

# World Journal of *Orthopedics*

*World J Orthop* 2010 November 18; 1(1): 1-30





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2010-2014

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*World J Orthop* 2010; 1(1): 10-19  
<http://www.wjgnet.com/2218-5836/full/v1/i1/10.htm>

**AIM AND SCOPE** *World Journal of Orthopedics* (*World J Orthop*, *WJO*, online ISSN 2218-5836, DOI: 10.5312) is a monthly peer-reviewed, online, open-access, journal supported by an editorial board consisting of 114 experts in orthopedics from 26 countries.  
The aim of *WJO* is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of orthopedics. *WJO* covers diagnostic imaging, arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthropathy, bone tumors and osteoporosis, minimally invasive therapy, traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of applied and basic research in fields related to orthopedics, such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

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**NAME OF JOURNAL**  
*World Journal of Orthopedics*

**LAUNCH DATE**  
November 18, 2010

**SPONSOR**  
Beijing Baishideng BioMed Scientific Co., Ltd.,  
Room 903, Building D, Ocean International Center,  
No. 62 Dongsihuan Zhonglu, Chaoyang District,  
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Baishideng Publishing Group Co., Limited,  
Room 1701, 17/F, Henan Building,  
No.90 Jaffe Road, Wanchai, Hong Kong, China  
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**ONLINE SUBSCRIPTION**  
One-Year Price 216.00 USD

**PUBLICATION DATE**  
November 18, 2010

**CSSN**  
ISSN 2218-5836 (online)

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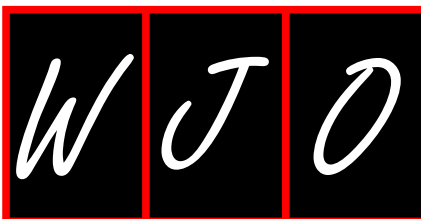
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## What is the purpose of launching *World Journal of Orthopedics*?

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Telephone: +86-10-59080036 Fax: +86-10-85381893

Received: October 14, 2010 Revised: November 5, 2010

Accepted: November 12, 2010

Published online: November 18, 2010

### Abstract

The first issue of *World Journal of Orthopedics (WJO)*, whose preparatory work was initiated on March 11, 2010, will be published on November 18, 2010. The *WJO* Editorial Board has now been established and consists of 114 distinguished experts from 26 countries. Our purpose of launching *WJO* is to publish peer-reviewed, high-quality articles *via* an open-access online publishing model, thereby acting as a platform for communication between peers and the wider public, and maximizing the benefits to editorial board members, authors and readers.

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**Key words:** Maximization of personal benefits; Editorial board members; Authors; Readers; Employees; *World Journal of Orthopedics*

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Ma LS. What is the purpose of launching *World Journal of Orthopedics*? *World J Orthop* 2010; 1(1): 1-2 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v1/i1/1.htm>  
DOI: <http://dx.doi.org/10.5312/wjo.v1.i1.1>

### INTRODUCTION

I am very pleased to announce that the first issue of *World Journal of Orthopedics (World J Orthop, WJO)*, online ISSN 2218-5836, DOI: 10.5312, whose preparatory work was initiated on March 11, 2010, will be published on November 18, 2010. The *WJO* Editorial Board has now been established and consists of 114 distinguished experts from 26 countries. What is the purpose of launching *WJO*? And what is the scope and how are the columns designed?

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. To realize these desired attributes of a journal and create a well-recognized journal, the following four types of personal benefits should be maximized.

### MAXIMIZATION OF PERSONAL BENEFITS

The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others.

#### **Maximization of the benefits of editorial board members**

The primary task of editorial board members is to give a peer review of an unpublished scientific article *via* online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that



field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution.

### **Maximization of the benefits of authors**

Since *WJO* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJO* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading.

### **Maximization of the benefits of readers**

Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion<sup>[1]</sup>.

### **Maximization of the benefits of employees**

It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal<sup>[2,3]</sup>. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

## **CONTENTS OF PEER REVIEW**

In order to guarantee the quality of articles published in the journal, *WJO* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the experiment is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

## **SCOPE**

The aim of *WJO* is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment,

rehabilitation and nursing in the field of orthopedics. *WJO* covers diagnostic imaging, arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthropathy, bone tumors and osteoporosis, minimally invasive therapy, traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of applied and basic research in fields related to orthopedics, such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

## **COLUMNS**

The columns in the issues of *WJO* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide Guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in orthopedics; (9) Brief Articles: To briefly report the novel and innovative findings in orthopedics; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJO*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of orthopedics; and (13) Guidelines: To introduce consensus and guidelines reached by international and national academic authorities worldwide on the research orthopedics.

## **REFERENCES**

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## Bone fragility in type 2 diabetes mellitus

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 Received: June 24, 2010 Revised: July 27, 2010

Accepted: August 4, 2010  
 Published online: November 18, 2010

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### Abstract

The number of patients with osteoporosis or type 2 diabetes mellitus (T2DM) is increasing in aging and westernized societies. Both disorders predispose elderly people to disabling conditions by causing fractures and vascular complications, respectively. It is well documented that bone metabolism and glucose/fat metabolism are etiologically related to each other through osteocalcin action and Wnt signaling. Bone fragility in T2DM, which is not reflected by bone mineral density (BMD), depends on bone quality deterioration rather than bone mass reduction. Thus, surrogate markers are needed to replace the insensitivity of BMD in assessing fracture risks of T2DM patients. Pentosidine, the endogenous secretory receptor for advanced glycation endproducts, and insulin-like growth factor-I seem to be such candidates, although further studies are required to clarify whether or not these markers could predict the occurrence of new fractures of T2DM patients in a prospective fashion.

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**Key words:** Osteoporosis; Type 2 diabetes mellitus; Fracture risk; Osteocalcin; Wnt signaling

**Peer reviewers:** Andrea Giusti, MD, Department of Gerontology and Musculoskeletal Sciences, Galliera Hospital, Via Montallegro 32a/5, Genova 16100, Italy; Vijay K Goel, PhD, Distinguished University Professor, Endowed Chair and McMaster-

### BONE METABOLISM AND GLUCOSE/FAT METABOLISM ARE ASSOCIATED WITH EACH OTHER THROUGH THE ACTION OF OSTEOCALCIN AND WNT SIGNALING

Although osteoporosis and type 2 diabetes mellitus (T2DM) are traditionally viewed as separate disease entities that increase in prevalence with aging, accumulating evidence indicates that there are similar pathophysiological mechanisms underlying them.

Osteocalcin (OC), one of the osteoblast-specific secreted proteins, has several hormonal features and is secreted in the general circulation from osteoblastic cells<sup>[1,2]</sup>. Recent animal studies have shown that uncarboxylated OC (ucOC) action is related to bone metabolism and glucose metabolism and fat mass<sup>[3,4]</sup>. Lee *et al*<sup>[3]</sup> have shown that OC functions as a hormone that improves glucose metabolism and reduces fat mass, because OC-deficient mice aggravate these processes. Moreover, Ferron *et al*<sup>[4]</sup> have shown that recombinant ucOC administration regulates gene expression in  $\beta$  cells and adipocytes (including adiponectin expression), and prevents the development of metabolic diseases, obesity, and T2DM in wild-type mice fed a high-fat diet. Several clinical studies including our own<sup>[5-8]</sup> have recently shown that serum OC level is associated with glucose and total adiponectin levels, fat mass, as well as atherosclerosis parameters in humans. We have recently shown that serum OC level is negatively correlated



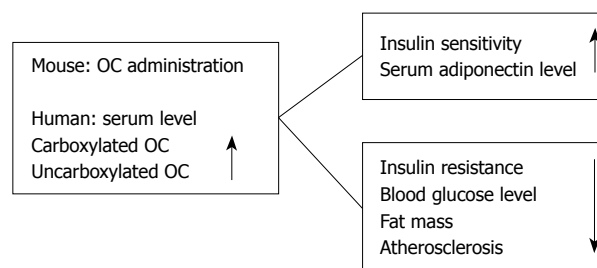
with plasma glucose level and atherosclerosis parameters in T2DM patients<sup>[5]</sup>. Kindblom *et al*<sup>[6]</sup> have shown that OC level is inversely related to plasma glucose level and fat mass in elderly non-DM persons. Fernández-Real *et al*<sup>[7]</sup> have shown that serum OC level is positively associated with insulin sensitivity in non-DM subjects. Pittas *et al*<sup>[8]</sup> have shown that serum OC concentration is inversely associated with fasting plasma glucose (FPG), fasting insulin, homeostasis model assessment for insulin resistance, high-sensitivity C-reactive protein, interleukin-6, body mass index (BMI), and body fat in cross-sectional analyses. They also have found that OC levels are associated with changes in FPG in prospective analyses. We also have found that ucOC is negatively associated with plasma glucose level and fat mass, and positively with adiponectin in T2DM patients<sup>[9]</sup>. These experimental and clinical findings suggest that bone metabolism and glucose/fat metabolism are etiologically related to each other through the action of ucOC or OC (Figure 1).

Wnt signaling is also thought to be a common pathogenetic feature of osteoporosis and DM. Mani *et al*<sup>[10]</sup> have shown that a single missense mutation in low-density lipoprotein receptor-related protein 6, the co-receptor for the Wnt-signaling pathway, is genetically linked to osteoporosis as well as DM, hyperlipidemia, and coronary artery disease. In addition, several studies have documented that T-cell-specific transcription factor (TCF)-4, the partner of  $\beta$ -catenin in the canonical Wnt-signaling pathway, is the strongest T2DM susceptibility gene<sup>[11-14]</sup>. Manolagas and other researchers have suggested that antagonism of Wnt signaling by oxidative stress diverts  $\beta$ -catenin from TCF to Forkhead box O (FoxO)-mediated transcription, and contributes to the development of osteoporosis as well as insulin resistance and hyperlipidemia<sup>[15-18]</sup>. Activation of FoxO by reactive oxygen species in early mesenchymal progenitors also leads to decreased osteoblastogenesis by diverting  $\beta$ -catenin away from Wnt signaling<sup>[19]</sup>, the mechanism of which might be implicated in DM-related bone fragility that is described in the following section.

## FRACTURE RISK IN T2DM IS NOT REFLECTED BY BONE MINERAL DENSITY

Many clinical studies have also investigated the association between DM and osteoporosis, given that these disorders affect a large proportion of the elderly population. Although bone mineral density (BMD) is considered as a gold standard for evaluating fracture risk in non-DM osteoporosis, accumulating evidence has shown that patients with T2DM have a high fracture rate in spite of the absence of BMD reduction. A recent meta-analysis has shown that T2DM patients have higher hip BMD than non-DM controls (z-score: 0.27), despite an increased risk of hip fracture (1.4-fold)<sup>[20]</sup>, which suggests that BMD values do not reflect bone fragility in T2DM. Another meta-analysis also has shown that hip fracture risk of T2DM patients was increased by 1.7-fold<sup>[21]</sup>.

In contrast, little is known about the risk of vertebral fracture (VF) and its association with BMD. We examined



**Figure 1** When osteocalcin was administered to obese mice, it increased insulin secretion, and decreased blood glucose level, fat mass, and triglyceride level. In humans, serum carboxylated and uncarboxylated osteocalcin levels were positively correlated with insulin sensitivity and adiponectin level, whereas they were negatively correlated with blood glucose level, fat mass, and atherosclerosis index. Thus, osteoporosis and diabetes are pathophysiologically related to each other through osteocalcin (OC) action in mice and humans.

