed with aluminum and vanadium or Ti-6Al-4VELI (extra low interstitials). When using these alloys, however, it is important to ensure the correct proportions, as they reduce the biocompatibility of titanium above a certain percentage by weight [8].

In short, titanium is widely used because of its high mechanical strength, good corrosion resistance, relatively low material density, and lower elastic modulus compared to other stainless steels. It also has lower thermal and electrical conductivity compared to other metals and does not exhibit ferromagnetic properties, which is important for certain tests (MRI, NMRI). Furthermore, the oxide layer that forms on its surface, in addition to its corrosion resistance, plays a role in the so-called bone integration phenomenon, which allows a direct, fixed contact between the implant surface and the surrounding tissue [4-6].

This is because if the bone tissues were to penetrate sufficiently into the properly formed porous surface of the implant, the prostheses could be fixed naturally. The advantage of this is that, if no other defects occur, no further revision surgery is needed to correct any implant loosening, and the prosthesis,

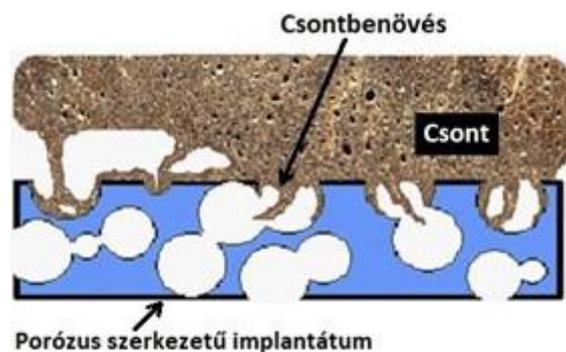
once in place, can last a lifetime. An additional advantage is that titanium has a low density, which reduces implant mass, and the flexibility of additive manufacturing allows the implant to be adapted to the bone.

## 7. Surface design

However, in order for the bone implant to assemble properly, it is necessary to create surfaces that enhance integration and stimulate biological activity. The desired surface shaping is achieved primarily by using biochemical and physical methods. In the chemical approach, coatings are applied to the implant surface to promote the desired biological interactions, such as hydroxyapatite (HA), which is also found in bones [4]. These coatings create a concrete connection between the surfaces of the implanted structure and the bone tissue. The advantages of chemical coatings are cost-effectiveness, ease of control, and the fact that they do not require significant alteration of the surface morphology to achieve the correct adhesion [4,6].

Physically, the implant is mechanically shaped to create a porous surface into which bone tissue can grow to the desired extent. Numerous experiments have been carried out to find the optimum geometry, from which it can be concluded that the degree of bone integration depends on a few factors (**Figure 2**).

- (i) The size of the pores
- (ii) The gaps between the bone and the implant
- (iii) The porosity of the implanted device
- (iv) The shapes and spatial arrangement of the pores
- (v) The presence of holes exposed to the surface
- (vi) The presence of pores connected to the channels [10-13]



**Figure 2.** Bone integration phenomenon [4]

In conclusion, the primary requirements for the replacement of bone defects are implants with high mechanical strength that is similar to that of natural bone and a porous structure that promotes the formation of vascular networks and bone integration. However, these two characteristics have opposing effects, and it is therefore very important to find a balance between biological and mechanical needs.

One of the solutions could be to develop devices with a solid “core” inside, responsible for the load-bearing capacity, and pores in the outer layers to reduce the stiffness differences that are responsible for ossification and stress shielding. In addition, it is advisable to use metals with a high strength as a basic material in order to achieve the required structural properties, as their porosity can be modified accordingly [4].

## 8. Customized titanium implants

Based on the points mentioned previously, it is clear that in order to produce ideal implants, it is necessary to map the bone gap in detail, to create a suitable structural model and develop a material shaping method that allows the creation of arbitrary geometric structures, essentially without any formal constraints. The

additive manufacturing technologies mentioned above are the most suited for this purpose, since they do not achieve the desired structural shapes by material selection like traditional methods but use only as much material as the predefined structure requires, and the workpiece is built layer by layer directly from a pre-modelled three-dimensional CAD (Computer Aided Design) construction [14].

### 9. Computer modelling

To design a suitable implant structure, accurate data on the geometry of the area to be replaced and the patient's bone structure and its condition should be taken into consideration. The most appropriate method is known as "reverse engineering," [15] whereby a 3D CAD model is derived from an existing physical object and the resulting realistic shape is used to estimate the shape and the mechanical properties of the bone structures to be replaced.

One of the commonly used methods is to first obtain CT images of the problem area at an appropriate resolution. At this stage, the scanned shapes are represented as spatial point clouds, from which a triangular approximation is generated using a software to generate a Standard Tessellation Language (STL) file of the selected bones or bone fragments. This file essentially stores the mesh structure of the model in binary or ASCII format, where the given parameters are the coordinates of the vertices of the triangles in the  $x$ ,  $y$ ,  $z$  directions. The smaller the descriptive triangles, the more accurate the approximation of the measured surface, but the larger the data set required [15-17].

Once the out-of-body normal vectors of the descriptive triangles are defined, the 3D mesh model can be effectively constructed using CAD software. The bone model generated from the CT images is then used to model the implant to be produced according to the measured data and to shape the desired features [15-17] (Figure 3).

