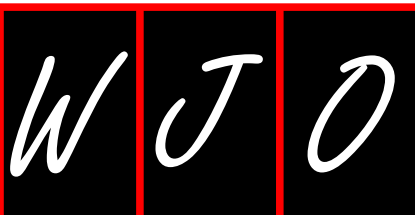


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Classification criteria for spondyloarthropathies

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Abstract

Spondyloarthropathies (SpA) are a group of inflammatory arthritis which consist of ankylosing spondylitis (AS), reactive arthritis, arthritis/spondylitis associated with psoriasis (PsA), and arthritis/spondylitis associated with inflammatory bowel diseases. It is now more important than ever to diagnose and treat SpA early. New therapeutic agents including blockers of tumor necrosis factor have yielded tremendous responses not only in advanced disease but also in the early stages of the disease. Sacroiliitis on conventional radiography is the result of structural changes which may appear late in the disease process. However, magnetic resonance imaging (MRI) can visualize active inflammation at sacroiliac joints and spine in recent onset disease. The modified New York criteria, the European Spondyloarthropathy Study Group criteria and the Amor criteria do not include advanced imaging techniques like MRI which is very sensitive to the early inflammatory changes. Assessment of SpondyloArthritis international Society has defined MRI methods for the assessment of sacroiliac joints and spine, criteria for inflammatory back pain and developed new criteria for classification of axial and peripheral spondyloarthritis. These new criteria are intended to be used for patients with SpA at the very early stage of their disease. Also, classification

of psoriatic arthritis study group developed criteria for the classification of PsA. The widespread use of these criteria in clinical trials will provide evidence for a better definition of early disease and recognize many patients who may further develop classical AS or PsA. These efforts will guide therapeutic trials of potent drugs like biological agents in the early stage of these diseases.

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Key words: Classification criteria; Spondyloarthritis; Psoriatic arthritis; Ankylosing spondylitis

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INTRODUCTION

Spondyloarthropathies (SpA) are a group of inflammatory arthritis that consist of ankylosing spondylitis (AS), reactive arthritis, arthritis/spondylitis associated with psoriasis (PsA) and arthritis/spondylitis associated with inflammatory bowel diseases (IBD). The association with human leukocyte antigen (HLA)-B27, peripheral joint involvement predominantly of the lower extremities, sacroiliitis, spondylitis, enthesitis, dactylitis, uveitis, enteric mucosal lesions and skin lesions are the shared manifestations of the diseases^[1,2]. Categorization of an individual patient into a subset of SpA can be difficult

Table 1 Inflammatory back pain criteria sets and mnemonic for assessment of spondyloarthritis international society criteria^[11-13,17]

Calin's criteria for IBP	Berlin criteria for IBP	ASAS IBP criteria mnemonic for criteria "iPAIN"
Age at onset < 40 yr	Morning stiffness of > 30 min duration	Insidious onset
Duration of back pain > 3 mo	Improvement in back pain with exercise but not with rest	Pain at night (with improvement upon getting up)
Insidious onset		
Morning stiffness	Nocturnal awakening (second half of the night only)	Age at onset < 40 yr
Improvement with exercise	Alternating buttock pain	Improvement with exercise
		No improvement with rest
Requires the presence of four of five criteria	The sensitivity is 70% specificity 81% if two of the four criteria are fulfilled	The sensitivity is 77.0% and specificity 91.7% if at least four out of five criteria are fulfilled

IBP: Inflammatory back pain; ASAS: Assessment of spondyloarthritis international society; iPAIN: Inflammatory PAIN.

due to the lack of well-defined criteria for the diagnosis^[3]. The newly developed Assessment of SpondyloArthritis International Society (ASAS) classification criteria proposes to classify the SpA according to leading clinical manifestations; predominantly axial or predominantly peripheral, with or without associated psoriasis, IBD or preceding infection^[4,5].

The new developments in the clinical and scientific aspects of SpA were pursued by the need for new strategies for definition of early diagnosis and outcome criteria for clinical studies. There is a long delay, approximately 5-6 years, between the first occurrence of the SpA symptoms and the diagnosis of the disease especially for female, juvenile onset or HLA-B27 negative patients^[6,7]. The major reason for this delay may be the low awareness of AS among the physicians as well as a lack of well defined criteria for identifying patients with inflammatory back pain (IBP) from chronic low back pain of mechanical origin. Relatively late appearance of sacroiliitis on plain radiographs, due to insidious nature of AS, is another reason for delay. Recent developments demonstrated that inflammation of sacroiliac joints could be well visualized by magnetic resonance imaging (MRI) long before than radiographic changes take place^[8].

WHAT ARE CLASSIFICATION CRITERIA?

Classification criteria serve to define disease groups for clinical and epidemiological studies^[9]. These sets of classification criteria combine different types of information like symptoms, signs, laboratory findings, imaging, genetic factors and etiological agents.

Classification criteria should not contain too many false positives and should have high specificity. Because of the inverse relationship, it has low sensitivity. In clinical

studies, classification criteria provide homogeneous patient groups which thus enable comparisons. On the other hand, diagnostic criteria should have high sensitivity in order to make a correct diagnosis; this means that it may contain false positives and may have low specificity. Most of the rheumatic diseases do not have unique or specific diagnostic tests and classification criteria have been developed to identify homogeneous patient populations for clinical trials. It should be noted that most of the criteria sets in rheumatology have been developed as classification criteria for clinical research but unfortunately are widely used as diagnostic tools in daily practice. This is, for example, the case with the formerly the American Rheumatism Association criteria (for the classification of rheumatoid arthritis) and the European Spondylarthropathy Study Group (ESSG) preliminary criteria for the classification of spondyloarthropathies^[10].