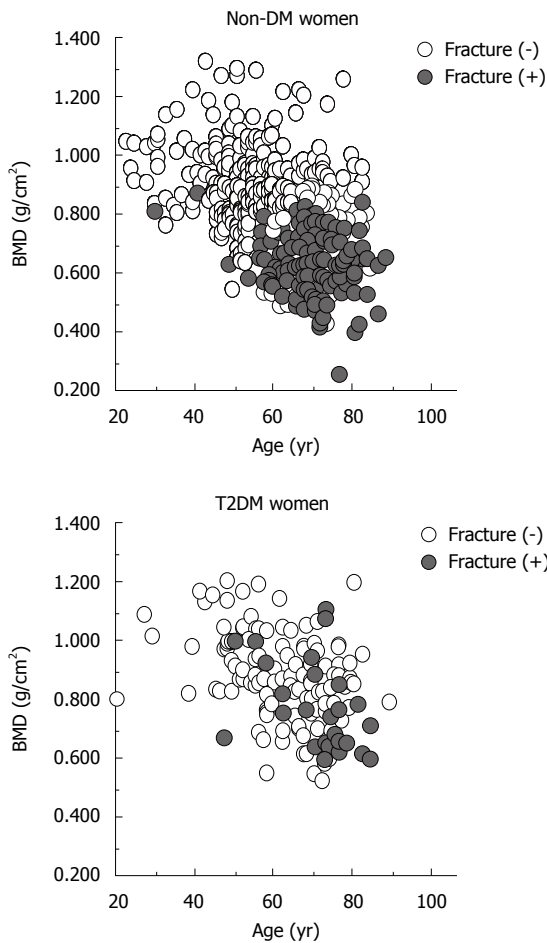
Japanese T2DM patients and non-DM controls about this issue<sup>[22,23]</sup>. We have found that the presence of T2DM is an independent risk factor for prevalent VFs in women (OR = 1.9) as well as men (OR = 4.7) after adjustment for age, BMI and lumbar BMD by logistic regression analysis. BMD at any site, however, is not significantly associated with the presence of prevalent VFs in T2DM patients, in contrast to the significant association in controls. Comparison of T2DM patients with and without VFs showed no significant differences in BMD values, bone markers, or diabetes status. Receiver operating characteristic analysis has shown that the absolute lumbar, femoral neck, and radial BMD values for detecting prevalent VFs were higher in T2DM patients than controls, whereas their sensitivity and specificity were lower. Figure 2 shows the distribution of lumbar BMD as a function of age in T2DM women. In the control subjects, those with VFs (black dots) were clearly grouped in the region with higher age and lower lumbar BMD. In contrast, T2DM subjects with VFs were scattered widely and there was no association with age or lumbar BMD. Thus, T2DM patients might have an increased risk of VFs independent of BMD or diabetic complication status, which suggests that bone quality, but not bone mass, define bone fragility and cause hip and vertebral fractures in T2DM.

## SURROGATE MARKERS FOR ASSESSING FRACTURE RISK IN T2DM

BMD is not sensitive enough to assess the risk of osteoporotic fractures in T2DM, therefore, the etiology of DM-related bone fragility and diagnostic markers other than BMD need to be explored.

### Pentosidine

Formation of advanced glycation end products (AGEs) results from sequential non-enzymatic chemical glycoxidation of protein amino groups<sup>[24]</sup>, collectively called the Maillard reaction. AGEs accumulate in various tissues including kidney, brain, and coronary artery atherosclerotic plaques during normal aging, whereas hyperglycemia re-



**Figure 2** Distribution of bone mineral density in subjects with and without vertebral fractures (black dots and open circles, respectively) as a function of age. BMD: Bone mineral density; T2DM: Type 2 diabetes mellitus.

sults in an accelerated rate of AGE formation, which suggests that AGEs have a pivotal role in the development of complications in DM patients<sup>[25,26]</sup>. In addition, previous studies have revealed that AGEs accumulate in bone tissue as well<sup>[27,28]</sup>, and that receptor for AGE (RAGE) is expressed in human bone-derived cells<sup>[29]</sup>, which suggests that AGEs are associated with DM-related bone fragility.

Several experimental studies have shown that AGEs have a negative impact on bone. AGEs inhibit the synthesis of type 1 collagen and OC, as well as mature bone nodule formation in osteoblasts<sup>[30-32]</sup>. We have previously demonstrated that the combination of high glucose and AGEs additionally or synergistically inhibits the mineralization of osteoblastic cells, through glucose-induced increase in expression of RAGE<sup>[33]</sup>. These findings suggest that AGE accumulation in bone causes osteoblastic dysfunction. AGEs are also known to increase osteoclast activity. Previous *in vitro* and *in vivo* experiments<sup>[34]</sup> have indicated that the number of resorption pits is increased when osteoclasts are cultured on AGE-modified dentin slices, and that AGE-bone particles are resorbed to a much greater extent than non-AGE bone particles when implanted subcutaneously in rats. In addition, RAGE knockout mice display a decreased number of osteoclasts as well as a significantly higher bone mass compared to

wild-type mice<sup>[35]</sup>. AGEs accumulation inhibits the differentiation and mineralization of osteoblasts, while it enhances the activity of osteoclasts, which possibly leads to uncoupling of bone turnover and resultant bone fragility.

AGE accumulation in bone is also negatively associated with material properties<sup>[27,28,36]</sup>. Collagen crosslinks are known to play crucial roles in the determination of bone strength<sup>[37]</sup>. AGE-type crosslinks, which are formed spontaneously by non-enzymatic glycation and oxidation reactions, are thought to be associated with brittleness of collagen fibers<sup>[38,39]</sup>, whereas physiological (enzymatic) crosslinks strengthen links of collagen fibers, and lead to the enhancement of bone strength<sup>[28,40]</sup>. Spontaneously diabetic WBN/Kob rats have been reported to display a decrease in enzymatic crosslinks and an increase in AGE-type crosslinks despite the lack of BMD reduction, which results in deterioration of bone strength<sup>[41]</sup>.

Among the few AGEs characterized to date, pentosidine is one of the well-known AGEs and is chemically well defined<sup>[42-44]</sup>. Because the formation of pentosidine requires both glycation and oxidation, serum pentosidine levels are considered to be a useful marker for glycoxidation. Several studies have revealed that pentosidine content in cortical or trabecular bone from vertebra or femur is negatively associated with mechanical properties<sup>[27,28,36]</sup>, and that pentosidine content of cortical and trabecular bone derived from patients with femoral neck fracture is higher than that of age-matched controls<sup>[45,46]</sup>. However, assessment of pentosidine content in bone is not easily done in clinical situations, because invasive procedures like bone biopsy are necessary for preparing specimens. A recent study has revealed that content of pentosidine in plasma shows a significant linear correlation with that in cortical bone<sup>[47]</sup>, which suggests that serum pentosidine level could be used as a surrogate marker for its content in bone and could evaluate bone strength. We have previously shown that serum pentosidine levels are associated with prevalent VFs in postmenopausal women with T2DM (OR = 2.50 per SD increase, Table 1)<sup>[48]</sup>. This association is independent of BMD, which suggests that it might reflect bone quality rather than BMD. In addition, an observational cohort study has shown that urine pentosidine levels are associated with increased clinical fracture incidence in those with DM (relative hazard 1.42 per SD increase in log pentosidine)<sup>[49]</sup>. Therefore, serum and urine pentosidine levels might be useful for assessing fracture risk in T2DM women, for which BMD or traditional bone markers are insensitive.

### Endogenous secretory RAGE

RAGE belongs to the immunoglobulin superfamily of cell-surface receptors and is capable of interacting with multiple ligands, including AGEs<sup>[50]</sup>. When transgenic mice that overexpressed human RAGE in vascular cells were crossbred with a transgenic line that developed insulin-dependent DM shortly after birth, more progressive histological changes of DM nephropathy were observed compared to controls<sup>[51]</sup>, which confirms that RAGE is associated with the development of DM complications. Endogenous secretory RAGE (esRAGE) is a splice variant

**Table 1 Odds ratio of surrogate markers for the presence of prevalent vertebral fractures**

	Presence of vertebral fractures	
	OR (95% CI)	P
Pentosidine (male)	0.79 (0.41-1.52)	0.47
Pentosidine (female)	2.50 (1.09-5.73)	0.03
esRAGE (male)	0.46 (0.25-0.84)	0.012
esRAGE (female)	0.32 (0.16-0.67)	0.002
IGF-I (female)	0.44 (0.23-0.81)	0.009

Multivariate logistic regression analysis was performed with the presence of vertebral fractures as a dependent variable and each of levels of serum insulin-like growth factor (IGF)-I, C-peptide, osteocalcin, and uNTX adjusted for age, duration of diabetes, body weight, height, creatinine, albumin, and HbA1c as independent variables. esRAGE: Endogenous secretory receptor for advanced glycation end product; OR: Odds ratio; CI: Confidence interval.

of one of the naturally occurring secretory forms, and is known to carry all of the extracellular domains but lacks the transmembrane and cytoplasmic domains<sup>[52]</sup>. esRAGE in the extracellular space is thought to act as a decoy receptor that binds AGEs and reduces the activity of intercellular signal pathways *via* RAGE<sup>[52]</sup>. Indeed, administration of a genetically engineered murine soluble RAGE suppresses the development of diabetic atherosclerosis in a dose-dependent manner in streptozotocin-induced apoE-null DM mice<sup>[53]</sup>. These experimental findings suggest that enhanced RAGE activity is clinically linked to reduced bone strength in DM patients. Given the neutralizing nature of esRAGE, it is possible that the ratio of serum esRAGE to AGE levels could be linked to clinical bone problems, such as fractures, more prominently than either parameter alone.

We have found that the esRAGE/pentosidine ratio in T2DM patients with VFs is significantly lower than in those without VFs. Multivariate logistic regression analysis adjusted for age, height, weight, hemoglobin A<sub>1c</sub>, serum creatinine, DM duration, therapeutic agents, DM complications, osteoporotic risk factors, and lumbar BMD identified the serum esRAGE level and esRAGE/pentosidine ratio as factors associated with the presence of VFs, independent of BMD in men (OR = 0.46 and 0.34, respectively) and in women (OR = 0.32 and 0.14, respectively) (Table 1)<sup>[54]</sup>. These results show that serum esRAGE level and esRAGE/pentosidine ratio are more useful than BMD for assessing the risk of VFs in T2DM patients.

### Insulin-like growth factor-I

Bone remodeling is regulated by systemic hormones and locally produced factors, which both act in concert to maintain bone mass<sup>[55-57]</sup>. Insulin-like growth factors (IGFs) are synthesized in osteoblasts and are among the most important regulators of bone cell function due to their anabolic effects on the skeleton<sup>[58]</sup>. The key role of the IGF system in the local regulation of bone formation is demonstrated by the finding that about 50% of basal bone cell proliferation can be blocked by inhibiting the actions of IGFs that are endogenously produced by bone cells in serum-free culture<sup>[59]</sup>. In osteoblast-specific knock-

out mice for IGF-I receptor, a significant reduction in trabecular bone mass and deficient mineralization have been observed<sup>[60]</sup>. In contrast, circulating IGF-I, which is mainly produced in the liver *via* regulation by growth hormone and diet, acts in an endocrine manner, which also activates bone remodeling and exerts anabolic effects on bone tissues<sup>[61-63]</sup>. Liver-specific IGF-I gene null mice show a marked reduction in bone volume, periosteal circumference, and medial lateral width, which suggests that circulating levels of IGF-I also directly regulate bone growth and density<sup>[64]</sup>. Indeed, our clinical studies have shown that serum IGF-I levels are positively associated with BMD and inversely with the risk of VFs in postmenopausal non-DM women<sup>[65,66]</sup>. These findings suggest that serum IGF-I levels could be clinically useful for assessing bone mass and the risk of VFs in the non-DM population.

IGFs are also thought to be linked to the pathogenesis of DM-related complications<sup>[67]</sup>. Impaired production of IGFs could also cause bone complication in DM by diminishing bone cell function<sup>[58]</sup>. An *in vivo* study has demonstrated that IGF-I levels in serum and cortical bone are significantly reduced in spontaneously diabetic Goto-Kakizaki rats, which display a significant decrease in BMD in the long bone metaphyses and vertebrae<sup>[68]</sup>. In contrast, several *in vitro* studies have shown that the stimulatory actions of IGF-I on osteoblasts are blunted by high glucose concentrations or AGEs. High glucose concentrations significantly impair the proliferative and functional responses of osteoblastic MG-63 cells to IGF-I<sup>[69]</sup>. AGEs also significantly decrease IGF-I secretion in osteoblastic MC3T3-E1 cells<sup>[70]</sup>. Thus, high glucose concentrations or AGEs might cause resistance of osteoblasts to IGF-I actions in the local environment.