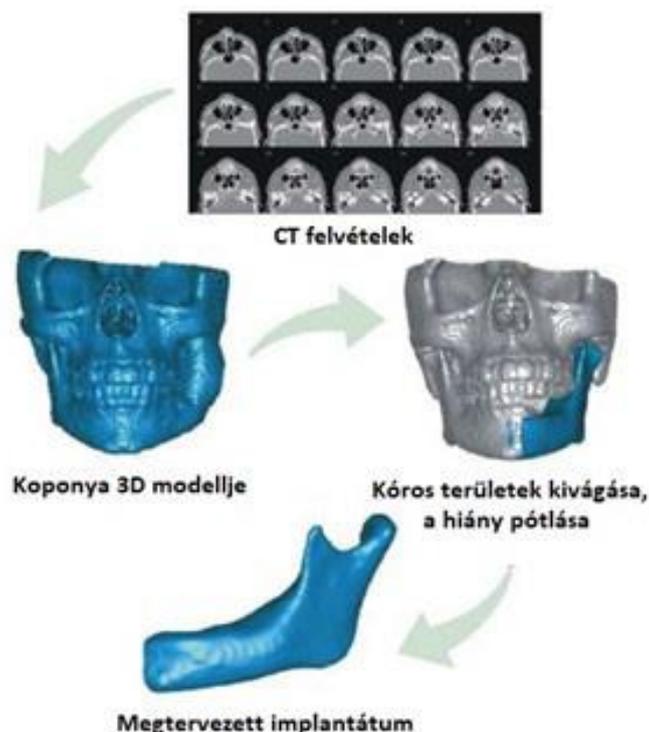


Figure 3. Mandibular implant modelling based on CT images [16]

After the modelling, the modified STL file is transferred to the computer of the production equipment, where the workpiece is segmented after the appropriate settings have been made, and the layer-by-layer production is started (Figure 4).

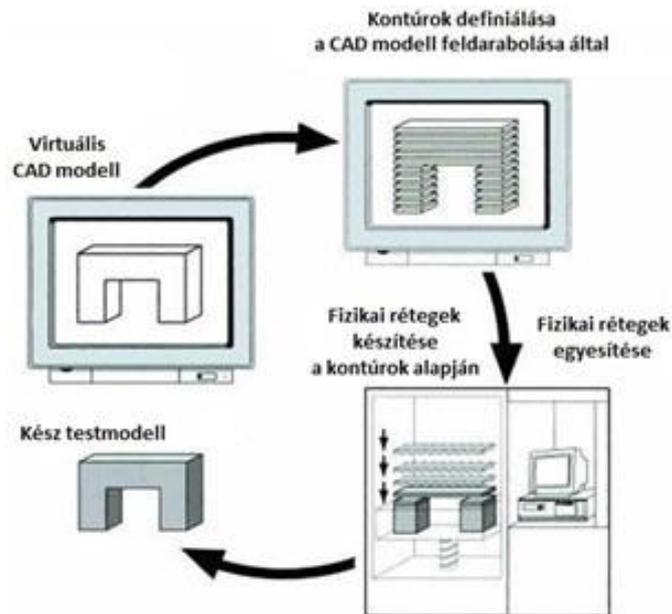


Figure 4. Principle of additive manufacturing <sup>[18]</sup>

## 10. Technologies used in additive manufacturing

Among the additive manufacturing technologies, the most suitable ones for metal implant manufacturing are powder-based systems, namely DMLS (Direct Metal Laser Sintering), SLM (Selective Laser Melting) and EBM (Electron Beam Melting) <sup>[20]</sup>. In this paper, the DMLS technology will be explained in detail.

## 11. Direct Metal Laser Sintering

The first step of the DMLS method is where a smoothing bar is used to spread the granules obtained from the powder feeder on the work surface in a layer thickness according to the preset settings, while the excess metal powder is collected in a collection chamber, which can be reused after filtration. The first layer of the model to be produced is then sintered in the x-y plane by focusing a high-energy laser beam at specific locations, and the workpiece is fixed to the worktable during the building process. The laser first scans the contour of the shape predefined in the STL file, then continuously passes over the entire cross-section, several times per line. The metallic powder, which is kept below the melting point temperature, is then heated to the melting point at the points hit by the laser beam, and the energy from the beam causes the powder particles to solidify <sup>[16,20]</sup>.

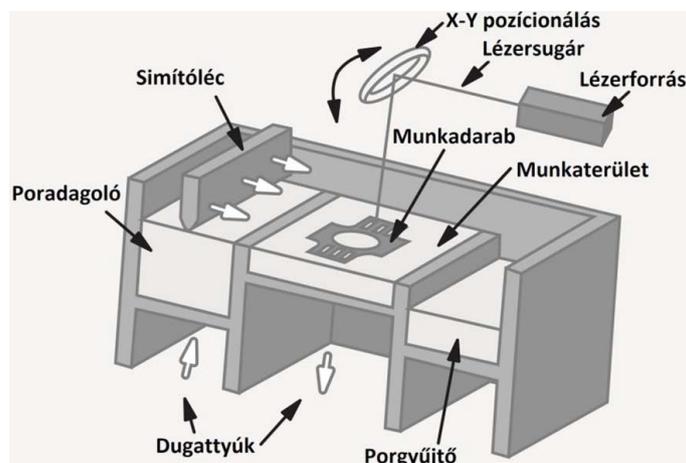


Figure 5. General structure of DMLS equipment

After the first layer is completed, the worktable is lowered to the predefined thickness, and a powder dispenser is used to spread the required amount of powder. The laser beam then focused on a optics mirror system, and the beam will be reflected into the required positions to combine the next layer of material, which will then also bond to the underlying surface. The lower layer is then lowered, and the new layer is sintered. This process is repeated until the model is completed. Before the completed model is removed from the powder bed, the system must be allowed to cool and any support material(s) must be removed [16,20] (**Figure 5**).

## **12. Key parameter settings**

Setting the right layer thickness is very important, because if it is too thick, the desired degree of fusion between layers cannot be achieved; if the layers are too thin, the dust cover may touch the surfaces, which causes the layer to move out of place. During the build-up of the workpiece, it is also important to avoid oxidation during the sintering of metals, so the process is carried out in an argon gas-filled medium for titanium powders [13,20,21].