Inflammatory back pain

Inflammatory back pain is the leading symptom of the SpA and mirrors inflammation of sacroiliac joints, spine and spinal entheses. However its value for the diagnosis, classification and screening in primary care settings is not well recognized. Clinical history has been proposed as a screening test to identify patients with SpA among those who have chronic back pain^[11]. In general, criteria for IBP were derived from studies comparing patients with AS and patients with back pain of other etiologies and from studies based on expert opinion. Although IBP is considered as the foremost clinical symptom for axial SpA, its sensitivity and specificity with respect to diagnosis of axial SpA does not exceed 80%^[12].

Calin *et al*^[13] examined 42 patients with AS and 24 patients with other origin of back pain for 5 features of back pain: (1) insidious onset; (2) age at onset < 40 years; (3) duration of back pain \geq 3 mo; (4) associated with morning stiffness; and (5) improvement with exercise. IBP was considered in the presence of 4 of 5 features, and these were the first criteria for IBP (Table 1). However, Calin's criteria had some limitations. Duration of morning stiffness was later reported by Gran; a duration more than 30 min is associated with AS, and has 64% sensitivity and 58% specificity^[14]. In the original study, Calin's criteria have 95% specificity and 76% sensitivity but the subsequent studies showed low sensitivity and specificity^[14,15]. Adding a single criterion "getting out of the bed at night" improved the sensitivity of these criteria^[14].

Modified New York Criteria (mNY) for AS integrated features of the Calin's criteria made the definition of back pain in patients with AS: low back pain and stiffness more than 3 mo, improving with exercise but is not relieved by rest^[16]. Various combinations of IBP features were evaluated in 101 patients with AS and 112 patients with mechanical low back pain by Rudwaleit *et al*^[11]. Clinical features of back pain were: (1) morning stiffness > 30 min; (2) age of onset; (3) no improvement by rest; (4) awakening because of the pain in the second half of the night only; (5) alternating buttock pain; and (6) duration

Table 2 Modified New York criteria for ankylosing spondylitis^[16]

Low back pain for at least 3 mo duration improved by exercise and not relieved by rest
Limitation of lumbar spine motion in sagittal and frontal planes
Chest expansion decreased relative to normal values for age and sex
Unilateral sacroiliitis grade 3–4
Bilateral sacroiliitis grade 2–4
Definite ankylosing spondylitis if (4a or 4b) and any clinical criterion (1–3)

of back pain. None of the single parameters differentiated AS from MLBP. Based on a good balance between sensitivity, specificity and feasibility the Berlin criteria were proposed with 70% sensitivity and 81% specificity (Table 1).

In 2009, thirteen internationally well-known rheumatologists, considered as experts in AS/SpA and members of ASAS, participated in the development of new classification criteria for IBP. They presented new ASAS IBP criteria without major differences from formerly established IBP criteria (Table 1). ASAS IBP criteria have 77.0% sensitivity and 91.7% specificity when at least four out of five parameters are present. Calin criteria had a higher sensitivity but a lower specificity. Berlin criteria had a lower sensitivity and a higher specificity with respect to newly developed criteria^[12]. Mnemonic for ASAS IBP criteria (iPAIN: Inflammatory PAIN) has been recently published^[17] (Table 1).

Imaging

Imaging of the sacroiliac joints and the spine has an important role in the diagnosis, classification and monitoring for patients with SpA. Sacroiliitis on conventional radiography became an important diagnosis in AS and was given an outstanding role in the development of classification criteria in 1961 and mNY criteria in 1984 (Table 2). Usually bilateral grade ≥ 2 or unilateral grade ≥ 3 sacroiliitis are considered critical for the diagnosis of AS^[16]. However, radiographic sacroiliitis reflects structural changes which may appear late in the disease process at least in a subset of patients^[18]. Thus, it has low specificity especially for patients at the early stages of the disease.

Magnetic resonance imaging can visualize active inflammation at sacroiliac joints and spine in established or in early pre-radiological axial disease, regardless of disease stage^[19]. The mNY, ESSG criteria and the Amor criteria do not contain MRI as an imaging tool. Actually, MRI of the sacroiliac joints was defined however it was not well established or standardized, when these criteria were developed.

ASAS classification criteria for axial SpA have imaging and clinical arms. The imaging arm includes either sacroiliitis on conventional radiography or sacroiliitis on MRI, which is highly important for recognition of pre-radiographic changes in early SpA^[4].

Regarding spondylitis, which may also occur before sacroiliitis, a definition of a “positive MRI” for the spinal inflammation is also needed^[20]. However, there is insufficient data for the use of spinal MRI and little is yet known about the specificity of spinal features in the axial SpA^[21].

Active inflammatory lesions such as bone marrow edema/osteitis, synovitis, enthesitis and capsulitis associated with SpA can be detected by MRI. Also structural damage such as sclerosis, erosions, fat deposition and ankylosis can be detected by MRI. ASAS/OMERACT imaging group defined minimum amount of bone marrow edema (one lesion at least two adjacent slices or more than one lesion at least one slice) which is required for the definitive diagnosis sacroiliitis^[22]. Figure 1A–D represents a normal radiograph of the pelvis and early changes on sacroiliac MRI of a male patient at the early stages of the disease (pre-radiographic stage). Figure 2A–C represents inflammatory changes and structural damage on spinal MRI.

HLA B-27

HLA B-27 positivity is extremely relevant to the early diagnosis of SpA. Five to 10% of the population are HLA B-27 positive and in patients with AS and SpA the positivity of HLA B-27 changes to 70% to 95% and nearly 70%, respectively^[23].

SPECTRUM OF SPONDYLOARTHROPATHIES

Ankylosing spondylitis

Ankylosing spondylitis is the most common and most typical form of SpA. It is two to three times more common in men than women. Ankylosing spondylitis usually begins with back pain and stiffness at a young age but various presentations, such as peripheral arthritis and enthesopathy may antedate back symptoms in some patients. Late onset after the age of 45 is uncommon in AS however some patients may reasonably be diagnosed late. Inflammatory low back pain is one of the presenting features but not solely specific to AS. History of uveitis, positive family history for AS, impaired spinal mobility or chest expansion supports the diagnosis^[1].