In T2DM patients, however, the relationship between serum IGF-I levels and bone metabolism has been little documented. We have indicated that serum IGF-I levels are significantly and inversely associated with the presence of VFs in postmenopausal T2DM women (OR = 0.44 per SD increase) in a fashion independent of age, body stature, DM status, renal function, insulin secretion, or lumbar BMD (Table 1)<sup>[71]</sup>. Accordingly, circulating IGF-I might have a protective effect on VFs, and this effect might be related to bone quality but not to BMD in postmenopausal T2DM women. Thus, serum IGF-I levels as well as esRAGE and pentosidine might be useful for assessing the risk of VFs in T2DM women.

## FRACTURE RISK ASSESSMENT OF T2DM PATIENTS IN CLINICAL PRACTICE

As a result of the ineffectiveness of BMD in assessing fracture risks in T2DM, the major clinical problems are how to assess the risks and when to start therapy for preventing fractures in daily practice. Although the above-mentioned markers are potential candidates for such purposes, it is unclear whether or not they could predict the occurrence of new fractures in T2DM patients in a prospective fashion.



In contrast, the presence of prevalent VFs could be used for the assessment of bone quality in individual patients, because a large study on the incidence of VFs in postmenopausal osteoporosis has shown that patients with previous VFs were more likely to suffer from new VFs<sup>[72,73]</sup> and hip fractures<sup>[72]</sup> independent of BMD, than those without VFs, during a study period of several years. A patient history of non-VFs is also an established risk factor for additional fractures<sup>[74]</sup>. We found that 38% of T2DM men and 31% of T2DM women had prevalent VFs by X-ray films, and that 16% each of T2DM men and women had a history of previous non-VFs<sup>[23]</sup>. Thus, if T2DM patients undergo spinal X-ray examination or are questioned about their fracture histories, it is likely that about half of them will be identified as those who have bone fragility and need osteoporosis treatment for fracture prevention. These procedures are simple and are recommended for all physicians who are engaged in T2DM treatment.

Recently, the fracture risk assessment (FRAX) algorithm has been developed by the WHO, which could assess the fracture risk of an individual even if BMD is not measured<sup>[74,75]</sup>. This algorithm integrates the influence of several well-validated risk factors for fractures that are independent of BMD, therefore, it might be useful for the case-finding strategy that identifies diabetic patients at high risk for fracture.

## CONCLUSION

The fact that BMD is not useful for assessing fracture risks in T2DM seems problematic, because T2DM populations are increasing in every country. T2DM patients may drop out from fracture prevention if doctors diagnose osteoporosis based on BMD values alone. Practitioners should be aware of the importance of detecting pre-existing VFs and fracture histories by spinal X-ray examination and interview, respectively. These procedures could broaden the spectrum of osteoporosis treatments into the T2DM population. Simultaneously, further studies are needed to clarify whether surrogate biochemical markers such as pentosidine, esRAGE, and IGF-I, as well as the WHO FRAX algorithm, could be useful for predicting prospectively the occurrence of new fractures in T2DM patients, with sensitivity and specificity comparable to those of BMD in non-DM osteoporosis.

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Stanislaw Peter Stawicki, MD, Series Editor

## Portable ultrasonography in mass casualty incidents: The CAVEAT examination

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**Author contributions:** Stawicki SP, Pryor JP and Dean AJ designed original concept; Stawicki SP, Howard JM and Dean AJ contributed to the literature background search; Stawicki SP, Howard JM, Pryor JP, Bahner DP, Whitmill ML and Dean AJ wrote the manuscript; Stawicki SP, Pryor JP, Bahner DP, Whitmill ML and Dean AJ made critical manuscript review; Stawicki SP, Dean AJ, Whitmill ML and Howard JM contributed to figures and tables; Stawicki SP, Bahner DP, Whitmill ML and Dean AJ contributed to sonographic images; and Stawicki SP, Bahner DP, Dean AJ and Whitmill ML contributed to technique descriptions.

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Received: August 10, 2010 Revised: October 21, 2010

Accepted: October 28, 2010

Published online: November 18, 2010

weight, robust, user-friendly, and low-cost portable ultrasound equipment is particularly suited for use in the physically and temporally challenging environment of a multiple casualty incident (MCI). Currently established ultrasound applications used to identify potentially lethal thoracic or abdominal conditions offer a base upon which rapid, focused protocols using hand-carried emergency ultrasonography could be developed. Following a detailed review of the current use of portable ultrasonography in military and civilian MCI settings, we propose a protocol for sonographic evaluation of the chest, abdomen, vena cava, and extremities for acute triage. The protocol is two-tiered, based on the urgency and technical difficulty of the sonographic examination. In addition to utilization of well-established bedside abdominal and thoracic sonography applications, this protocol incorporates extremity assessment for long-bone fractures. Studies of the proposed protocol will need to be conducted to determine its utility in simulated and actual MCI settings.

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**Key words:** Focused Assessment with Sonography in Trauma; Chest, abdomen, vena cava, and extremities for acute triage; Ultrasonography; Disaster; Field triage; Pre-hospital care; Mass casualty incident

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### Abstract

Ultrasonography used by practicing clinicians has been shown to be of utility in the evaluation of time-sensitive and critical illnesses in a range of environments, including pre-hospital triage, emergency department, and critical care settings. The increasing availability of light-

Stawicki SP, Howard JM, Pryor JP, Bahner DP, Whitmill ML, Dean AJ. Portable ultrasonography in mass casualty incidents: The CAVEAT examination. *World J Orthop* 2010; 1(1): 10-19 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v1/i1/10.htm> DOI: <http://dx.doi.org/10.5312/wjo.v1.i1.10>

## INTRODUCTION

Bedside ultrasonography performed by practicing clinicians has gained widespread acceptance over the past two decades<sup>[1]</sup>. Its use has been described as an adjunct in a wide variety of commonly encountered clinical settings<sup>[2-8]</sup>. In fact, the use of ultrasonography has been described at almost every tier of emergency and critical care management from field evaluation and triage, to transport, emergency departments, surgical suites, and critical care units<sup>[9-18]</sup>. Ultrasound has also been shown to be of utility to providers with differing levels of training, background, and clinical focus<sup>[19-26]</sup>. One of the areas in which its use has been most extensively investigated is Traumatology<sup>[27,28]</sup>. The Focused Assessment with Sonography in Trauma (FAST) examination has become the standard of care for the diagnosis of post-traumatic pericardial tamponade and intraperitoneal bleeding, which essentially eliminates diagnostic peritoneal lavage from most trauma care protocols<sup>[29]</sup>. More recently described applications allow emergency personnel to use ultrasound in the diagnosis of chest and extremity trauma, as well as in the evaluation of shock states, particularly intravascular volume depletion<sup>[4,30-34]</sup>.

Mass casualty incidents (MCIs) are unique clinical situations that call for quick and reliable triage of large numbers of injured patients, usually in a setting of severely limited resources<sup>[35]</sup>. A rapidly deployable, flexible, resource-sparing emergency medical response might be the key element to improve the chance for survival of victims during MCIs<sup>[6,36-39]</sup>. In MCIs, the ability to identify injured patients who could benefit from early intervention is often undermined by the relative lack of healthcare personnel, a chaotic environment, and the lack of a stable social infrastructure (structural integrity, shelter from the elements, sanitation, electricity, skilled technical personnel)<sup>[6,7]</sup>. This severely limits the availability of most modern diagnostic tools, especially imaging modalities, because they are resource intensive, and require a high degree of infrastructural integrity<sup>[35]</sup>. Thus, in an MCI, responders could be forced to rely solely on traditional clinical evaluation based mainly upon the history and physical examination - a relatively time-consuming and often inaccurate approach in this setting<sup>[40-43]</sup>.

Technological advances have made modern ultrasound equipment increasingly portable, robust, easy to use, and inexpensive<sup>[44,45]</sup>. These advances allow ultrasound to be brought to the patient to obtain diagnostic information in real time<sup>[4,46-48]</sup>. Clinician-performed ultrasonography obviates the need for specially trained technicians to obtain images, facilities to process and store them, and for specialist physicians to interpret them<sup>[4,5,47]</sup>. There is extensive literature that describes the use of ultrasound by clinicians with diverse backgrounds and training who are managing a variety of diseases at all levels of the healthcare system<sup>[5,44,49,50]</sup>. In addition, a number of reports have described its use in remote, austere, and resource-poor settings, including outer space, high altitudes, areas of extreme poverty, and combat set-

tings<sup>[10,21,51-54]</sup>. These qualities of ultrasonography make it uniquely suited for deployment in the care of patients in the setting of a MCI.

In this review, we discuss current uses of ultrasound in disaster and MCI settings. We then present the concept of a comprehensive sonographic examination in the evaluation of chest, abdomen, vena cava, and extremities in acute triage (CAVEAT). We conclude with a description of the proposed CAVEAT protocol for the use of ultrasound in civilian and combat disaster casualty triage.

## PORTABLE ULTRASONOGRAPHIC TECHNOLOGY

As noted previously, technological advances have increased the clinical utility of ultrasound in a variety of ways. Among these advances is miniaturization<sup>[9,55]</sup>. Many battery-powered devices with excellent imaging quality and Doppler capabilities weigh less than 5 kg. Several have been designed to meet stringent military specifications for durability. Some models that weigh as little as 500 g have appeared on the market<sup>[9,55]</sup>. The use of digital hand-held sonographic units allows for early performance of FAST and extended-FAST (E-FAST, incorporating thoracic windows for the assessment of pneumothorax) examinations and can accurately and safely improve the traditional clinical evaluation<sup>[56-58]</sup>. Portable ultrasound has also been found to be of benefit during ground/aeromedical trauma transport, as well as in forward deployed medical/surgical teams and combat support where it has been reported to be a useful adjunct in the field triage of injured soldiers<sup>[9,10,18,59,60]</sup>.

In MCIs caused by a natural disaster, the deployment of portable ultrasound with its ability to identify life-threatening injuries in the field or in pre-designated staging areas could help to increase triage accuracy, and enhance the efficiency of scarce personnel utilization, patient transport, and directing medical resources to patients who stand to most benefit from these resources<sup>[6,17]</sup>.

Recent technological advances in teleultrasonography could probably extend the usefulness of ultrasonography in MCIs. Recent studies have shown how portable ultrasound images can be safely transmitted for remote viewing by experts<sup>[20,21,51,61-63]</sup>. With this technology, it might be possible for mobile triage units equipped with portable ultrasound equipment, basic medical supplies, and limited medical training to be deployed to a remote MCI site, to obtain sonographic images for transmission to experts who could interpret them and make decisions about triage, *in situ* treatment, and/or evacuation. Commercial satellite<sup>[33]</sup> and low-bandwidth internet links<sup>[64]</sup> have been used to transmit ultrasound images for real-time interpretation, and have also been transmitted from the International Space Station to Earth for interpretation at the Mission Control Center<sup>[21]</sup>.

## DISASTER TRIAGE

Disasters that result in large numbers of deaths and injuries

**Table 1** Classification of multiple casualty incidents

Natural disasters	Man-made disasters
<b>Causes of large scale physical destruction to manmade objects and infrastructure</b>	Hazardous material incidents and Industrial accidents
<b>Earthquakes</b>	Radiation exposure
<b>Volcanoes</b>	Chemical exposure
<b>Mudslides</b>	Inhalation injury
<b>Avalanches</b>	<b>Explosive disasters</b>
<b>Floods</b>	<b>Transportation accidents</b>
<b>Tsunami</b>	<b>Aircraft</b>
<b>Tropical storms, hurricanes, tornadoes</b>	<b>Marine</b>
Climatic	<b>Railroad</b>
Extreme heat, cold	<b>Highway</b>
Famine	<b>War related</b>
Fire related	<b>Military casualties</b>
Thermal injury	<b>Civilian casualties</b>
Inhalation injury	<b>Innocent bystanders</b>
Infrastructure, agriculture, and domiciliary damage	<b>Military targets</b>
	<b>Terrorism</b>
	<b>Mass casualty</b>
Epidemics	Bioterrorism
	Genocide
	Major societal dislocations and refugee populations
	Malnutrition, epidemics

Disasters that cause gross physical damage (most likely to cause injuries identifiable by ultrasound) are in bold: There can be a certain degree of overlap between the two categories ("gross physical trauma" and "no gross physical trauma"). Detailed history of the incident should be gathered to determine whether "physical trauma" is present alone, in combination with other factors, or not at all.

can be categorized in several ways (Table 1). Ultrasound images provide diagnostic information about anatomical structures, therefore, their utility is primarily in MCI settings with gross physical trauma. However, ultrasound is also of utility in diagnosis and management of secondary conditions such as volume depletion or visceral changes caused by sequelae of some types of MCI (e.g. pleural effusion, pulmonary consolidation, or ascites)<sup>[4,5,46,63]</sup>.