It is also important to reduce the internal stresses that develop, which can be achieved by applying heat treatments to the finished object or by modifications prior to sintering. Previous experiences has shown that reducing the scanning depth of the laser, increasing the distance between the laser scans, and increasing the thickness of the layers results in lower internal stresses. Stress reduction can also be achieved by continuously changing the scanning directions of the laser and reducing its length. In addition, the workpiece should be placed in the workspace in such a way that minimal support is needed during the building process and that these supports can be easily removed after the model is completed without damaging the surface of the workpiece [13,20,21].

By modifying the parameters of the process, it is also possible to control the porosity of the layers and the size, the shape, and the distribution of these pores. This allows us to control the overall structure of the model, which is in this case the production of a fully biocompatible implant. However, in the meantime, it is important that the shaped workpieces meet predefined standards, both in terms of their chemical composition and mechanical and physical properties.

## **13. Marketability of custom orthopedic implants**

From what has been described so far, it is clear that this technology is suitable from a manufacturing point of view, but in order for the manufactured implants to be marketable and usable in practice, conformity approvals and certifications are required. The basis for this is Directive 93/42/EEC. On the basis of this Directive, medical devices are classified into risk classes, which determine the approval and authorization procedures that the devices must undergo.

Individual-specific implants can be categorized as “ready-to-use” devices, so the procedure defined in Annex 8 of the Directive should be taken into account. This means that the information listed here should be provided, in order to attest to the safe use of these devices for their intended purpose. These documents must include, inter alia, the name and address of the manufacturer, the name of the ordering practitioner, and a statement that the device is intended exclusively for a specific patient [22].

## **14. Prospects**

The medical history of the use of additive manufacturing technologies, such as the implant development methods discussed in this paper, offers a wealth of opportunities. These technologies will allow the production of customized implants with much higher biocompatibility and biofunctionality than the devices available currently, while making them more cost-effective, faster, and simpler to manufacture. However, the development of the system also requires the optimization of pre-production processes, including the

development and optimization of radiological image processing and modelling methods to ensure better image quality, research of the most favorable grid structures for bone integration, and analyses of the performance of finite elements. The ultimate goal is to develop bone defect treatment services to the maximum level, both in Hungary and internationally.

## 15. Summary

This paper was written to summarize as much knowledge as possible about the production of titanium custom implants using additive technology. To achieve that, the available literature was analyzed in order to provide an overview of the requirements for implementation, especially in terms of material knowledge, model design, and manufacturing with DMLS technology, and to investigate the basic legalities for marketability. This information is essential for the successful implementation of the desired service.

## Disclosure statement

The author declares no conflict of interest.

## References

- [1] Meskó B, 2015, 12 Things We Can 3D Print in Medicine Right Now, viewed November 29, 2017, <https://3dprintingindustry.com/news/12-things-we-can-3d-print-in-medicine-rightnow-42867/>
- [2] Nagy J, 2011, Medical Technology Application of Biocompatible Materials, viewed November 29, 2017, <https://adoc.pub/1-bevezetes-nagy-jozsef-1.html>
- [3] Oláh L, 2004, Polymer Technical Aspects of Implant Materials. *Journal of Material Testers*, 2004(2): 63–65.
- [4] Nouri A, Hodgson PD, Wen C, 2010, Biomimetic Porous Titanium Scaffolds for Orthopedic and Dental Applications, in *Biomimetics: Learning from Nature*, InTechOpen. <https://doi.org/10.5772/8787>
- [5] Oldani C, Dominguez A, 2012, Titanium as a Biomaterial for Implants, *Recent Advances in Arthroplasty*, in *Recent Advances in Arthroplasty*, InTechOpen. <https://doi.org/10.5772/27413>
- [6] Wang W, Poh CK, 2013, Titanium Alloys in Orthopaedics, *Titanium Alloys – Advances in Properties Control*, viewed November 29, 2017, <https://www.intechopen.com/books/titanium-alloys-advances-in-properties-control/titanium-alloys-in-orthopaedics>
- [7] Niinomi M, Masaaki N, 2011, Titanium-Based Biomaterials for Preventing Stress Shielding Between Implant Devices and Bone. *International Journal of Biomaterials*, 2011: 836587. <https://doi.org/10.1155/2011/836587>
- [8] Hosseini S, 2012, Fatigue of Ti-6Al-4V, in *Biomedical Engineering – Technical Applications in Medicine*, InTechOpen, 76–92. [https://cdn.intechopen.com/pdfs/38773/InTech-Fatigue\\_of\\_ti\\_6al\\_4v.pdf](https://cdn.intechopen.com/pdfs/38773/InTech-Fatigue_of_ti_6al_4v.pdf)
- [9] Interactions and the Structure of Matter: Crystal Lattice, n.d., viewed November 29, 2017, <http://tudasbazis.sulinet.hu/hu/szakkepzes/elektronika-elektrotechnika/a-muszaki-palyak-vilaga-elektronika-alapfogalmai/kolcsonhatasok-es-az-anyag-szerkezete/kristalyracs>
- [10] Stangl R, Rinne B, Kastl S, et al., 2001, The Influence of Pore Geometry in cp Ti-Implants. *Eur Cell Mater*, 2: 1–9 <https://www.ncbi.nlm.nih.gov/pubmed/14562260.12>
- [11] Warnke PH, Douglas TEL, Wollny P, et al., 2009, Rapid Prototyping: Porous Titanium Alloy Scaffolds Produced by Selective Laser Melting for Bone Tissue Engineering. *Tissue Eng Part C Methods*, 15(2):