Axial involvement is one of the characteristics of the disease and 90% of patients have radiographic sacroiliitis during the course of the disease. The first classification criteria for AS were proposed in 1963 at the European Congress of Rheumatology in Rome, based on the clinical experience of rheumatologists. Later in 1966, thoracic pain and uveitis were removed from the criteria set because of low specificity and low sensitivity. This preceded the framework of New York criteria which was modified in 1984 by using inflammatory back pain components reported by Calin *et al.*^[13]. A patient can be classified as having definite AS if at least one clinical criterion (IBP, limitation of lumbar spine or limitation of chest expansion) plus radiologic criterion (bilaterally grade 2 or unilateral

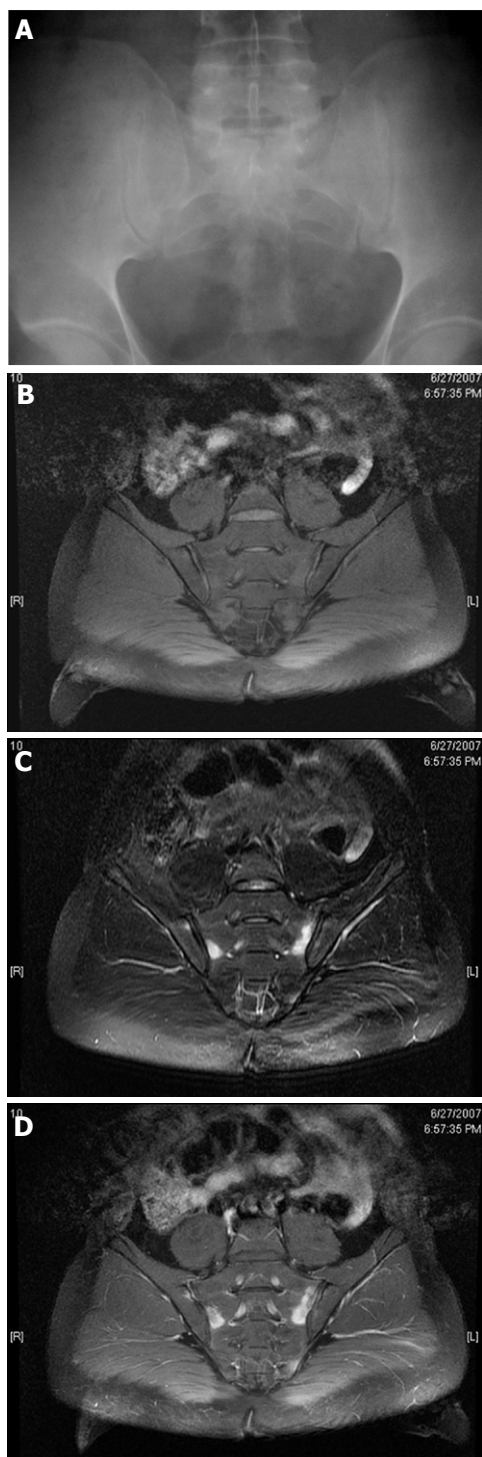


Figure 1 Normal radiograph of the pelvis and early changes on sacroiliac magnetic resonance imaging of a male patient at the early stages of the disease at the pre-radiographic stage. A: Thirty-five year old male, normal anterior posterior pelvis radiograph; B: T1-weighted Fast Spin Echo semi-oblique coronal scans of the sacroiliac joints; C: T2-weighted fat suppressed images shows bone edema at both sacral and iliac bones; D: T1-weighted post-contrast image shows enhancement of the contrast media revealing acute inflammation.

grade 3-4 sacroiliitis) are fulfilled^[16]. These classification criteria are inevitably used for the diagnosis of AS by most clinicians (Table 2).

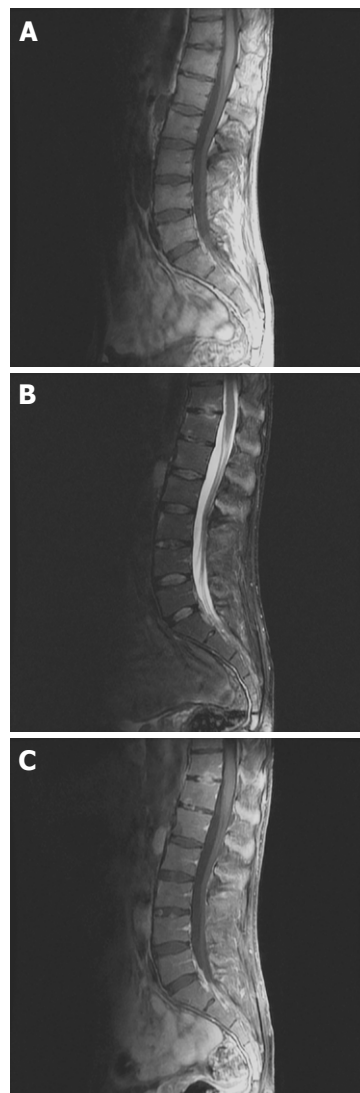


Figure 2 Inflammatory changes and structural damage on spinal magnetic resonance imaging. A: T1-weighted fast spin echo sagittal magnetic resonance scan of the lumbar spine shows hypointense lesion on end plates of thoracic 11 and 12 vertebrae; B: T2-weighted fat suppressed sagittal image shows hyperintense signals at the lesion and also at the upper anterior of the L3 and lower anterior of the L2 vertebra; C: T1-weighted post-contrast images shows enhancement of the contrast media at the borders of the lesion revealing acute spondylodiscitis.