By definition, an MCI is an event in which two or more patients are injured and present with a severity of illness that exceeds the resources of the treatment facility<sup>[22,66,67]</sup>. This categorization depends solely on an imbalance between patient needs and available resources. Thus, by this definition, the terrorist attack on the World Trade Center in 2001 was not an MCI, because the rescue and hospital resources exceeded the numbers of injured survivors<sup>[23]</sup>. Triage and medical care during MCIs require a significant deviation from customary medical prioritization in which the goal for each patient is definitive care, with delivery prioritized by severity of illness<sup>[6,66,67]</sup>. During MCIs, the available medical resources are allocated with the goal of salvaging the greatest number of victims, with the understanding that this will result in the loss of some patients with extreme, complex, and/or resource-intensive injuries<sup>[38-40,66]</sup>. In such situations, critically ill patients receive lower priority than those with less severe, but more easily treated injuries.

Current disaster triage schemes rely on information obtained by history (medical and mechanistic) and the physical examination to make triage decisions<sup>[68,69]</sup>. The most commonly used MCI triage classification in the United States involves assignment of patients to one of the four color-coded categories based on his or her vital signs and ability to breathe, talk, and walk (Table 2)<sup>[68]</sup>. Red category indicates patients who require immediate medical attention and can probably be stabilized and survive with immediate limited interventions. Yellow designation pertains to patients who require medical attention within 1 h. Green indicates patients who are deemed medically non-urgent. Patients who are placed into the black (expectant or dead) category are treated last<sup>[41,42,71]</sup>.

The benefit of such disaster triage classifications is that they can be easily and rapidly applied in adverse circumstances. However, because they are based on somewhat crude clinical parameters, it is likely that they could result in inappropriate triage. Over-triage can be defined as allocation of medical resources for a patient who is eventually found to be without significant injuries<sup>[72,73]</sup>. Under-triage occurs when a patient does not receive medical resources for injuries that without treatment will lead to deterioration of his or her condition<sup>[73]</sup>. Both over- and under-triage are difficult to study scientifically in the MCI setting because detailed data and outcomes are difficult to obtain and/or record. One report has identified an over- and under-triage rate of 12% and 4% for trauma patients transported to a major trauma center<sup>[74]</sup>. In a recent simulation study of FAST ultrasound used as an adjunct to triage using the START (simple triage and rapid treatment) mass casualty system, it was estimated that secondary triage using ultrasound technology might have identified nearly 7% of patients with evidence of delayed hemoperitoneum<sup>[37]</sup>. Any rapidly and easily deployable tool that could be used to increase the accuracy of triage decisions probably could, for a priori reasons, enhance patient care in the MCI setting.

## CIVILIAN DISASTER EXPERIENCE

Despite numerous recent natural MCIs, there is scant literature to describe the specific role of ultrasonography during the medical response to these events<sup>[17,36,38]</sup>. This might be due to the inherent difficulties of studying any aspect of medical care in the MCI setting, or due to the relative novelty of both clinician-performed ultrasonography and of portable ultrasound equipment<sup>[17,18,58]</sup>. In one study, ultrasound was performed by relief teams after the 1988 Armenian earthquake as a primary screening procedure in 400 of 750 injured MCI patients admitted to a large hospital within 72 h of the event<sup>[17]</sup>. The average time spent on evaluation of a single patient was approximately 4 min. Traumatic injuries of the abdomen were detected in 12.8% of the patients, with few false-negative (1%) and no false-positive examinations<sup>[17]</sup>. In another study, ultrasonography was used after an MCI in Guatemala in which the dead far outnumbered the injured. In that setting, ultrasound was useful for excluding internal trauma, and the

Table 2 Commonly accepted triage coding categories

Priority	Need for treatment	Color code	Characteristics
1	Immediate	Red	Life-threatening shock or hypoxia is present or imminent, but the patient can be likely stabilized and will probably survive if given immediate care
2	Urgent	Yellow	Injuries have systemic effects or implications, but the patient is not yet in life-threatening shock or hypoxia. Despite the chance that systemic decline may ensue, this group can likely withstand a 45- to 60-min wait without immediate risk. Patient likely to survive if given appropriate care
3	Non-urgent	Green	Localized injuries without immediate systemic implications. With minimal care, these patients are unlikely to deteriorate for several h (or not at all)
4	Expectant	Black	Most severely injured patients who have poor chance for survival regardless of care rendered. No distinction is made between clinical and biological death. In multiple casualty incidents, any patient who is unresponsive or who has no spontaneous ventilation or circulation is classified as dead

Modified from<sup>[70]</sup>.

preponderance of conditions identified were concurrent problems that were not directly caused by the physical trauma of the natural disaster (e.g. pregnancy and non-traumatic causes of abdominal pain)<sup>[75]</sup>. The current consensus seems to support sonographic screening of mass casualties as a quick and effective means for detection of internal evidence of truncal injuries<sup>[17,36,38,75]</sup>.

## MILITARY EXPERIENCE

Ultrasound has been utilized in military deployments in Kosovo, Afghanistan and Iraq<sup>[59,60,76]</sup>. The British Air Assault Surgical Groups deployed to Kuwait during 2003 included the use of a hand-held ultrasound scanner by the forward medical units<sup>[76]</sup>. FAST examinations performed by trained emergency physicians using portable equipment at a large military combat hospital in Iraq had very high sensitivity (100%), specificity (99%), and negative predictive value (100%), as confirmed by subsequent operative reports and computed tomography (CT) imaging<sup>[60]</sup>. In that particular experience, ultrasonography was performed in patients who sustained blunt, blast, and penetrating trauma<sup>[60]</sup>.

In a review of the United States Army Forward Surgical Team experience, one of the benefits of FAST was in its ability to identify occult blood loss in young, highly conditioned patients whose physiological reserve undermined the reliability of vital signs until late stages of shock<sup>[10]</sup>. A recent report from the Madigan Army Medical Center in Tacoma (WA, USA) highlights the prospects of utilization of ultrasonography in austere and remote environments for detection and triage of patients with pneumothoraces<sup>[50]</sup>. The advantages of telesonography are likely to be particularly useful in combat environments, and its use in military settings is under ongoing investigation<sup>[20,50,64,77]</sup>.

## PRE-HOSPITAL EXPERIENCE

Effective pre-hospital use of sonography in triage relies on pre-hospital personnel trained in basic ultrasound techniques. Several studies have suggested that non-physicians are able to perform the FAST examination reliably<sup>[9,21,49,78]</sup>. In one, flight nurses, technologists, emergency physicians and emergency medicine residents were assessed

for their ability to evaluate real and simulated patients with the FAST examination under different aeromedical conditions<sup>[78]</sup>. No significant obstacles in accomplishing sonographic examinations were noted, and the pilots did not report any adverse effect of in-flight sonography on flight safety. Conversely, several studies have suggested that, in 16%-34% of cases during aeromedical transport, significant impediments to ultrasonography could exist due to technological, environmental, or operator problems<sup>[9,49,79,80]</sup>. In experimental weightlessness simulated *via* parabolic-flight patterns, 80% of images obtained by in-flight sonographers were considered determinate<sup>[79]</sup>. Similarly, FAST examinations that have been successfully performed by non-physician crew members of the International Space Station under the direction of a ground-based sonographer, suggest that appropriately trained non-physicians could perform guided sonography in remote locations<sup>[21]</sup>.

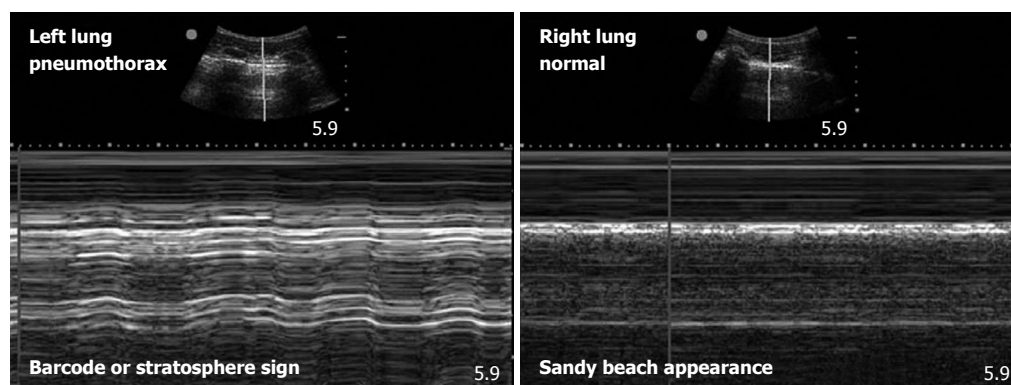
## COMPONENTS OF THE CAVEAT EXAMINATION

In view of the extensive literature that describes the utility of ultrasonography in a variety of austere, remote, and MCI situations, we propose a protocol for the evaluation of the CAVEAT in such settings. The sonographic assessments of each of the four anatomical regions are presented individually, and then an integrated algorithm is suggested.

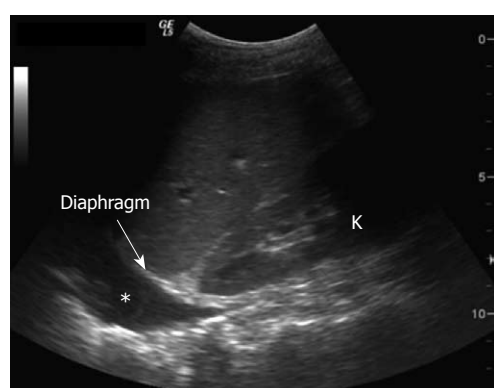
### Chest

Ultrasonographic imaging of the chest allows for the identification of many of the most time-critical internal injuries associated with blunt truncal trauma, including pericardial tamponade, massive hemothorax, pneumothorax, and tension pneumothorax<sup>[34,50,81]</sup>. Its accuracy in the diagnosis of these conditions might exceed that of plain-film roentgenography, which is not usually available in MCI settings<sup>[34,50]</sup>. Timely chest sonography probably allows for more rapid triage and performance of life-saving procedures including tube thoracostomy, pericardiocentesis, evacuation, and/or operative intervention for chest injuries<sup>[31,82]</sup>. In addition to the traditional FAST and E-FAST studies,





**Figure 1 Pneumothorax on bedside ultrasonography.** These two images utilize M-mode echography to gather more information on the pleural interfaces seen as a hyperechoic line in the B-mode images above. The M-mode tracings below represent a single line of sight through the B-mode images. Over time, the gray-scale appearance of M-mode images changes with the movement of the tissue. In normal lungs the pleurae slide across each other and this movement takes on a “granular” or “sandy beach” appearance (image on the right). As a result of the lack of pleural sliding in the presence of pneumothorax, a pattern of horizontal striations that do not demonstrate the granular appearance of movement is present. This M-mode pattern that is characteristic of pneumothorax has been described as a “barcode” or the “stratosphere” sign (image on the left).



**Figure 2 Hemothorax on bedside ultrasonography.** Hemothorax can be seen as hypoechoic area (asterisk) above the liver. Of note, movement of the lung within the pleural fluid can often be appreciated during the progression of the respiratory cycle. The kidney (K) and the diaphragm (arrow) can be easily seen, with the wedge of the liver located above.

portable ultrasound technology has also been successfully utilized in diagnosis of traumatic hemothorax<sup>[81,83]</sup>. In a study of 61 patients with thoracic trauma, the sensitivity of ultrasound examination in detection of hemothorax was 92%, with specificity of 100%<sup>[83]</sup>. Others have reported successful sonographic visualization of hemothorax, even in the absence of any clinical or roentgenographic findings<sup>[84]</sup>. Sonographic examples of pneumothorax and hemothorax can be found in Figures 1 and 2, respectively.