- [12] Wysocki B, Idaszek J, Szlajak K, et al., 2016, Post Processing and Biological Evaluation of the Titanium Scaffolds for Bone Tissue Engineering. *Materials* (Basel), 9(3): 197. <https://doi.org/10.3390/ma9030197>
- [13] Dobrzanski LA, Dobrzanska-Danikiewicz AD, Ahtelik-Franczak A, et al., 2016, Porous Selective Laser Melted Ti and Ti6Al4V Materials for Medical Applications, in *Powder Metallurgy – Fundamentals and Case Studies*, InTechOpen. <https://www.intechopen.com/books/powder-metallurgy-fundamentals-and-case-studies/porous-selective-laser-melted-ti-and-ti6al4v-materials-for-medical-applications>
- [14] Balamurugan KG, Rajendran DK, 2016, A Review on Status of Research in Metal Additive Manufacturing, in *Advances in 3D Printing & Additive Manufacturing Technologies*, Springer Singapore, 95–100.
- [15] Kodácsy J, Pintér Z, Pokriva P, n.d., Quality of Surfaces Produced by the Reverse Engineering Method, viewed November 29, 2017, [https://www.muszeroldal.hu/measurenotes/reverse\\_engineering.pdf](https://www.muszeroldal.hu/measurenotes/reverse_engineering.pdf)
- [16] Jardini AL, Larosa MA, Bernardes LF, et al., 2011, Proceedings of the 6th Brazilian Conference on Manufacturing Engineering, April 11–15, 2011: Application of Direct Metal Laser Sintering in Titanium, Caxias do Sul.
- [17] Sánta I, 2012, Special Laser Beam Technologies, DocPlayer, viewed November 29, 2017, <https://docplayer.hu/2760445-Kulonleges-lezersugaras-technologiak-santa-imre.html>
- [18] Project Plan – 3D Printer, n.d., viewed, November 29, 2017, <https://wiki.aalto.fi/display/MEX/Project+plan+-+3D+Printer>
- [19] Additive Manufacturing Technologies: An Overview, viewed November 29, 2017, <https://www.3dhubs.com/knowledge-base/additive-manufacturing-technologies-overview#/>
- [20] Mangano FG, Chambrone L, van Noort R, et al., 2014, Direct Metal Laser Sintering Titanium Dental Implants: A Review of the Current Literature, 2014: 461534. <https://doi.org/10.1155/2014/461534>
- [21] Bineli ARR, Peres APG, Jardini AL, et al., 2011, Proceedings of the 6th Brazilian Conference on Manufacturing Engineering, April 11–15, 2011: Direct Metal Laser Sintering (DMLS) – Technology for Design and Construction of Microreactors, Caxias do Sul.
- [22] EüM Decree on Medical Devices, n.d., viewed November 29, 2017, [https://net.jogtar.hu/jr/gen/hjegy\\_doc.cgi?docid=A0900004.EUM](https://net.jogtar.hu/jr/gen/hjegy_doc.cgi?docid=A0900004.EUM)

**Publisher's note**

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

# Hip Fracture Due to Osteomalacia Secondary to Celiac Disease

Alberto Hernández Fernández\*, Cristian Pinilla-Gracia, Luis Rodríguez Nogué, Luis Rodríguez Chacón, Carlos Bejarano Lasunción

Miguel Servet University Hospital, Zaragoza 50009, Spain

\*Corresponding author: Alberto Hernández Fernández, [alberto.hdez.fdez@gmail.com](mailto:alberto.hdez.fdez@gmail.com)

**Copyright:** © 2023 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

**Abstract:** *Background:* Hip fracture is uncommon among younger patients but can have devastating consequences. Therefore, hip fracture caused by minimal trauma requires examinations on calcium metabolism to identify the primary cause. *Methods:* We present a clinical case of an 18-year-old male patient who suffered a subcapital fracture of the left hip due to minimal trauma while playing soccer. The patient immediately underwent surgery, which is closed reduction and internal fixation with two cancellous screws installed. Subsequently, metabolic tests showed severe vitamin D deficiency (27.1 nmol/L - normal above 75 nmol/L) and high levels of IgA anti-transglutaminase antibodies (2502.40 U/mL). Digestive biopsy confirmed the diagnosis of celiac disease, and he was treated with a gluten-free diet and calcium and vitamin D supplements. *Results:* After two years of follow-up, the patient is pain-free, with full hip mobility. There were no complications (osteosynthesis failure, avascular necrosis or pseudarthrosis) and serum levels of vitamin D, and IgA anti-transglutaminase antibodies had normalized. *Conclusion:* In young patients presenting with low energy trauma fractures, vitamin D deficiency should be considered as a possible etiology, and the reason for such osteomalacia, such as celiac disease, should be identified.

**Keywords:** Celiac disease; Osteomalacia; Femoral neck fractures; Spontaneous fractures

**Online publication:** June 9, 2023

## 1. Key concepts

Numerous studies have provided data on a possible lack of intestinal absorption of vitamin D in the presence of enteropathy secondary to celiac disease. Thus, the development of fractures due to deficient bone mineralization is also possible. However, the development of a hip fracture in a young patient, in which functional consequences can be devastating, has only been described as an initial manifestation of celiac disease. This paper describes a case study of a patient that underwent treatment for a subcapital hip fracture, while additional examinations were also carried out to reach a diagnosis of celiac disease as the pathology of origin. It is necessary to maintain a high clinical suspicion in a hip fracture of a young patient that did not experience a high energy mechanism injury. In this way, it will be possible to complete the examinations that will lead to the diagnosis of the initial disease to reverse its consequences and avoid future clinical manifestations.

## 2. Introduction

Hip fracture is common among the elderly, which is caused by low energy trauma, considering that the patient already has osteoporosis. On the other hand, this injury caused by low-energy trauma is uncommon

in young people; hip fractures in young people are usually caused by secondary to high energy mechanism, such as traffic accidents or falls from heights <sup>[1]</sup>. However, there are pathologies that cause a higher risk of hip stress fractures, such as chronic renal failure, high-dose corticotherapy or osteomalacia <sup>[2]</sup>. Osteomalacia is a disorder that causes a defect in bone mineralization secondary to vitamin D deficiency. A possible etiology of osteomalacia is celiac disease, characterized by inflammation of the intestinal mucosa, which in turn causes malabsorption of calcium and vitamin D <sup>[3]</sup>.

The article presents a case study of a young patient with osteomalacia secondary to undiagnosed celiac disease that was presented with a subcapital hip fracture.