All these criteria included presence of spinal/thoracic pain, restriction of spinal mobility and radiological sacroiliitis. Restriction of spinal mobility and radiological sacroiliitis may reflect structural damage and spinal/thoracic pain may reflect active inflammation and structural damage as well. It is obvious that these criteria do not perform well in patients with early/pre-radiographic phase of AS.

Axial spondyloarthritis

As mentioned above, sacroiliitis on plain radiographs takes years from the onset IBP and the symptoms of IBP alone are not diagnostic in many patients.

Berlin criteria were developed to assist physicians for early diagnosis of SpA. In this criterion set, the clinical

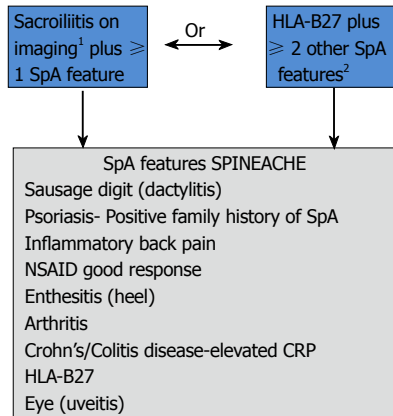


Figure 3 Assessment in SpondyloArthritis international Society classification criteria for axial spondyloarthritis and mnemonic for assessment of spondyloarthritis international society classification criteria^[4,17]. ¹Sacroiliitis on imaging active (acute) inflammation on magnetic resonance imaging highly suggestive of sacroiliitis associated with SpA or definitive radiographic sacroiliitis according to modified New York criteria; ²Elevated CRP is considered a SpA feature in the context of chronic back pain. SpA: Spondyloarthropathies; CRP: C-reactive protein; NSAID: Nonsteroidal antiinflammatory drugs; HLA: Human leukocyte antigen.

cal, laboratory (HLA B-27) and imaging (MRI of sacroiliac joints) features were included. The diagnosis of recent-onset axial SpA (pre-radiographic SpA) can be established in patients who have clinical features without radiographic changes but sacroiliitis on MRI. This study also analyzed the role of MRI as a diagnostic tool^[24]. The performance of Berlin criteria has been tested and showed that the diagnostic capacity in patients with axial undifferentiated SpA in the Chinese population was similar to ESSG and Amor criteria^[25].

In 2004, ASAS decided to improve current SpA criteria particularly to apply to patients in the early disease stages. It was proposed that SpA patients with predominantly axial symptoms but without radiographic sacroiliitis could be considered as patients with pre-radiographic phase of AS. The need for an early diagnosis in all patients with AS and axial SpA is put forward^[26].

In 2009, ASAS developed two candidate criteria sets for classification of axial SpA that include patients without definite radiographic sacroiliitis^[27]. The candidate sets were tested in the entire cohort of 649 patients from 25 centers in 16 countries. The new criteria consisted of a 'clinical arm' and 'imaging arm' (Figure 3). The entire set had 82.9% sensitivity and 84.4% specificity and for the 'imaging arm' alone sensitivity was 66.2% and specificity was 97.3%. The specificity of the new criteria was much better than ESSG criteria modified by adding MRI and slightly better than Amor criteria modified by adding MRI^[27]. The sensitivity is almost the same for the three criteria set. ASAS criteria are quite simple and easily applicable in daily clinical practice and a mnemonic is proposed to facilitate its use^[17] (Figure 3).

Peripheral spondyloarthritis

After the development of ASAS criteria for axial SpA,

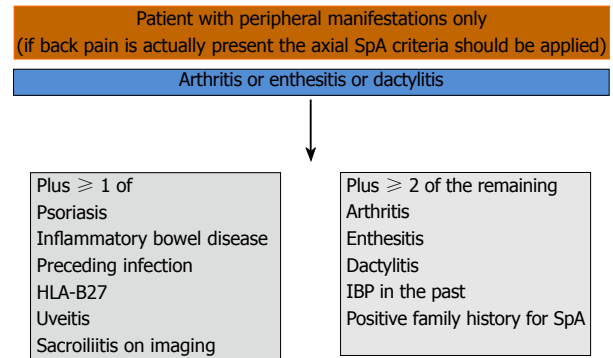


Figure 4 Assessment in spondyloarthritis international society classification criteria for peripheral spondyloarthritis or spondyloarthritis in general^[6]. SpA: Spondyloarthropathies; IBP: Inflammatory back pain; HLA: Human leukocyte antigen.

ASAS experts developed criteria for patients with SpA with predominant peripheral manifestations and compared these with ESSG and Amor criteria which were generated for the entire SpA group including peripheral SpA^[5]. Patients with peripheral manifestations including peripheral arthritis, dactylitis and enthesitis and without back pain were included. The sensitivity of the criteria was 77.8% and the specificity was 82.2% (Figure 4). The new ASAS classification criteria for peripheral arthritis would seem to perform better than ESSG and Amor criteria.

Spondyloarthritis in general

Spondyloarthropathies were formally classified in Amor criteria in 1990. Amor's criteria are a list of signs based on a scoring system of laboratory, radiologic and clinical features and do not require an entry criterion^[28]. The signs in the criteria contribute 1 point, 2 points or 3 points; a score of 6 or more classifies a patient as having SpA. Although sacroiliitis is not mandatory for the diagnosis of SpA, it had the highest score (3 points) and is considered to be very specific for SpA (Table 3).

ESSG criteria were proposed in 1991. In ESSG criteria IBP and/or peripheral arthritis are required as entry criteria. Patients with at least one entry criterion and one minor criterion are classified as having SpA^[29] (Figure 5). The aim of ESSG criteria is to include undifferentiated SpA which was not been proposed in Amor criteria. Both of these criteria were considered to be helpful for the diagnosis of SpA and had a broader definition of the spectrum however, they have low sensitivity particularly for the early diagnosis of SpA. For example, some of the leading symptoms like uveitis may be omitted by ESSG criteria but captured by Amor criteria.