## Abdomen

The FAST examination is based on the assumption that the majority of clinically significant abdominal injuries result in hemoperitoneum. The standard FAST protocol is directed to detection of fluid in the pericardial and peritoneal spaces. With regard to the CAVEAT protocol, the current section is limited to the discussion of intraperitoneal hemorrhage. Although frequently described in terms of four “windows”, the FAST is more accurately conceptualized as the interrogation of the potential spaces where abnormal fluid collections tend to accumulate in a supine

patient. Excluding the three spaces in the chest (bilateral pleural spaces and the pericardium), there are a total of seven potential spaces in the peritoneum. The three in the right upper quadrant (from superior to inferior) are the subphrenic, the hepatorenal, and the space around the inferior pole of the kidney (continuous with the hepatorenal space). In the left upper quadrant, the three analogous spaces are: the subphrenic, the splenorenal, and the space around the inferior pole of the kidney (continuous with the splenorenal space). The seventh potential space is in the pelvis (rectouterine in the female; rectovesicular in the male).

The sonographic threshold for detection of hemoperitoneum is subject to dispute. Some studies have shown that as little as 30–70 mL of blood can be detected ultrasonographically<sup>[85–87]</sup>. Other studies have suggested that a small anechoic stripe in the Morison’s pouch represents approximately 250 mL of fluid, while 0.5 and 1 cm stripes represent approximately 500 mL and 1 L of free fluid, respectively<sup>[85]</sup>. McKenney *et al*<sup>[88]</sup> have proposed a clinically practical hemoperitoneum score that helps predict the need for abdominal surgical intervention, and appears to be a better predictor of a “positive” laparotomy than initial blood pressure and/or base deficit. To increase the diagnostic yield of FAST, the examination can be performed serially, which allows for reassessment of patients with unanticipated changes of condition, or those who are being managed non-operatively<sup>[89–91]</sup>.

Reported sensitivities for ultrasound in detecting the hemoperitoneum vary, with ranges of 42%–99%<sup>[91–95]</sup>. On a cautionary note, one study has found that 29% of patients with confirmed abdominal injury had no reported hemoperitoneum on FAST or CT scanning<sup>[93]</sup>. In another study, 27% of patients with negative FAST required laparotomy for intra-abdominal injuries<sup>[95]</sup>. Thus, the reliance of hemoperitoneum as the sole indicator of abdominal visceral injury limits the utility of FAST as a diagnostic screening tool in hemodynamically stable patients with blunt abdominal trauma<sup>[93,95]</sup>. To identify subsets of patients who would most benefit from the FAST examina-

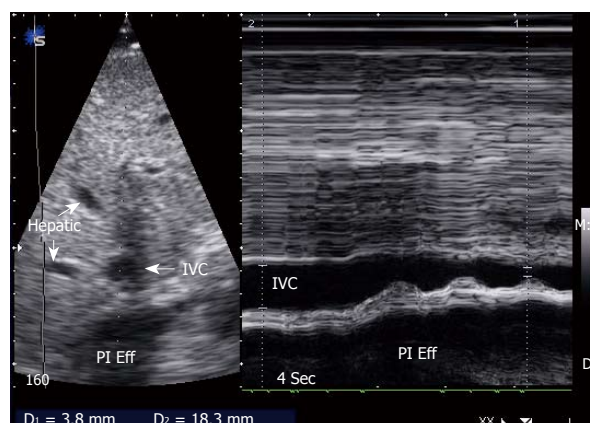
tion, Rozycki *et al.*<sup>[92]</sup> have found that ultrasound was most sensitive and specific in patients with penetrating chest wounds or in hypotensive blunt abdominal trauma patients (sensitivity and specificity nearly 100%).

Although CT imaging is optimal for stable patients with potential internal injury after trauma, this resource is rarely available in the MCI setting. In such situations, stable patients with a negative FAST examination should receive ongoing observation, serial abdominal examinations, and repeat FAST examination, tailored to available resources. Injuries that are commonly associated with false-negative FAST include retroperitoneal hemorrhage and hollow viscus perforation<sup>[96]</sup>. Few false-negative results have been reported with significant intraperitoneal bleeding<sup>[93,95,97]</sup>. Diagnostic options available in this situation include repeat FAST, diagnostic peritoneal lavage, laparoscopy, exploratory laparotomy, and CT, although of these, only the serial FAST is likely to be available in the setting of MCI<sup>[98]</sup>.

## EVALUATION OF INTRAVASCULAR VOLUME BY INFERIOR VENA CAVA ASSESSMENT

Intravascular volume status can be estimated by evaluation of the inferior vena cava (IVC). The vessel is usually evaluated in real-time in both the longitudinal and transverse planes. As a component of the CAVEAT examination, sonographic IVC evaluation is most probably directed towards the rapid identification of hypovolemia, which, with experience, can be quickly and effectively accomplished by a purely qualitative assessment of the size, shape, and collapsibility of the vessel. If measurements are made, they should be obtained in diastole (i.e. the moment when the IVC is smallest in the cardiac beat-to-beat cycle), and taken just inferior (1-3 cm) to the junction of the hepatic veins (Figure 3). The traditional window has been subxiphoid, although recent reports have suggested that equivalent results can be obtained using a right intercostal view with the liver as a sonographic window<sup>[99,100]</sup>. This approach is especially useful if the subxiphoid window is obstructed by bowel gas or dressings<sup>[101]</sup>. Longitudinal and transverse planes are equivalent for measurement of the IVC<sup>[102]</sup>; however, each has mutually complementary advantages and disadvantages, so the IVC should be assessed in both planes.

An extensive body of literature describes a relationship between the sonographic appearance of the IVC and intravascular volume and cardiac filling pressures<sup>[5,33,65,103-105]</sup>. Assessment of the IVC might be made qualitatively (shape), and quantitatively (absolute size and collapse index). There is strong evidence that, in any given patient, increasing intravascular volume results in an expanding IVC diameter and a diminution of the percentage variation in diameter related to the respiratory cycle (i.e. the IVC collapsibility index, Figure 3). Decreasing intravascular volume will have the opposite effects<sup>[33,65,103,106]</sup>. A wide range of normal and abnormal values for these parameters has been



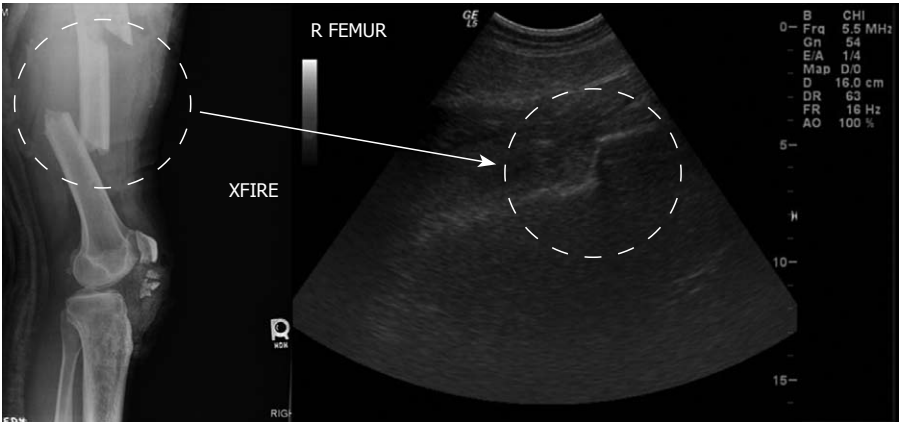
**Figure 3** Inferior vena cava collapsibility index can be obtained from measurements of end-expiratory and end-inspiratory vena cava diameters. The inferior vena cava collapsibility index (IVCCI) can be derived by subtracting the end-expiratory IVC diameter (IVC<sub>exp</sub>) from end-inspiratory IVC diameter (IVC<sub>insp</sub>), and the dividing the difference by IVC<sub>insp</sub>. The resultant fraction is then multiplied by 100% to produce a percentage IVC collapse. In this example, the IVCCI is  $[(18.3-3.8)/18.3] \times 100\% = 79.2\%$ , which indicates hypovolemia. PI Eff: Pleural effusion.

reported<sup>[33,107]</sup>. This is consistent with the role of the IVC as a capacitance vessel. Volume overload states are unlikely to be of concern in the MCI setting, and the key question to be answered in evaluation of the IVC is whether the vessel demonstrates adequate intravascular volume or not. Thus, the basic sonographic skill to be mastered by the sonographer who performs the CAVEAT examination is accurate identification of the vessel, and familiarity with the spectrum of IVC findings in normovolemic patients, to recognize the presence of a grossly collapsed or under-filled VC. If measurements are made, an adequate central venous pressure (CVP) can be predicted by an inspiratory IVC diameter > 10-12 mm, whereas an IVC diameter < 5 mm suggests abnormally low CVP<sup>[65]</sup>. Of note, IVC diameters in most normovolemic patients vary between 10 and 20 mm. Although the sensitivity and specificity of IVC assessment for estimation of intravascular volume are still poorly defined, an IVC collapsibility index of > 60%-70% predicts hypovolemia and helps identify patients who are likely to respond to intravascular volume expansion<sup>[4]</sup>. Finally, the correlation between IVC characteristics and vital signs traditionally used in triage (heart rate and blood pressure) is poor (our unpublished observations), which highlights the clinical challenges associated with failure to identify early compensated hypovolemic/hemorrhagic shock by heart-rate- or blood-pressure-based criteria. According to recent studies, bedside assessment of the IVC typically requires < 5 min<sup>[4,5,46]</sup>.

## Extremities

Ultrasonography has been used to identify fractures of the femur, humerus and ribs<sup>[18,31,32,108]</sup>. In a prospective study of 158 examinations performed on 95 patients, 94% of patients with extremity injuries were accurately identified, with no false-positive results<sup>[31]</sup>. Portable ultrasound is more accurate in the recognition of fractures in midshaft locations and less so in the metacarpal and





**Figure 4** Bedside sonographic appearance of a displaced femoral fracture. A correlation to plain radiography is shown. Bedside sonography provides a viable tool for quick and reliable assessment of suspected long-bone fractures. R FEMUR: Right femur; XFIRE: Cross table film.

**Table 3** The chest, abdomen, vena cava, and extremities for acute triage protocol summary

Description	Identification of immediately and potentially life-threatening injuries (FAST + pneumothorax)	Intravascular status evaluation (IVCCI)	Hemothorax assessment	Extremity assessment (lower → upper extremity sonography)
Skill level	Easy	Intermediate		Difficult
Urgency	Primary triage & assessment (Mandatory)		Secondary triage & assessment (Optional)	

The protocol is divided into two-tiered system of urgency (primary and secondary) and three skill levels (basic, intermediate, and advanced). Note that the chest, abdomen, vena cava, and extremities for acute triage examination can be performed after the primary survey, with the serial assessment performed, as indicated at a later time. FAST: Focused Assessment with Sonography in Trauma; IVCCI: Inferior vena cava collapsibility index.

metatarsal anatomical areas<sup>[59]</sup>. Ultrasonography can also demonstrate occult fractures that are not readily identifiable by traditional radiography<sup>[109,110]</sup>. Rapid ultrasound assessment of the extremities as a component of the CAVEAT examination is likely to result in more accurate reduction and stabilization of major fractures, prioritized utilization of radiographic resources, and more accurate triage of multiply injured patients<sup>[18,111]</sup>. Of note, extremity assessment should be considered an optional part of the sonographic assessment paradigm and should be utilized mainly as a secondary (versus initial/primary) triage tool. Figure 4 demonstrates the appearance of a midshaft, displaced femoral fracture, along with correlation to plain extremity radiograph.