### 3. Clinical case

An 18-year-old male presented to the Emergency Department of our hospital after suffering minimal trauma while practicing sports. Upon examination, the patient was presented with pain and functional impotence in the left hip, with shortening and external rotation of the limb.

The plain radiograph shows a displaced subcapital fracture of the left hip (Garden IV). An urgent closed reduction and internal fixation was performed along with the insertion of two cannulated compression screws (**Figures 1 & 2**).



**Figure 1.** Simple preoperative X-ray (Left hip subcapital fracture, with valgus displacement)



**Figure 2.** Simple postoperative X-ray (Osteosynthesis with 2 cannulated cancellous bone screws)

Since it was a young patient with a hip fracture following a low energy mechanism, further examinations were carried out. Laboratory studies showed a vitamin D deficiency. The serum 25 (OH) vitamin D level was 27.1 nmol/L (75–250nmol/L). Alkaline phosphatase values were 77.8 U/L (12.0–43.0 U/L), while N-MID osteocalcin presented levels of 82.8 ng/mL (5.8–39.8 ng/mL). Other parameters were normal: serum calcium (10.0 mg/dL), serum phosphorus (4.20 mg/dL) and hemoglobin (15.6 g/dL). Bone densitometry of the lumbar area indicated bone density loss (lumbar: 0.839 g/cm<sup>2</sup>; T score: -3.1; Z score: -

2.9). These findings confirmed the existence of a deficiency in bone mineralization secondary to vitamin D deficiency.

The patient experienced some gastrointestinal discomfort a year ago, which even forced him to go to the emergency department on one occasion, so he underwent screening for gastrointestinal diseases. Anti-transglutaminase IgA antibodies were high (2502.40 U/mL), so, in view of the suspicion of celiac disease, an endoscopy was performed. The endoscopy showed barely visible flattened folds with multiple fibrin-covered erosions in the second duodenal portion. The anatomopathological study of this duodenal portion showed villous atrophy with dense and diffuse lymphocytes and plasma cells infiltrate, confirming the diagnosis of celiac disease. The treatment used for the diagnosis of osteomalacia secondary to celiac disease was a gluten-free diet, along with calcium and vitamin D supplements during the first year of treatment.

#### **4. Follow-up**

The immediate postoperative period is uneventful, and the patient was advised on unloading the limb for the first six weeks. After this period, progressive partial support of the limb was allowed for the next six weeks; from the third month onwards, full weight bearing is approved. After a 2-year follow-up, the patient was pain-free, with full mobility of the coxofemoral joint. No complications such as osteosynthesis failure, avascular necrosis of the femoral head, or consolidation problems occurred.

Currently, the patient follows a strict gluten-free diet, without the need for vitamin supplements. The blood test and bone densitometry have normalized, and the patient showed no digestive or other symptoms.

#### **5. Discussion**

Hip fracture in young patients not associated with a traumatic context is uncommon and can have devastating consequences. Its diagnosis requires an exhaustive study of the loss of bone quality and its primary etiology. From the surgeon's point of view, the measures taken is not only limited to internal fixation of the hip fracture for its subsequent functional recovery, but also identifying the primary pathology and thus prevent new fractures and other non-osteoarticular manifestations.

This case study involves bone mineralization defect secondary to vitamin D malabsorption, due to celiac disease enteropathy. There are few cases in the literature that report hip fractures due to osteomalacia secondary to celiac disease. Ozgur *et al.* reported three cases of bilateral hip stress fracture successfully treated by cannulated screw osteosynthesis in their study [4]. Rubinstein *et al.* reported a clinical case of an elderly man with bilateral hip fracture with severe tetany [5].

The relationship between celiac disease and increased risk of hip fracture has previously been described in literature. For example, a cohort study including 7146 patients, relates persistent villous atrophy with an increase (Hazard ratio 1.67; 95% CI 1.05–2.66) in the risk of hip fracture [6]. On the other hand, García-Manzanares *et al.* found that there is a low risk of hip fracture in the presence of celiac disease, which increases to medium risk when there is villous atrophy [7].

However, although the increased risk of hip fracture in the presence of celiac disease has been demonstrated, routine screening for celiac disease is not recommended in the presence of a metabolic bone disease of unexplained origin, or in the absence of gastrointestinal symptoms or dermatitis herpetiformis [8]. Moreover, in economic terms, universal screening for celiac disease for the prevention of fractures in undiagnosed patients is not a viable alternative [9].

#### **6. Conclusion**

Subcapital hip fracture in young patients in the absence of a high energy mechanism is a rare occasion. When diagnosing the pathology, we have to rule out vitamin D deficiency as a possible cause, and the reason for such osteomalacia, such as celiac disease, must be identified.

Therefore, it is very important to maintain a high degree of suspicion in our daily clinical practice to diagnose this disease and avoid secondary clinical manifestations that can be catastrophic.

### Disclosure statement

The authors declare no conflict of interest.

### Author contributions

All authors have participated in the conceptualization, collection of information, the writing of the manuscript, and approval of its final version.