Both sets of criteria were evaluated in a multicenter cross-sectional study including 124 patients with SpA and 1964 controls. Overall performance of both sets was similar and the performance was better in patients with a definite diagnosis^[30]. These criteria were evaluated for a Turkish population in 157 patients with SpA and in 127 patients with various rheumatic diseases. Results showed that both criteria had a similar value for classification of

Table 3 Amor criteria for the classification of spondyloarthropathies^[28]

Amor criteria	
Clinical symptoms or history of scoring	Points
Lumbar or dorsal pain at night or morning stiffness of lumbar or dorsal pain	1
Asymmetrical oligoarthritis	2
Buttock pain	1
If alternate buttock pain	2
Sausage like toe or digit	2
Heel pain or other well-defined enthesopathy	2
Iritis	1
Nongonococcal urethritis or cervicitis within 1 mo before the onset of arthritis	1
Acute diarrhea within one month before the 1 mo onset of arthritis	1
Psoriasis, balanitis, or inflammatory bowel disease (ulcerative colitis or Crohn's disease)	2
Radiological findings	
Sacroiliitis (bilateral grade 2 or unilateral grade 3)	3
Genetic background	
Presence of HLA-B27 and/or family history of ankylosing spondylitis, reactive arthritis, uveitis, psoriasis, or inflammatory bowel disease	2
Response to treatment	
Clear-cut improvement within 48 h after NSAIDs intake or rapid relapse of the pain after their discontinuation	2
A patient is considered as suffering from a podyloarthropathy if the sum is ≥ 6	

NSAID: Nonsteroidal anti-inflammatory drug; HLA: Human leukocyte antigen.

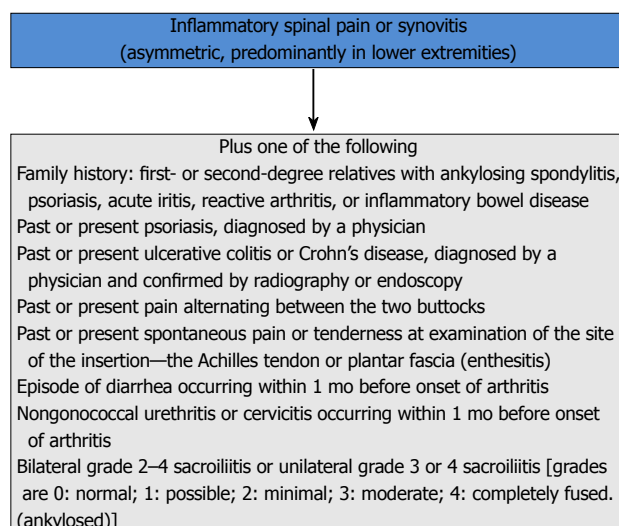
SpA and were comparable in terms of specificity and sensitivity^[31].

In a newly published study, performance of ESSG criteria, ASAS criteria and mNY criteria were compared in patients with SpA. The ASAS criteria had the highest sensitivity compared to ESSG criteria and mNY criteria 98.4%, 83.6% and 71.9%, respectively^[32]. In other studies of different ethnicities, lower sensitivity for mNY but similar sensitivity for ESSG was reported^[33-35].

Recently, the French Society of Rheumatology presented the DESIR cohort. Patients were recruited if they had IBP more than 3 mo and less than 3 years. A total of 708 patients were recruited and the mNY criteria, Amor criteria, ESSG criteria and axial ASAS criteria were fulfilled by 26%, 77%, 76% and 67% at entry, respectively^[36].

The diagnostic accuracy of the ESSG criteria, Amor criteria and the combination of them was analyzed in 24 patients who were misdiagnosed as SpA. The ratio of the misdiagnosed patients who fulfilled ESSG criteria, Amor criteria and combination were 45.8%, 16.7%, 16.7%, respectively. This study suggests that ESSG criteria may not be absolutely secure for the diagnosis of SpA^[37].

Performance of mNY criteria, ESSG criteria, Amor criteria and Berlin criteria in patients with IBP of a maximum of 2 years duration was evaluated. Fourteen of the 68 patients had AS according to mNY and all fulfilled three of SpA criteria sets. The highest classification rate

**Figure 5** European Spondyloarthropathy Study Group Criteria for the classification of spondyloarthropathies^[29].

was found with the ESSG criteria (84%), followed by the Amor criteria (71%) and the Berlin criteria (65%). The ESSG criteria were the most sensitive and the mNY criteria for AS appeared to be most specific sets of criteria^[38].

Psoriatic arthritis

Psoriatic arthritis (PsA) is defined as an inflammatory arthritis associated with cutaneous psoriasis. Patients may have peripheral arthritis (oligoarthritis or polyarthritis), enthesitis, dactylitis or sacroiliitis/spondylitis^[39]. At the beginning of the century PsA was thought to coincidentally occur with rheumatoid arthritis (RA) and psoriasis. Psoriatic arthritis was adopted as a distinct disease for the first time in 1964. The distinction between RA and PsA was made based on the clinical and radiological features^[40].

In 1973 Moll and Wright^[41] reported a proposal for the classification of PsA. When a patient with psoriasis has inflammatory arthritis and is negative for rheumatoid factor (RF) PsA can be classified in five distinct clinical subsets as: (1) oligoarticular asymmetric arthritis (< 5 tender and swollen joints); (2) polyarticular arthritis; (3) distal interphalangeal joint predominant; (4) spondylitis predominant; and (5) arthritis mutilans predominant.