**CAVEAT protocol**

The CAVEAT protocol is an integrated sonographic survey to be used as an adjunct in disaster and combat care triage and diagnosis. The suggested order of the component parts of the ultrasound examination are listed in rough order of clinical priority of diagnosis and by required skill level (Table 3). With increasing skill, the sonologist will be able to deviate from this suggested order based on the individual patient's injuries<sup>[112]</sup>. The authors anticipate that the completion of the entire CAVEAT protocol by a proficient sonologist will take approximately 5 min longer than the performance of the traditional FAST examination. Additional time might be spent, at the discretion of the sonographer, during the secondary triage assessment. However, such secondary examinations (including detailed extremity scans) are optional and based on resource/time availability.

The examination begins with a sonographic evalua-

tion of the pleura to identify the presence of pneumothorax. The examiner then performs a complete FAST examination, to include assessment of the costophrenic recesses bilaterally for identification of hemothorax. After the FAST examination, the IVC is assessed to determine gross perturbations of intravascular volume; in particular, volume depletion (see previous section). The theoretical possibility of identifying retroperitoneal injuries with sonographic contrast material is not practical in the MCI setting<sup>[113]</sup>. The CAVEAT examination concludes with an ultrasound examination of the long bones, with particular attention to regions of pain, tenderness, or deformity. Of note, the extremity assessment is not mandatory, and has been included in the proposed protocol mainly as an adjunct to secondary patient assessment (Table 3). In this role, extremity sonography could be performed as a secondary triage tool at a later time to help direct appropriate resources to orthopedic injuries that are not immediately life threatening but require prompt attention, and might be otherwise undetected in a resource-limited environment.

**LIMITATIONS AND NEED FOR FURTHER STUDIES**

The CAVEAT examination will not detect most intracranial, pulmonary, retroperitoneal, or pelvic injuries. Except in the hands of the most experienced sonologists, it will miss most solid organ and great vessel injuries that do not cause frank internal hemorrhage. Although the benefit of the CAVEAT protocol is yet to be established, as this review suggests, there is extensive scientific literature to

support the utility of its component parts. Studies are needed within the pre-hospital and emergency department environments to establish the feasibility of the CAVEAT protocol, and whether the addition of sonographic information improves triage accuracy. A significant potential impediment to the CAVEAT protocol, shared with other applications of clinician-performed ultrasonography, is the need for sonologist training. It is hoped that as ultrasonography is incorporated in both undergraduate and graduate medical training, care providers in MCI settings will increasingly possess the skills needed for the CAVEAT examination.

## CONCLUSION

Ultrasonography has a wide range of applications in diagnostic imaging and procedural guidance, without the deleterious effects of ionizing radiation. Recent technological advances have resulted in increasingly affordable, robust, portable, and user-friendly equipment. Many modern ultrasound units are battery-powered, and store images digitally, which allows for electronic and/or wireless data transfer. These advances make ultrasound increasingly suited to the rapid evaluation of the critically ill, particularly in remote, austere, and resource-poor settings. We have reviewed applications of portable ultrasonography in military and civilian mass casualty settings. Similar to other algorithms for the use of ultrasound in the assessment of the critically ill, the CAVEAT protocol seeks to integrate diverse uses of ultrasonography in a systematic coordinated way. The CAVEAT protocol proposes a graduated approach based on a combination of urgency, sonographic skill-sets, and technical difficulty of the examination.

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S- Editor Cheng JX L- Editor Kerr C E- Editor Lin YP

## Whole body vibration therapy in fracture prevention among adults with chronic disease

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Received: October 11, 2010 Revised: November 5, 2010

Accepted: November 12, 2010

Published online: November 18, 2010

### Abstract

Due to various physical impairments, individuals with chronic diseases often live a sedentary lifestyle, which leads to physical de-conditioning. The associated muscle weakness, functional decline and bone loss also render these individuals highly susceptible to falls and fragility fractures. There is an urgent need to search for safe and effective intervention strategies to prevent fragility fractures by modifying the fall-related risk factors and enhancing bone health. Whole body vibration (WBV) therapy has gained popularity in rehabilitation in recent years. In this type of treatment, mechanical vibration is delivered to the body while the individual is standing on an oscillating platform. As mechanical loading is one of the most powerful stimuli to induce osteogenesis, it is proposed that the mechanical stress applied to the human skeleton in WBV therapy might be beneficial for enhancing bone mass. Additionally, the vibratory signals also constitute a form of sensory stimulation and can induce reflex muscle activation, which could potentially induce therapeutic effects on muscle strength and important sensorimotor functions such as postural control. Increasing research evidence suggests that WBV is effective in enhancing hip bone mineral density, muscle strength and balance ability in elderly patients, and could have potential for individuals with chronic

diseases, who often cannot tolerate vigorous impact or resistance exercise training. This article aims to discuss the potential role of WBV therapy in the prevention of fragility fractures among people with chronic diseases.

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**Key words:** Falls; Vibration; Exercise; Rehabilitation; Balance; Bone density; Muscle

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Pang MYC. Whole body vibration therapy in fracture prevention among adults with chronic disease. *World J Orthop* 2010; 1(1): 20-25 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v1/i1/20.htm> DOI: <http://dx.doi.org/10.5312/wjo.v1.i1.20>

### FRAGILITY FRACTURES AND CHRONIC CONDITIONS

Individuals with chronic diseases might sustain varying degrees of impairments in different body systems that considerably reduce their capacity to engage in physical activity, which gives rise to secondary bone loss<sup>[1]</sup>. Certain chronic diseases (e.g. stroke and multiple sclerosis) also directly impair muscle function. For example, muscle weakness or atrophy is a common manifestation among individuals with osteoarthritis and chronic obstructive pulmonary disease (COPD)<sup>[2,3]</sup>, whereas spasticity is often observed in patients with stroke or multiple sclerosis<sup>[4,5]</sup>. As it is well known that muscle function is strongly correlated with the integrity of bone tissue<sup>[6-10]</sup>, people with impaired muscle function are particularly prone to secondary osteoporosis.

In addition to the problem of secondary bone loss,

people living with chronic diseases often have a number of fall-related risk factors, such as poor balance, compromised sensory function, impaired vision, and depression<sup>[11]</sup>. The combination of a sedentary lifestyle and impaired functional status could lead to further reduction in physical activity level, thereby triggering a vicious cycle of physical de-conditioning, bone loss, and falls. It is thus not surprising that individuals who live with chronic diseases often sustain an exaggerated fracture risk. For example, in stroke patients, a population that is known to have accelerated bone loss on the paretic side of the body<sup>[6,7,12,13]</sup> and elevated risk of accidental falls<sup>[14-17]</sup>, the risk of fragility fractures is more than seven times higher within the first year post-stroke, when compared with people with no history of stroke<sup>[18]</sup>. At 8 years post-stroke, the excess risk of hip fracture remains 23% higher than in the reference population<sup>[18]</sup>. Among individuals with Parkinson's disease, another population that is highly susceptible to falls<sup>[19-24]</sup> and secondary osteoporosis<sup>[25-28]</sup>, approximately 27% will sustain a hip fracture within 10 years of diagnosis, compared with only 9% among age-matched healthy subjects over the same follow-up period<sup>[29]</sup>. It is also worth mentioning that certain pharmacological agents used in patients with chronic diseases can exacerbate bone loss and increase the risk of fractures. One example is the long-term use of corticosteroids<sup>[30]</sup> in patients with advanced COPD<sup>[31]</sup> and rheumatoid arthritis<sup>[32]</sup>. Research has shown that corticosteroid treatment is associated with increased vertebral fracture risk in COPD patients<sup>[33,34]</sup>.

Fragility fractures have become a major public health issue<sup>[35]</sup>. As the global population is rapidly aging, the number of individuals who live with chronic conditions, and hence the incidence of osteoporosis, falls and fragility fractures can only be projected to increase. Fragility fractures can lead to serious consequences, including increased morbidity, mortality, and health care costs<sup>[36-38]</sup>. The outcomes are even more unfavorable if fragility fracture is superimposed on a pre-existing chronic disease. Di Monaco *et al*<sup>[39]</sup> have demonstrated that patients with a chronic neurological disease (stroke or Parkinson's disease) have a significantly longer period of hospital stay after a hip fracture than their peers without a history of chronic neurological disease. It has also been shown by Ramnemark *et al*<sup>[40]</sup> that the 1-year mortality rate following a hip fracture is significantly higher among patients with a stroke history (29.3%) than those without (16.8%). Moreover, among the hip-fractured patients who were independent in mobility pre-admission, only 38% of those with a stroke history could regain independent mobility status upon discharge from the hospital, compared with 69% of patients without a stroke history<sup>[40]</sup>.

In summary, patients living with chronic illnesses are highly susceptible to falls, bone loss and fragility fractures, which can lead to disabling, and sometimes fatal consequences. Hence, identifying effective intervention strategies to prevent or reduce fragility fractures through modification of fall-related risk factors and enhancement of bone health is of paramount clinical relevance.

## WHOLE BODY VIBRATION: POTENTIAL APPLICATION IN PATIENTS WITH CHRONIC DISEASES

It has long been demonstrated that high-frequency mechanical stimuli can produce a strong osteogenic effect in animal models<sup>[41-45]</sup>. The encouraging findings from animal studies have raised the possibility that the dynamic mechanical stress involved in whole body vibration (WBV) therapy could be a viable method to enhance bone density in humans<sup>[46]</sup>. In WBV therapy, the individual is required to stand on an oscillating platform that is capable of generating mechanical vibration signals of varying frequency, magnitude, and duration. As the vibratory signals also constitute a form of sensory stimulation and can induce reflex muscle activation<sup>[47,48]</sup>, WBV therapy is also proposed to have potential therapeutic effects on muscle strength and other important sensorimotor functions such as postural control<sup>[46]</sup>.

Mounting research evidence has suggested that WBV therapy is an effective treatment method to improve bone health, and modify fall-related risk factors (e.g. muscle strength, and balance ability) in older adults. A number of randomized controlled studies have examined the effects of WBV therapy on hip and lumbar spine BMD in postmenopausal women<sup>[49-55]</sup>. A recent meta-analysis by Slatkowska *et al*<sup>[56]</sup> has shown that WBV has a small but significant effect on hip BMD in postmenopausal women. No overall significant effect on lumbar spine BMD, however, can be identified<sup>[56]</sup>. In addition to the reported positive outcomes on bone health, WBV has also been shown to have a significant effect on improving leg muscle strength and balance performance in several studies<sup>[49-51,54,57-68]</sup>.

Patients living with chronic diseases could be potential beneficiaries of WBV therapy, considering that many of these individuals suffer from impaired muscle function, secondary osteoporosis, physical de-conditioning, and an elevated fracture risk. Research on the application of WBV in people with chronic diseases has flourished in recent years. The following section provides a summary of the findings on the effects of multiple sessions of WBV treatment in patients with chronic diseases. The WBV protocols employed in these studies are outlined in Table 1.