### References

- [1] Sachse D, Bludau F, Obertacke U, 2010, Schenkelhalsfrakturen bei jüngeren Patienten (15-50 Jahre). Systematische Literaturrecherche zur medialen Schenkelhalsfraktur beim jungen Patienten [Fractures of the Neck of the Femur in Younger Patients (15–50 Years Old): Systematic Literature Research on Medial Fractures of the Neck of the Femur in Young Patients]. *Unfallchirurg*, 113(1): 69–74. <https://www.doi.org/10.1007/s00113-009-1699-6>
- [2] Krestan CR, Nemeč U, Nemeč S, 2011, Imaging of Insufficiency Fractures. *Semin Musculoskelet Radiol*, 15(3): 198–207. <https://www.doi.org/10.1055/s-0031-1278420>
- [3] Kamycheva E, Goto T, Camargo CA Jr, 2017, Celiac Disease is Associated with Reduced Bone Mineral Density and Increased FRAX Scores in the US National Health and Nutrition Examination Survey. *Osteoporos Int*, 28(3): 781–790. <https://www.doi.org/10.1007/s00198-016-3791-4>
- [4] Selek O, Memisoglu K, Selek A, 2015, Bilateral Femoral Neck Fatigue Fracture due to Osteomalacia Secondary to Celiac Disease: Report of Three Cases. *Arch Iran Med*, 18(8): 542–544.
- [5] Rubinstein A, Liron M, Bodner G, et al., 1982, Bilateral Femoral Neck Fractures as a Result of Coeliac Disease. *Postgrad Med J.*, 58(675): 61–62. <https://www.doi.org/10.1136/pgmj.58.675.61>
- [6] Lebwohl B, Michaëlsson K, Green PH, et al., 2014, Persistent Mucosal Damage and Risk of Fracture in Celiac Disease. *J Clin Endocrinol Metab*, 99(2): 609–616. <https://www.doi.org/10.1210/jc.2013-3164>
- [7] García-Manzanares A, Tenias JM, Lucendo AJ, 2012, Bone Mineral Density Directly Correlates with Duodenal Marsh Stage in Newly Diagnosed Adult Celiac Patients. *Scand J Gastroenterol*, 47(8–9): 927–936. <https://www.doi.org/10.3109/00365521.2012.688217>
- [8] Fisher AA, Davis MW, Budge MM, 2004, Should We Screen Adults with Osteoporotic Fractures for Coeliac Disease? *Gut*, 53(1):154–155. <https://www.doi.org/10.1136/gut.53.1.154-a>
- [9] Park KT, Tsai R, Wang L, et al., 2013, Cost-Effectiveness of Universal Serologic Screening to Prevent Nontraumatic Hip and Vertebral Fractures in Patients with Celiac Disease. *Clin Gastroenterol Hepatol*, 11(6): 645–653. <https://www.doi.org/10.1016/j.cgh.2012.12.037>

#### Publisher's note

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## Author Guidelines

Before your submission, please check that your manuscript has been prepared in accordance to the step-by-step instructions for submitting a manuscript to our online submission system. We recommend that you keep this page open for your reference as you move through the submission process.

If there are any differences in author guidelines between the print and online version, it is recommended that authors refer to the online version for use.

### Manuscript Format

*Bone and Arthroscopy Science* accepts manuscript that is in MS Word or LaTeX format. All manuscripts must be written in clear, comprehensible English. Both American and British English are acceptable. Usage of non-English words should be kept to a minimum and all must be italicized (except for e.g. and i.e.) If you have concerns about the level of English in your submission, please ensure that it is proofread before submission by a native English speaker or a scientific editing service.

### Cover letter

All submissions for *Bone and Arthroscopy Science* should include a cover letter as a separate file. A cover letter should contain a brief explanation of what was previously known, the conceptual advancement with the findings and its significance to broad readership. The cover letter is confidential and will be read only by the editors. It will not be seen by reviewers.

### Title

The title should capture the conceptual significance for a broad audience. The title should not be more than 50 words and should be able to give readers an overall view of the paper's significance. Titles should avoid using uncommon jargons, abbreviations and punctuation.

### List of Authors

The names of authors must be spelled out rather than set in initials with their affiliations footnoted. Authors should be listed according to the extent of their contribution, with the major contributor listed first. All corresponding authors (maximum 2) should be identified with an asterisk. Affiliations should contain the following core information: department, institution, city, state, postal code, and country. For contact, email address of only one corresponding author is expected within the manuscript. Please note that all authors must see and approve the final version of the manuscript before submitting.

## **Abstract**

Articles must include an abstract containing a maximum of 200 words. The purpose of abstract is to provide sufficient information for a reader to choose either to proceed to the full text of the article. After the abstract, please give 3-8 key words; please avoid using the same words as those already used in the title.

## **Section Headings**

Please number all section headings, subheadings and sub-subheadings. Use boldface to identify major headings (e.g. **1**, **2**, **3**, etc.) and subheadings (e.g. **1.1**, **1.2**, **2.1**, **2.2** etc.) For the sub-subheadings, please distinguish it further using non-boldface numbers in parenthesis (e.g. (1), (2), (3), etc.)

## **Introduction**

Introduction should provide a background that gives a broad readership an overall outlook of the field and the research performed. It tackles a problem and states its importance regarding the significance of the study. Introduction can conclude with a brief statement of the aim of the work and a comment about whether that aim was achieved.

## **Materials and Methods**

This section provides the general experimental design and methodologies used. The aim is to provide enough detail to for other investigators to fully replicate your results. It is also required to facilitate better understanding of the results obtained. Protocols and procedures for new methods must be included in detail to reproduce the experiments.

## **Ethics**

Ethics information, including IACUC permit numbers and/or IRB name, if applicable. This information should be included in a subheading labelled "Ethics Statement" in the "Methods" section of your manuscript file, in as much detail as possible.

## **Results**

This section can be divided into subheadings. This section focuses on the results of the experiments performed.

## **Discussion**

This section should provide the significance of the results and identify the impact of the research in a broader context. It should not be redundant or similar to the content of the results section.

## **Conclusion**

Please use the conclusion section for interpretation only, and not to summarize information already presented in the text or abstract.

## **Conflict of Interest**

All authors are required to declare all activities that have the potential to be deemed as a source of competing interest in relations to their submitted manuscript. Examples of such activities could include personal or work-related relationships, events, etc. Authors who have nothing to declare are encouraged to add "No conflict of interest was reported by all authors" in this section.

## **Funding**

Authors should declare all financial and non-financial support that have the potential to be deemed as a source of competing interest in relations to their submitted manuscript in this section. Financial supports are generally in the form of grants, royalties, consulting fees and more. Examples of non-financial support could include the following: externally-supplied equipments/biological sources, writing assistance, administrative support, contributions from non-authors etc.