Over the passing years minor modifications have been made on these criteria. Gladman *et al.*^[42] suggested that there is no need to insist on seronegativity for RF, since it can be positive in healthy subjects and in their series, 12% of cases were RF (+) even when the patients who had a characteristic sign of RA, like rheumatoid nodules and extra-articular manifestations were excluded. It is also possible to differentiate seronegative RA from PsA by using other antibodies, anti-cyclic citrullinated peptide which has much higher specificity than RF for the diagnosis of RA.

Psoriasis is a common disease affecting nearly 1%-2% of the population. In some forms of arthritis coincidental psoriasis may also occur. Psoriasis may precede, si-

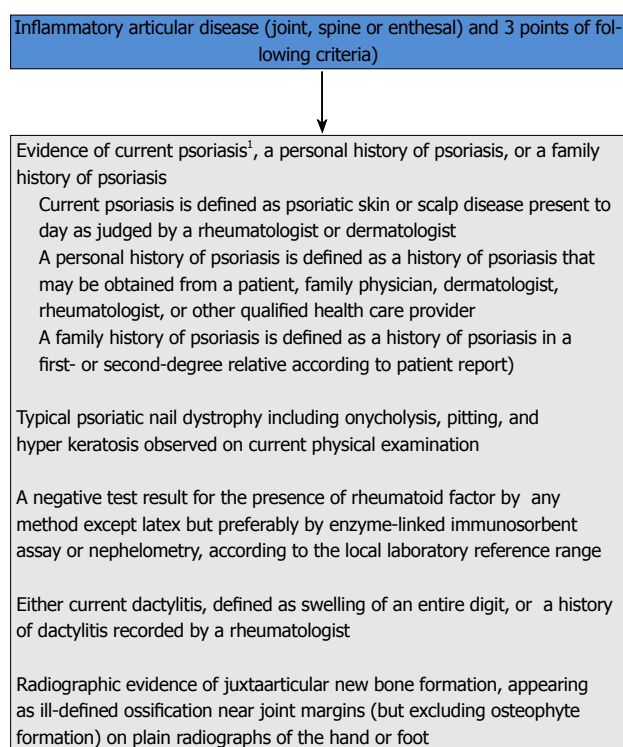


Figure 6 Classification of psoriatic arthritis study group criteria for the classification of psoriatic arthritis^[46]. ¹Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

multaneously occur or appear many years after the onset of arthritis. In latter cases patients may be misdiagnosed with other types of arthritis like seronegative RA or reactive arthritis; however, positive family history for psoriasis may be helpful in these cases. Patients with arthritis should be carefully examined for existence of “hidden” psoriatic lesions which may be located under the breasts, around the umbilicus or anus, over the hairline, nasal cleft or nails^[41].

Patients with PsA tend to have inflammatory axial involvement similar to AS. There are several differences from the classical AS^[41]: (1) asymmetrical sacroiliitis; (2) non-marginal syndesmophytes; (3) asymmetrical syndesmophytes; and (4) more frequent involvement of the cervical spine.

Bennett thought that Moll and Wright criteria tend to over diagnosing PsA and suggested new criteria in 1979. In these new set of criteria, clinical and radiological features were combined with synovial fluid analysis and histology. These criteria have not been widely used in prospective studies since synovial fluid analysis and histology are not practical. Psoriatic skin or nail involvement plus either peripheral joint or axial disease were required^[41]. Simplification of Bennett’s criteria has been made by Vasey and Espinoza^[42].

ESSG criteria were also valid for PsA. For the first time skin or nail involvement was not mandatory in these criteria. Cases in which arthritis precedes psoriasis are well recognized and family history of psoriasis can help

the diagnosis^[29].

A definition of PsA based on enthesopathy has been proposed by McGonagle *et al*^[43]. There is a significant problem with these criteria because of MRI requirements. It is not practical to use MRI in epidemiological research. MRI appearance shows both features of enthesopathy and synovitis and so the discrimination capacity would be markedly attenuated in established disease. Fournie *et al*^[44] proposed criteria from actual patient data to diagnose PsA which requires a score of 11 points for diagnosis.

There are few studies that compare different criteria for the diagnosis of PsA. A study which compared performance of the criteria revealed that the sensitivity of Vasey and Espinoza, McGonagle and Gladman were 99% whereas Bennett and ESSG criteria were significantly less sensitive. The specificity of the criteria was as high as 93% and 99%, and there were no statistically significant difference between criteria. Fournie criteria were the most difficult to use and Vasey and Espinoza, and Moll and Wright were the easiest. Vasey and Espinoza, Gladman or McGonagle are the most accurate and feasible in distinguishing RA from PsA^[45].

The classification of psoriatic arthritis (CASPAR) study group is an international group of investigators, all of whom have records of research in PsA. They proposed new data-driven classification criteria for PsA and collected prospective clinical and radiological data of 588 patients with PsA and 536 patients with other inflammatory arthritis, at least half of them with RA (Figure 6). The performance of the new criteria were also compared to other existing data^[46]. The sensitivity and specificity of the CASPAR criteria in the original study were 91.4% and 98.7%, respectively. These criteria were more specific but less sensitive than Vasey and Espinoza criteria.

The main limitation of the CASPAR criteria is the applicability to recent-onset disease. Very high sensitivity of CASPAR criteria in early and late PsA was also demonstrated in a study^[47]. This study analyzed patients referred to a special tertiary referral clinic and did not have a control population. It seems likely that only patients with secure clinical diagnoses are referred and enrolled into this clinic, possibly leading to an overestimation of the sensitivity of the criteria^[48].

Family history of psoriasis is the advantage of CASPAR criteria over Vasey and Espinoza as well as Moll and Wright criteria. It is also possible to make a diagnosis of PsA for patients who are RF positive and have polyarticular symmetric arthritis. The CASPAR, as a simple and user-friendly criteria set, has high potential to be introduced as the universal classification criteria for PsA^[42].