### Chronic diseases that primarily affect the musculoskeletal system

A recent randomized controlled study has examined the effect of WBV therapy on muscle strength and proprioception in older women with knee osteoarthritis<sup>[69]</sup>. The subjects were randomly assigned to one of three groups: WBV exercise performed on a stable platform, WBV exercise performed on a balance board, and controls. After 8 wk training, those who underwent WBV exercise on a stable platform had significantly greater gain in isokinetic knee extension/flexion torque and isometric knee extension strength than control subjects. In contrast, those who underwent WBV training on a balance board had signifi-



Table 1 Application of whole body vibration therapy in chronic diseases: Protocol and results

Study	Chronic condition	Study design	Sample size	WBV protocol					Main results
				Frequency of vibration (Hz)	Amplitude of vibration (mm)	Duration of WBV exposure per day	Treatment days per week	Duration of program	
Trans <i>et al</i> <sup>[69]</sup> , 2009	Osteoarthritis	RCT	52	24-30	Not reported	3-5 min	2	8 wk	WBV exercise on a stable platform resulted in significantly more gain in isokinetic knee extension/flexion torque and isometric knee extension strength than controls; WBV training on a balance board resulted in significantly more improvement in knee proprioception than controls
Ahlborg <i>et al</i> <sup>[70]</sup> , 2006	Cerebral palsy	RCT	14	25-40	Not reported	6 min	3	8 wk	No significant difference in ambulatory and gross motor function outcomes between the WBV group and resistance training group
Wunderer <i>et al</i> <sup>[71]</sup> , 2010	Multiple sclerosis	Single subject experimental design	3	40	2	30 min	2	6 wk	WBV resulted in increase in knee extensor muscle strength in all three subjects; WBV resulted in improvement in functional mobility (Timed Up and Go test) in two subjects
van Nes <i>et al</i> <sup>[72]</sup> , 2006	Stroke	RCT	53	30	3	4 min	5	6 wk	Gains in balance, mobility and activities of daily living were comparable to that in the conventional exercise group
Ebersbach <i>et al</i> <sup>[73]</sup> , 2008	Parkinson's disease	RCT	27	25	7-14	15 min/session, 2 sessions/d	5	3 wk	Gain in functional balance and gait velocity in WBV group was similar to those in the conventional physiotherapy group
Arias <i>et al</i> <sup>[74]</sup> , 2009	Parkinson's disease	Non-randomized controlled trial	21	6	Not reported	5 min	2-3	5 wk	Balance and mobility outcomes after WBV exercise were similar to those after control exercises without WBV
Baum <i>et al</i> <sup>[75]</sup> , 2007	Type II diabetes	RCT	40	30-35	2	4 min	3	12 wk	No significant difference in maximal isometric torque of the quadriceps and fasting glucose concentration after treatment among the WBV group, the strength training group and the flexibility training group
Roth <i>et al</i> <sup>[6]</sup> , 2008	Cystic fibrosis	Quasi-experimental (no control group)	11	12-26	7.8	6 min	3-5	6 mo	WBV resulted in no significant changes in the trabecular bone density of the tibia or spine; WBV induced an increase in explosive leg muscle strength
Rietschel <i>et al</i> <sup>[77]</sup> , 2008	Cystic fibrosis	Quasi-experimental (no control group)	10	20-25	0.6	9 min/session, 2 sessions/d	5	3 mo	WBV induced significant improvement in performance in the chair-rising test and the two-leg jump test

RCT: Randomized controlled trial; WBV: Whole body vibration.

cantly greater improvement in knee proprioception than the controls had<sup>[69]</sup>. However, it is unclear whether the reported benefits are related to the exercise itself or the addition of vibration during exercise.

### Chronic diseases that primarily affect the neurological system

A number of studies have examined the effects of WBV therapy in adults with different types of chronic neuro-

logical diseases, including cerebral palsy<sup>[70]</sup>, multiple sclerosis<sup>[71]</sup>, stroke<sup>[72]</sup> and Parkinson's disease<sup>[73,74]</sup>. In a small-scale study that involves 14 adults with cerebral palsy, Ahlborg *et al*<sup>[70]</sup> compared the effects of an 8-wk WBV program and a resistance training program. It was found that WBV was no better than resistance training in enhancing ambulatory function and gross motor skills. Using a single subject experimental design, Wunderer *et al*<sup>[71]</sup> examined the long-term effects of WBV in three patients with mul-

multiple sclerosis. Increase in knee extensor muscle strength was obtained in all three subjects, whereas improvement in mobility as measured by the Timed Up and Go test was observed in two of the subjects. Although this study suggests that the application of WBV in patients with multiple sclerosis has promise, further research using a randomized controlled design is required to establish the clinical efficacy of WBV in this patient group.

Other investigators have examined the effect of WBV in stroke patients. In a randomized controlled trial of 53 patients with subacute stroke, van Nes *et al*<sup>[72]</sup> have reported that their 6-wk WBV program has led to significant improvement in balance, mobility and activities of daily living that was comparable to that produced by the conventional exercise program. The effects of WBV on neuromuscular performance in patients with Parkinson's disease have also been examined by Ebersbach *et al*<sup>[73]</sup>, who showed that their 3-wk WBV protocol did not result in significantly greater gains in functional balance and gait velocity compared with a control group who received conventional physiotherapy. In a non-randomized controlled trial, Arias *et al*<sup>[74]</sup> demonstrated that although improvement in balance and mobility were improved following 5 wk WBV, the treatment effect was similar to control exercises without vibration, which indicates that WBV has no additional effect in improving neuromuscular outcomes in Parkinson's disease patients.

### **Chronic diseases that primarily affect the respiratory and cardiovascular systems**

Few studies have investigated the clinical efficacy of WBV therapy in chronic diseases that affect mainly the cardiovascular or respiratory systems. A randomized controlled study investigated the effects of a 12-wk WBV program in individuals with type II diabetes<sup>[75]</sup>. The 40 subjects were randomly assigned to one of three groups: a WBV group, a strength training group, and a flexibility training group. The results showed no significant difference in maximal isometric torque of the quadriceps and fasting glucose concentration after treatment in the WBV group, the strength training group and the flexibility training group.

In contrast, Roth *et al*<sup>[76]</sup> examined the effect of WBV in adults with cystic fibrosis. The subjects received a home-based WBV exercise program for 6 mo, which resulted in no significant changes in the trabecular bone density of the tibia or spine. Improvements were observed, however, in explosive leg muscle strength, as measured by two-leg jump test (increase in muscle power and velocity) and one-leg jump test (increase in muscle force). The effects of WBV in patients with cystic fibrosis were also studied by Rietschel *et al*<sup>[77]</sup>. In their pilot study of 10 subjects with cystic fibrosis<sup>[76]</sup>, it was found that the 3-mo WBV training program resulted in significant improvement in performance in the chair-rising test (reduced time, increased maximal force, maximal power and velocity) and the two-leg jump test (increased force and velocity). However, these studies did not have a control group, and therefore the interpretation of results warrants caution.

In summary, based on the available research data thus

far, there is no evidence to suggest that WBV is superior to other exercise approaches in improving various neuromuscular outcomes in adults with chronic disease. This is in contrast to a good number of WBV studies in the general older adult population that have demonstrated the positive effects of WBV on balance performance and leg muscle strength<sup>[49-51,54,57-68]</sup>. It is possible that WBV protocols used in the general older adult population are not the optimal for inducing a therapeutic effect on the various outcomes of interest in patients with chronic disease. Perhaps a greater intensity and longer duration of training is required to obtain a significant treatment effect among patients with disabilities. It is also possible the non-significant results were partly due to the fact that small sample sizes were used, which had low statistical power. It would thus be difficult to detect a statistically significant difference, even if a true treatment effect existed. Surprisingly, despite the fact that bone health is a major health issue among patients with chronic disease, only one study has incorporated bone mineral density as the outcome<sup>[76]</sup>. There is a need for more research in this important area.

### **Adverse events**

Similar to studies in older adults and postmenopausal women, very few adverse effects have been reported in WBV studies in patients with chronic disease. There have been isolated cases of head discomfort and increased fatigue<sup>[76]</sup>. One patient with a history of arthropathy developed joint effusion, but the symptoms subsided as training progressed<sup>[76]</sup>. One patient with cystic fibrosis and a history of venous thrombosis developed new thrombosis of the superior vena cava<sup>[75]</sup>. It is unclear how closely the adverse symptoms were monitored during the course of WBV therapy in these studies. It is also uncertain whether long-term adverse effects can result from WBV therapy. Based on the available data, however, WBV therapy seems to be a safe treatment technique when applied to individuals with chronic disease.

## **CONCLUSION**

The research evidence on the clinical efficacy of WBV for improvement of bone health and modification of fall-related risk factors among patients with chronic disease is limited. Good quality randomized controlled trials are scarce. More research is needed to determine whether WBV therapy has a role in fracture prevention in individuals with chronic disease.

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S- Editor Cheng JX L- Editor Kerr C E- Editor Lin YP



## Return to sports activity by athletes after treatment of spondylolysis

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 Received: August 30, 2010 Revised: October 28, 2010  
 Accepted: November 3, 2010  
 Published online: November 18, 2010

until their return to sports activities was longer after surgery than after conservative treatment.

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**Key words:** Spondylolysis; Athletes; Conservative treatment; Surgical treatment; Return to play; Literature review

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### Abstract

**AIM:** To clarify the efficacy of conservative and surgical treatment of spondylolysis in athletes.

**METHODS:** PubMed was used to perform a search of the literature for studies published during the period from 1990 to 2009 that reported data on the outcome of conservative or surgical treatment of spondylolysis in athletes. The articles were examined for data on the percentage of athletes who returned to sports activities and the interval between the start of treatment and their return.

**RESULTS:** Five studies were identified. Two studies were concerned with conservative treatment and the other three with surgical treatment (wire fixation or screw fixation with bone graft). The percentages of athletes who returned to sports activities ranged from 80.0% to 89.3% and from 81.9% to 100%, respectively, and the intervals until their return ranged from 5.4 to 5.5 mo and from 7 to 12 mo, respectively.

**CONCLUSION:** The percentages of athletes who returned to sports activities after conservative and surgical treatment appeared to be satisfactory, but the interval

Iwamoto J, Sato Y, Takeda T, Matsumoto H. Return to sports activity by athletes after treatment of spondylolysis. *World J Orthop* 2010; 1(1): 26-30 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v1/i1/26.htm> DOI: <http://dx.doi.org/10.5312/wjo.v1.i1.26>

### INTRODUCTION

Spondylolysis is a common injury that causes low back pain in athletes. Sports in which participants are subjected to repetitive hyperextension and rotation across the lumbar spine pose a risk for such injury, and football linemen, oarsmen, dancers, gymnasts, and athletes in sports that involve throwing have a high incidence of this condition<sup>[1,2]</sup>. Two prospective studies have shown that the incidence of low back pain in athletes with spondylolysis was 72.5% in high school rugby players, 79.8% in high school football players, and 80.5% in college football players<sup>[3,4]</sup>. Low back pain associated with spondylolysis often prevents athletes from continuing sports activities, and management of spondylolysis in athletes is a challenge.

Enabling patients to return to sports activities is at the heart of sports medicine, and achieving that goal frequent-

ly presents significant challenges to the sports physician<sup>[5]</sup>. Nevertheless, a review of the literature on spinal injuries in athletes and their return to play suggests that there are differing opinions regarding the evaluation and treatment of spondylolysis, and that there is less disagreement with regard to return to play<sup>[6]</sup>. Thus, not only is there no agreement on the optimal strategy for the management of spondylolysis in athletes, but there is a lack of research-based evidence in the literature with regard to return to play in athletes with spondylolysis. However, because athletes with sports injuries usually desire an early return to sports activities, it is naturally important for sports physicians to inform them of the likely outcome of several treatment options and the estimated duration of each treatment.

The primary goal of treatment of athletes with spondylolysis is healing of the injury and prevention of progression to nonunion of the pars interarticularis. Most sports physicians agree that the treatment of spondylolysis should include a period of rest, with or without bracing, to allow healing, rehabilitation, and return to play when asymptomatic<sup>[7]</sup>. Actually, earlier studies published in the 1980s have shown that treatment that consists of avoiding aggravating activities and rest enabled athletes to return to pain-free competition after an average interval of 7.3 mo<sup>[8]</sup>, and that after treatment with the modified Boston brace, 78% of athletes had either excellent or good results with no pain and returned to full activity<sup>[9]</sup>. Surgical treatment is indicated in athletes with persistent pain from non-healing of the pars after a minimum of 6 mo<sup>[10]</sup>. Wiring technique, direct repair with screw fixation, and pedicle screw-hook constructs across the pars interarticularis defect with bone grafting are effective options to achieve pars healing while preserving spinal motion<sup>[10]</sup>.

However, despite the obvious theoretical desirability of healing the pars interarticularis, there has been little correlation between bony healing and outcome, and numerous studies have shown good short-term outcomes for return to play regardless of healing status<sup>[11]</sup>. Because there have been no controlled trials of treatment of spondylolysis, and only a few of studies have addressed potential strategies, it is difficult to develop true evidence-based guidelines for this condition<sup>[11]</sup>. There have been no high level evidence studies that have led to specific recommendations for bracing, rehabilitation, or surgery, and no head to head study has ever proven superiority of treatment methods. To date, the outcomes of conservative or surgical treatment of spondylolysis in athletes have been documented<sup>[12-16]</sup>. The purpose of the present study was to clarify the efficacy of conservative and surgical treatment of spondylolysis in athletes; especially in terms of their ability to return to sports activities, by reviewing the recent literature.