## **Appendix**

This section is optional and is for all materials (e.g. advanced technical details) that has been excluded from the main text but remain essential to readers in understanding the manuscripts. This section is not for supplementary figures. Authors are advised to refer to the section on ‘Supplementary figures’ for such submissions.

## **Text**

The text of the manuscript should be in Microsoft Word or Latex. The length of the manuscript cannot be more than 50000 characters (inclusive of spaces) or approximately 7000 words.

## **Nomenclature for genes and proteins**

This journal aims to reach researchers all over the globe. Hence, for both reviewers’ and readers’ ease in comprehension, authors are highly encouraged to use the appropriate gene and protein nomenclature. Authors may prefer to utilize resources such as <http://www.ncbi.nlm.nih.gov/gene>

## **Figures**

Authors should include all figures into the manuscript and submit it as 1 file in the OJS system. Reference to the “Instructions for Typesetting manuscript” is strongly encouraged. Figures include photographs, scanned images, graphs, charts and schematic diagrams. Figures submitted should avoid unnecessary decorative effects (e.g. 3D graphs) as well as be minimally processed (e.g. changes in

brightness and contrast applied uniformly for the entire figure). It should also be set against a white background. Please remember to label all figures (e.g. axis etc.) and add in captions (below the figure) as required. These captions should be numbered (e.g. **Figure 1**, **Figure 2**, etc.) in boldface. All figures must have a brief title (also known as caption) that describes the entire figure without citing specific panels, followed by a legend defined as description of each panel. Please identify each panel with uppercase letters in parenthesis (e.g. A, B, C, etc.)

The preferred file formats for any separately submitted figure(s) are TIFF or JPEG. All figures should be legible in print form and of optimal resolution. Optimal resolutions preferred are 300 dots per inch for RGB coloured, 600 dots per inch for greyscale and 1200 dots per inch for line art. Although there are no file size limitation imposed, authors are highly encouraged to compress their figures to an ideal size without unduly affecting legibility and resolution of figures. This will also speed up the process of uploading in the submission system if necessary.

The Editor-in-Chief and Publisher reserve the right to request from author(s) the high-resolution files and unprocessed data and metadata files should the need arise at any point after manuscript submission for reasons such as production, evaluation or other purposes. The file name should allow for ease in identifying the associated manuscript submitted.

## **Tables, lists and equations**

Tables, lists and equations must be submitted together with the manuscript. Likewise, lists and equations should be properly aligned and its meaning clear to readers. Tables created using Microsoft Word table function are preferred. Place each table in your manuscript file right after the paragraph in which it is first cited. Do not submit your tables in separate files. The tables should include a concise but sufficiently explanatory title at the top. Vertical lines should not be used to separate columns. Leave some extra space between the columns instead. All tables should be based on three horizontal lines to separate the caption, header and body. A few additional horizontal lines MAY be included as needed (example below). Any explanations essential to the understanding of the table should be given in footnotes at the bottom of the table. SI units should be used.

## **Supplementary information**

This section is optional and contains all materials and figures that have been excluded from the entire manuscript. This information are relevant to the manuscript but remains non-essential to readers' understanding of the manuscript's main content. All supplementary information should be submitted as a separate file in Step 4 during submission. Please ensure the names of such files contain 'suppl. info'.

## **In-text citations**

Reference citations in the text should be numbered consecutively in superscript square brackets. Some examples:

1. Negotiation research spans many disciplines <sup>[3, 4]</sup>.
2. This result was later contradicted by Becker and Seligman <sup>[5]</sup>.
3. This effect has been widely studied <sup>[1-3, 7]</sup>.

Personal communications and unpublished works can only be used in the main text of the submission and are not to be placed in the Reference section. Authors are advised to limit such usage to the minimum. They should also be easily identifiable by stating the authors and year of such unpublished works or personal communications and the word 'Unpublished' in parenthesis.

E.g. (Smith J, 2000, Unpublished)

## References

This section is compulsory and should be placed at the end of all manuscripts. Do not use footnotes or endnotes as a substitute for a reference list. The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should be excluded from this section.

For references in reference list, all authors must be stated. Authors referenced are listed with their surname followed by their initials. All references should be numbered (e.g. 1. 2. 3. etc.) and sequenced according to the order it appears as an in-text citation. References should follow the following pattern: Author(s) followed by year of publication, title of publication, full journal name in italics, volume number, issue number in parenthesis, page range and lastly the DOI (if applicable). If the referred article has more than three authors, list only the first three authors and abbreviate the remaining authors to italicized 'et al.' (meaning: "and others").

## Journal

*Journal article (print) with one to three authors*

[1] Yao Y., Xia B. Application of Phase Frequency Feature Group Delay Algorithm in Database Differential Access. *Computer Simulation*, 2014, 31(12): 238-241.

*Journal article (print) with more than three authors*

[2] Gamelin F.X., Baquet G., Berthoin S., et al. Effect of high intensity intermittent training on heart rate variability in prepubescent children. *European Journal of Applied Physiology*, 2009, 105: 731–738.

*Journal article (online) with one to three authors*

[3] Jackson D., Firtko A., Edenborough M. Personal resilience as a strategy for surviving and thriving in the face of workplace adversity: a literature review. *Journal of Advanced Nursing*, 2009, 60(1): 1–9,

*Journal article (online) with more than three authors*

[4] Hargreave M., Jensen A., Nielsen T.S.S., et al. Maternal use of fertility drugs and risk of cancer in children—A nationwide population-based cohort study in Denmark. *International Journal of Cancer*, 2015, 136(8): 1931–1939.

## **Book**

### *Book with one to three authors*

[5] Schneider Z., Whitehead D., Elliott D. Nursing and midwifery research: methods and appraisal for evidence-based practice. 3rd edn. 2009, Elsevier Australia, Marrickville, NSW.