CONCLUSION

Chronic low back pain is a common and important problem and patients with this disorder are seen by a variety of specialists including rheumatologists, orthopedic surgeons, physiatrists, family physicians etc. Inflammatory

low back pain is usually the leading symptom of spondyloarthropathies and physicians should always be aware. For a correct diagnosis IBP should be differentiated from mechanical back pain. A detailed screening of signs and symptoms in terms of insidious onset, morning stiffness, pain at night, improvement with exercise and favorable response to NSAIDs may ease the discrimination. Other common features of SpA like dactylitis, enthesitis, arthritis and history of preceding infections should also be checked. Imaging has an important role in the early diagnosis of SpA and the very early phase of sacroiliitis or spondylitis could be detected by documenting active inflammatory lesions like bone marrow edema, enthesitis, capsulitis or synovitis on MRI. HLA B-27 positivity is extremely relevant to the early diagnosis of SpA.

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Stochastic resonance whole body vibration reduces musculoskeletal pain: A randomized controlled trial

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Abstract

AIM: To examined the effects of stochastic resonance whole-body vibration training on musculoskeletal pain in young healthy individuals.

METHODS: Participants were 43 undergraduate students of a Swiss University. The study was designed as a randomized controlled trial (RCT) with randomized group allocation. The RCT consisted of two groups each given 12 training sessions during four weeks with either 5 Hz- Training frequency (training condition) or 1.5 Hz Training frequency (control condition). Outcome was current musculoskeletal pain assessed in the evening on each day during the four week training period.

RESULTS: Multilevel regression analysis showed musculoskeletal pain was significantly decreased in the training condition whereas there was no change in the

control condition ($B = -0.023$, $SE = 0.010$, $P = 0.021$). Decrease in current musculoskeletal pain over four weeks was linear.

CONCLUSION: Stochastic resonance whole-body vibration reduced musculoskeletal pain in young healthy individuals. Stochastic resonance vibration and not any other exercise component within training caused pain reduction.

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Key words: Randomized controlled trial; Musculoskeletal pain; Training study; Stochastic vibration

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INTRODUCTION

Stochastic resonance training (SR-WBV) is a form of whole-body vibration training with randomized vibration. Because the vibration is stochastic, the direction and the force-time behaviour of the vibrations is not foreseeable and the body will be constantly challenged to adapt the muscle reactions to regain balance^[1-3]. SR-WBV seems to provoke an interaction of different types of sensors and the adjustment of afferent and efferent signals, possibly acting as "training" for the sensorimotor system, even more so than other conventional sinusoidal vibration^[4].

A strength increase is mainly attributed to neural adaptation, leading to improved inter- and intramuscular coordination that allows to more fully activate prime movers in specific movements and to better coordinate the activation of all relevant muscles^[5]. A low injury-risk and the only rare appearance of side-effects make whole body vibration training an interesting preventive intervention^[6]. Until today there is first evidence that SR-WBV can have positive effects on pelvic floor muscle strength^[4] and musculoskeletal pain in metal manufacturing workers^[7]. There is, however still a specific lack of high quality studies in healthy volunteers with randomized allocation of participants to an effective training group and a control group that similar except that the training frequency is so low that no effect can be expected. As Pang^[6] put it in his recent review on WBV effects an important problem until now is that “It is unclear whether the reported benefits are related to the exercise itself or the addition of vibration during exercise”. The present study is a randomized trial with training and control conditions that differ only in frequency of training frequency and participants who are blinded with respect to conditions fulfilling high qualitative methodological standard on randomized controlled trial (RCT)^[8].

In most studies on SR-WBV, the control group does no training at all (waiting group), or does an alternative training that is rather different. As a consequence, the results are not clear with respect to specific effects of SR-WBV: In waiting control groups positive training effects might simply reflect the unspecific effect “of doing something” instead of “doing nothing” and in studies that include an alternative training SR-WBV not only differs stochastic vibration principle but in many other aspects (frequency, posture, *etc.*). Consequently the unique advantage of stochastic vibration is unclear unless control groups differ in frequency only. Hence, a control group should include such a low training frequency that participants are still blinded with respect to their condition (i.e., they still think to take part in an useful training group) while the frequency is certainly ineffective. In this study, the frequency of vibration was 1.5 Hz, resulting in floor plates that move with lowest frequency that is possible aside standing still and is precluded to have a training effect that is specifically caused by stochastic vibration. Instead, a potential training effect of the 1.5 Hz training must rely on effort in posture control. The frequency of 5 Hz was chosen for the “functional” 5 Hz training group as the lowest stochastic vibration frequency reported to be effective^[9]. Thus, the present study compares a four-week stochastic resonance training in a “functional” 5 Hz training group to a “nonfunctional” 1.5 Hz control group.

MATERIALS AND METHODS

Ethics

All participants gave their informed consent prior to their inclusion in the study. The study was performed in consensus with all requirement defined by the Swiss Society

of Psychology. The study was conducted with the understanding and the consent of the human subject. The Ethical Committee of the responsible University faculty has approved the study.

Subjects

Forty-three undergraduate students volunteered to participate (30 female and 13 male psychology majors, mean age = 23.8 years, SD = 2.8 years). Inclusion criterion was experience of musculoskeletal pain in last four weeks. Exclusion criteria for participation were: acute, past or chronic arthropathologies, troubles in the cardiovascular system, psychopathology, spondylolysis, spondylolisthesis, tumors, disc prolapse with neurological failure, rheumatism, articular gout, osteoporosis, activated arthritis with inflammatory signs, stage 4 arthritis, fever, cold etc. No interested participant had to be excluded from the study.

SR-WBV

Study took place at University facility in November 2010. During four weeks, participants trained three times a week, on Monday till Friday. A special device was used for the SR-WBV (©Zeptor med plus Noise, FreiSwiss AG, Zurich, Switzerland). Its main features are two independently and one-dimensional (up/down) stochastically oscillating footboards, with two passive degrees of freedom (forward/backward, right/left).