## MATERIALS AND METHODS

PubMed was used to search the literature for studies published during the period from 1990 to 2009, which presented data on the outcomes of conservative or surgical treatment of spondylolysis in athletes; especially in terms of their ability to return to sports activities. The key words

used in the search were “spondylolysis”, “sport”, “sports”, “athlete”, and/or “athletes”. Inclusion criteria were full-length English-language papers or abstracts, conservative treatment, surgical treatment, athlete’s outcomes, adequate information about the ability of athletes to return to sports activities, prospective studies, and retrospective studies. Exclusion criteria were non-English-language papers or abstracts, case reports, review papers, non-athlete’s outcomes, and inadequate information about the ability of athletes to return to sports activities.

The efficacy of conservative and surgical treatment of spondylolysis in athletes was clarified. The primary endpoint was the percentage of athletes who returned to sports activities. The secondary endpoint was the interval between the start of treatment and their return to sports activity. In addition, the outcomes of conservative and surgical treatment methods were compared by calculating the ratio (surgical/conservative) of the percentage of athletes who returned to sports activities and 95% confidence interval (CI). The statistical analysis was performed by using Excel Analysis 2008 Software (Social Survey Research Information Co., Ltd, Tokyo, Japan) on a personal computer. A significance level of  $P < 0.05$  was used for all comparisons.

## RESULTS

### Studies in athletes

Five studies were identified<sup>[12-16]</sup>. All of them were case series studies. One was a prospective study, and four were retrospective. Two studies were concerned with conservative treatment, and the other three with surgical treatment (wire fixation or screw fixation with bone graft).

### Outcomes of conservative and surgical treatment

Table 1 shows the outcomes of conservative and surgical treatment. The percentages of athletes who returned to sports activities ranged from 80.0% to 89.3% and from 81.9% to 100%, respectively, and the intervals until their return ranged from 5.4 to 5.5 mo and from 7 to 12 mo, respectively. The percentages of athletes who returned to sports activities after conservative and surgical treatment appeared to be satisfactory, but the interval until their return to sports activities was longer after surgery than after conservative treatment.

### Outcomes of conservative versus surgical treatment

The combined results of the two studies of conservative treatment showed that 60 of the 68 athletes returned to sports activities. Overall, the percentage of athletes who returned to sports activities after conservative treatment was 88.2%. The combined results of the three studies of surgical treatment showed that 42 of the 46 athletes returned to sports activities, and overall, the percentage of athletes who returned to sports activities after surgical treatment was 91.3%.

The ratio of the percentage of athletes who returned to sports activities after surgical treatment to the percentage who returned after conservative treatment was 1.03 (95% CI: 0.60-1.78), and the results of the statistical



Table 1 Outcomes of five studies

Investigator, yr	Study design	No. of cases	Mean age (yr)	Subjects	Treatment	Percentage of athletes who returned	Interval until to return
Sys <i>et al</i> <sup>[12]</sup> , 2001	Retrospective	28	17.2	Highly competitive athletes	Conservative (Boston Overlap Brace)	89.3	5.5 mo
Iwamoto <i>et al</i> <sup>[13]</sup> , 2004	Retrospective	40	20.7	Various levels of athletes	Conservative (rest and anti-lordotic brace)	87.5	5.4 mo
Reitman <i>et al</i> <sup>[14]</sup> , 2002	Retrospective	4	17.8	High school and collegiate athletes	Surgery (screw fixation with bone graft)	100	< 1 yr
Debnath <i>et al</i> <sup>[15]</sup> , 2003	Prospective	22	20.2	Young athletes	Surgeries (wire fixation or screw fixation with bone graft)	81.9	7 mo
Nozawa <i>et al</i> <sup>[16]</sup> , 2003	Retrospective	20	23.7	Athletes	Surgery (segmental wire fixation)	100	No information

analysis confirmed that the overall percentage of athletes who returned to sports activities after surgical treatment was not significantly different from the overall percentage of those who returned after conservative treatment ( $P = 0.506$ ).

## DISCUSSION

There is convincing evidence that athletes with early or progressive stage lesions of the pars interarticularis should be advised to rest for 3 mo, with the aim of achieving bony union because of the good potential for healing (especially if unilateral), whereas athletes with chronic lesion of the pars interarticularis should be advised to rest, with the aim of relieving low back pain because of the very little chance to achieve bony union<sup>[11]</sup>. Thus, conservative treatment with the aim of relieving low back pain, as well as surgical treatment with the aim of achieving bony union of the pars interarticularis is an acceptable means of treating athletes with chronic lesions to enable them to return to sports activities. The present study revealed that similar percentages of athletes returned to sports activities after surgical and conservative treatment (81.9%-100% *vs* 87.5%-89.3%), although the interval until their return to sports activities was longer after surgery than after conservative treatment (7-12 mo *vs* 5.4-5.5 mo).

The outcome of conservative treatment appears to be satisfactory in athletes, especially in terms of their return to sports activities. Iwamoto *et al*<sup>[13]</sup> were able to return 87.5% of athletes to sports activities by treating with rest and anti-lordotic bracing after an average interval of 5.4 mo. They stated that their goal was obtain stability by fibrous union of chronic lesions, and not necessarily bone union. Sys *et al*<sup>[12]</sup> have reported that 89.3% of athletes managed to return to their same level of competitive activities within an average of 5.5 mo after the start of non-operative treatment (Boston Overlap Brace). They also have stated that nonunion did not seem to compromise overall outcome or sports resumption in the short-term. These consistent results support the evidence that excellent clinical outcomes can be achieved even in the absence of bony healing<sup>[17]</sup>. However, there could be a criticism that, despite the satisfactory outcome of conservative treatment of spondylolysis, prolonged and failed conser-

vative treatment could cause formation of communicating synovial pseudoarthrosis at the pars interarticularis, which might prevent healing.

d'Hemecourt *et al*<sup>[18]</sup> have reported that 80% of athletes with spondylolysis that were treated with the Boston Overlap Brace had a favorable clinical outcome. They have speculated that athletes with symptomatic spondylolysis treated with an anti-lordotic brace can expect improvement in their clinical course, and return to sports participation in 4-6 wk. However, this is not an evidence-based opinion, but only speculation. It might take longer (5-6 mo) for athletes to return to their same level of sports activities after conservative treatment, including athletic rehabilitation programs (4-6 wk).

As to the natural course of spondylolysis, Miller *et al*<sup>[19]</sup> have shown that most young athletes conservatively treated for early spondylolysis (radiography negative, nuclear scintigraphy positive) maintained good functional outcome for up to 11 years, and that unilateral defects underwent full bony healing, but took longer than 12 wk. However, bilateral defects underwent further degeneration and slip with time. Congeni *et al*<sup>[20]</sup> also have shown that, among athletes with subtle fractures of the pars interarticularis (normal radiographs and positive bone scans), 45% of athletes had chronic non-healing fractures, 40% developed acute fractures in various stages of healing, and 15% had no obvious fractures according to computed tomography scans. These results suggest the limitations of conservative treatment in athletes with bilateral defects, and that the risk of nonunion of the defect, degeneration and slip increases unless athletes with spondylolysis are treated properly. Computed tomography scans can play a very important role in diagnosis, assessment of the defect, short-term and long-term management decisions, and in determining prognosis.

A high percentage of athletes might be able to return to sports activities after surgery (wire fixation or screw fixation with bone graft). Nozawa *et al*<sup>[16]</sup> have reported that 100% of the athletes that they treated by segmental wire fixation returned to sports activities. Reitman *et al*<sup>[14]</sup> and Debnath *et al*<sup>[15]</sup> have reported that 100% and 81.9%, respectively, of the athletes treated by wire fixation or screw fixation with bone graft returned to sports activities in 1 year and after an average interval of 7 mo, respectively.

The indication for surgery in both studies was failure to respond to conservative treatment, including rest, bracing, rehabilitation, and/or medication<sup>[14-16]</sup>. However, the interval until their return to sports activities was longer after surgical treatment than after conservative treatment.

One possibility for this result is that surgery inevitably involves invasion of the back muscles and it would take at least several months before bony union is achieved. Actually, the results of a survey of the membership of the Scoliosis Research Society<sup>[21]</sup> have shown that almost half of the surgeons who perform fusion to treat children and adolescents with spondylolysis and spondylolisthesis do not permit return to non-contact activities such as running or tennis before 6 mo, and that approximately one-third of the responders permit a return to collision sports such as football and hockey after 1 year.

Other possibilities are that the degree of the lesion might be more severe in those who undergo surgery, which could prolong any return to sports activities; athletes who have prolonged cessation of play might return later; concomitant rehabilitation might influence recovery after surgery; and not all surgical procedures have the same success rate.

It is generally accepted that sports movements that require lumbar hyperextension and rotation contribute to the risk of development of spondylolysis; especially when the spine is immature<sup>[22-26]</sup>. Spondylolysis is a stress fracture of the pars interarticularis that sometimes occurs during the growth phase, and severe symptoms might only develop when sporting activities become more intense in the mature phase<sup>[13]</sup>. Micheli *et al.*<sup>[27]</sup> have demonstrated that adolescent athletes are ultimately shown to have a stress fracture of the pars interarticularis, whereas adult athletes are found to have spondylolysis associated with low back pain. Thus, strategies to prevent stress fractures of the pars interarticularis might be most important in athletes who are in the growth phase.

The limitations of the present study need to be discussed. First, there was no standard definition of return to sports activities. Second, the sports levels might not have been consistent across the studies. Third, most of the studies were retrospective studies with small sample sizes, which suggests lower quality of derived evidence according to evidence-based medicine. Thus, further clinical studies of spondylolysis are needed, particularly longitudinal studies, to increase our understanding of the natural history of this disorder, and controlled clinical trials to study the type and extent of treatment necessary to optimize patient outcomes.

The results of this study showed that the outcomes of conservative and surgical treatment of spondylolysis in athletes appeared to be satisfactory in terms of their ability to return to sports activities. Although the percentage of athletes who returned to sports activities after conservative and surgical treatment was similar, the interval until their return to sports activities was longer after surgery than after conservative treatment. Further clinical studies of spondylolysis are needed to determine the type

and extent of treatment necessary to optimize outcomes in athletes in terms of their ability to return to sports activities.

## COMMENTS

### Background

Spondylolysis is a common injury that causes low back pain in athletes. Enabling patients to return to sports activities is at the heart of sports medicine, and achieving that goal frequently presents significant challenges to the sports physician. However, the efficacy of conservative and surgical treatment of spondylolysis in athletes has not been established.

### Innovations and breakthroughs

This study showed that the outcomes of conservative and surgical treatment of spondylolysis in athletes appeared to be satisfactory in terms of their ability to return to sports activities. Although the percentage of athletes who returned to sports activities after conservative and surgical treatment was similar, the interval until their return to sports activities was longer after surgery than after conservative treatment.

### Applications

Further clinical studies of spondylolysis are needed to determine the type and extent of treatment necessary to optimize outcomes in athletes in terms of their ability to return to sports activities.

### Terminology

Spondylolysis is a stress fracture of the pars interarticularis that sometimes occurs during the growth phase, and severe symptoms might only develop when sporting activities become more intense in the mature phase.

### Peer review

Overall this is a well presented overview, however, there are some major comments on the design to be addressed.

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## Acknowledgments to reviewers of *World Journal of Orthopedics*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Orthopedics*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

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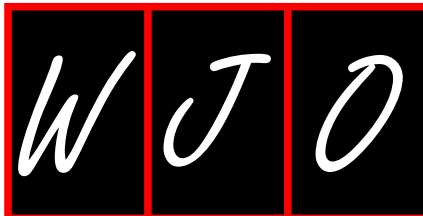
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- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID: 2516377 DOI: 10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI: 10.1097/01.ju.0000067940.76090.73]

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI: 10.1136/bmj.325.7357.184]

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- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI: 10.1046/j.1526-4610.42.s2.7.x]

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- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI: 10.10

97/00003086-200208000-00026]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

### Books

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- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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- 12 **Breedlove GK**, Schorfeide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

**Electronic journal** (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

**Patent** (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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