### *Book with more than three authors*

[6] Davis M., Charles L., Curry M.J., et al. Challenging spatial norms. 2013, Routledge, London.

### *Chapter or Article in Book*

[7] Knowles M.S. Independent study. In Using learning contracts. 1986, Jossey-Bass, San Francisco, 89–96.

## **Others**

### *Proceedings of meetings and symposiums, conference papers*

[8] Chang S.S., Liaw L. and Ruppenhofer J. (eds). Proceedings of the twenty-fifth annual meeting of the Berkeley Linguistics Society, February 12–15, 1999: general session and parasession on loan word phenomena. 2000, Berkeley Linguistics Society, Berkeley.

### *Conference proceedings (from electronic database)*

[9] Bukowski R.M. Prognostic factors for survival in metastatic renal cell carcinoma: update 2008. Innovations and challenges in renal cancer: proceedings of the third Cambridge conference. Cancer, 2009, 115 (10): 2273, viewed 19 May 2009, Academic OneFile database.

### *Online Document with author names*

[10] Este J., Warren C., Connor L., et al. Life in the clickstream: the future of journalism, Media Entertainment and Arts Alliance, 2008. viewed 27 May 2009, [http://www.alliance.org.au/documents/foj\\_report\\_final.pdf](http://www.alliance.org.au/documents/foj_report_final.pdf)

### *Online Document without author name*

[11] Developing an argument n.d., viewed March 30 2009, [http://web.princeton.edu/sites/writing/Writing\\_Center/WCWritingResources.htm](http://web.princeton.edu/sites/writing/Writing_Center/WCWritingResources.htm)

### *Thesis/Dissertation*

[12] Gale L. The relationship between leadership and employee empowerment for successful total quality management. 2000, University of Western Sydney.

### *Standard*

[13] Standards Australia Online. Glass in buildings: selection and installation. AS 1288–2006. 2006, SAI Global database.

### *Government Report*

[14] National Commission of Audit. Report to the Commonwealth Government, Australian Government Publishing Service, 1996, Canberra.

*Government report (online)*

[15] Department of Health and Ageing. Ageing and aged care in Australia, 2008, viewed 10 November 2008, <http://www.health.gov.au/internet/main/publishing.nsf/Content/ageing>

*No author*

[16] Guide to agricultural meteorological practices. 2nd edn, Secretariat of the World Meteorological Organization, 2010, Geneva.

Note: When referencing an entry from a dictionary or an encyclopedia with no author there is no requirement to include the source in the reference list. In these cases, only cite the title and year of the source in-text. For an authored dictionary/encyclopedia, treat the source as an authored book.

### **Submission Preparation Checklist**

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
2. The submission file is in OpenOffice, Microsoft Word, RTF, or WordPerfect document file format.
3. Where available, URLs for the references have been provided.
4. The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
5. The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines, which is found in About the Journal.
6. If submitting to a peer-reviewed section of the journal, the instructions in Ensuring a Blind Review have been followed.



## Integrated Services Platform of International Scientific Cooperation

Innoscience Research (Malaysia), which is global market oriented, was founded in 2016. Innoscience Research focuses on services based on scientific research. By cooperating with universities and scientific institutes all over the world, it performs medical researches to benefit human beings and promotes the interdisciplinary and international exchanges among researchers.

Innoscience Research covers biology, chemistry, physics and many other disciplines. It mainly focuses on the improvement of human health. It aims to promote the cooperation, exploration and exchange among researchers from different countries. By establishing platforms, Innoscience integrates the demands from different fields to realize the combination of clinical research and basic research and to accelerate and deepen the international scientific cooperation.

### Cooperation Mode



Clinical Workers



In-service Doctors



Foreign Researchers



Hospital



University



Scientific institutions

# OUR JOURNALS



The *Journal of Architectural Research and Development* is an international peer-reviewed and open access journal which is devoted to establish a bridge between theory and practice in the fields of architectural and design research, urban planning and built environment research.

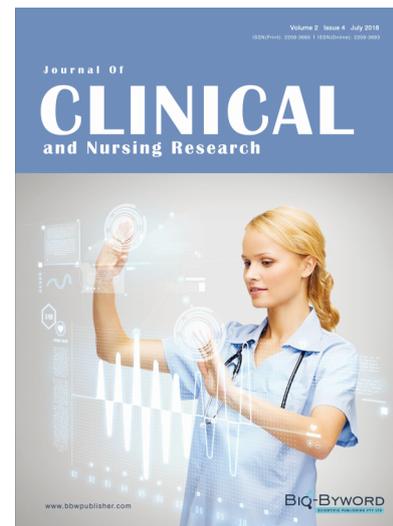
Topics covered but not limited to:

- Architectural design
- Architectural technology, including new technologies and energy saving technologies
- Architectural practice
- Urban planning
- Impacts of architecture on environment

*Journal of Clinical and Nursing Research (JCNR)* is an international, peer reviewed and open access journal that seeks to promote the development and exchange of knowledge which is directly relevant to all clinical and nursing research and practice. Articles which explore the meaning, prevention, treatment, outcome and impact of a high standard clinical and nursing practice and discipline are encouraged to be submitted as original article, review, case report, short communication and letters.

Topics covered by not limited to:

- Development of clinical and nursing research, evaluation, evidence-based practice and scientific enquiry
- Patients and family experiences of health care
- Clinical and nursing research to enhance patient safety and reduce harm to patients
- Ethics
- Clinical and Nursing history
- Medicine



*Journal of Electronic Research and Application* is an international, peer-reviewed and open access journal which publishes original articles, reviews, short communications, case studies and letters in the field of electronic research and application.

Topics covered but not limited to:

- Automation
- Circuit Analysis and Application
- Electric and Electronic Measurement Systems
- Electrical Engineering
- Electronic Materials
- Electronics and Communications Engineering
- Power Systems and Power Electronics
- Signal Processing
- Telecommunications Engineering
- Wireless and Mobile Communication