All exercising sessions were supervised and the participants were advised on adequate posture. Participants were instructed to stand in an upright position on the footboards with arms hanging loose to the side and slightly bent knees and hip. Vibration frequency was fixed previously according to the training condition. A session consisted of three sets of vibration, lasting one minute each, with a one-minute break in between. Three such sessions per week were planned for each participant. This setting was based on empirical experience and practical application more than on scientific evidence, because the training parameters of SR-WBV show a wide range of application that are not as well known as they are in strength or endurance training^[9]. The conducted 60-second interventions and 60-second rest periods and 5 Hz frequency training condition was used as the minimum effective vibratory stimulation loading parameter while the 1.5 Hz frequency condition can be expected to have no training effect^[9]. Participants were blind with respect to their training frequency condition. All displays of Zeptor who showed the frequency were covered during training. The investigator did the setting of frequency before the training sessions while another person who was blind to training conditions welcomed, introduced, and instructed the participants.

Daily pain assessment

Pain was rated in the evening of each day during the four week training period. The questionnaire thus had one page per day for seven days, including Saturdays and Sundays. The item for current musculoskeletal pain was

Table 1 Prediction of daily pain in multilevel analysis

Predictor variables	Parameter estimate	SE	P value
Level 2 (Individual)			
Sex (0=F, 1=M)	-0.378	0.395	0.342
Age	-0.012	0.056	0.832
BMI	0.016	0.084	0.849
SR-WBV (5 Hz = 1, 1.5 Hz = 0)	0.558	0.365	0.126
Level 1 (day)			
Training today? (1 = yes, 0 = 0)	0.083	0.085	0.327
Day of training period (1-28)	-0.004	0.007	0.569
Day of training period X SR-WBV	-0.023	0.010	0.021
Intercept	2.567	0.258	
Variance level 2	0.952	0.221	
Variance level 1	2.074	0.086	

$n = 1204$ daily pain ratings reported by 43 participants during 28 d. Parameter estimate is the fixed parameter estimate of unstandardized regression coefficients. SE is the standard error in unstandardized regression coefficients estimation; Significance levels were calculated by t -values (Parameter Estimate/SE) with $j-p-1$ degrees of freedom, where j is the number of units on level 2 and p is the number of explanatory variables^[12]. SE: Standard error; BMI: Body mass index; SR-WBV: Stochastic resonance whole-body vibration training

phrased according to the chronic pain grade questionnaire^[10] with adjustments for the time scope in daily measurement. The current pain measurement was introduced by: "Throughout the day, how do you rate your pain in muscles and joints (back pain, shoulder and neck pain, pain in leg muscles *etc.*)?". The pain item included a ten-point numerical rating scale (1 = no pain to 10 = strongest imaginable pain), which shows good sensibility and responsiveness to change, is easy to administer, shows high compliance and good correlations with other pain assessment instruments^[11].

Statistical analysis

Data was analyzed with longitudinal multilevel analysis^[12] using the MLwiN software package version 2.10^[13]. The level of significance was $P < 0.05$ (two tailed). Dependent variable was musculoskeletal pain, with daily pain reports (level 1) nested within persons (level 2). Training period ranged from training day 1 to 28 [last day of training period). A dummy variable represented the intervention (5 Hz SR-WBV (Verum:1) *vs* 1.5 Hz SR-WBV (Sham:0)).

Because differences between participants, as well as within participants over time in outcomes were expected, the intercept was conceptualized as random effect on both levels. Since overall effect of SR-WBV and mean rate of change was of primary interest in the present study (each day), time, training effect and training effect over time as predictors were all set as fixed effects. Hence, the regression model assumed the reduction of musculoskeletal pain over time and in dependence of training therefore to be equal for all participants, i.e., no variation in individual regression slopes was postulated.

The general model used to test the preventive effects of SR-WBV on musculoskeletal pain contained only these three variables. It is represented by the following equation: $\text{pain}_{ij} = \beta_{0ij}\text{constant} + \beta_{1ij}\text{day of training period} + \beta_{2ij}\text{SR-WBV verum } \text{vs} \text{ sham condition} + \beta_{3ij}\text{SR-WBV condition X day of training period}$

$$\beta_{0ij} = \beta_0 + u_{0j} + e_{0ij}$$

Subscript i indicates the level 1 (time) variable and j indicates the level 2 (person) variable.

RESULTS

Before the training study started, participants reported musculoskeletal pain (yes/no) in the last four weeks. Back pain (30.2%) and neck pain (27.9%) were most prevalent, followed by pain in the knee (25.6), shoulder and arm (14%), ankle and foot (11.6%), and pain in the hip (9.3%). However, only 3 participants reported a medical consultation in last four weeks, two participants because of pain in shoulders and one participant because of pain in the knee. The 43 participants were randomly picked from a list and a number between 1 and 43 was assigned to them. Using a software random sequence generator (random.org[©])^[14] the numbers were randomly assigned to study groups. The resulting groups of 21 and 22 participants did not differ significantly in reported musculoskeletal pain in four weeks before SR-WBV started, current musculoskeletal pain at first training day, age, and sex composition.

The overall level of daily musculoskeletal pain during four weeks of SR-WBV was low ($M = 2.54$, $SD = 1.76$). Zero order bivariate correlation showed no significant coefficient between pain and participant demographic characteristics of sex, age, or BMI. Furthermore, the training conditions were not significantly related to daily pain. There was, however a small but significant negative association between training day and pain ($r = -0.08$, $P = 0.009$) indicating less pain with training progress. In prediction of daily pain in multilevel analysis (Table 1), no significant overall training effect was observed, but a significant interaction between training condition and training day ($t = 2.30$, $P = 0.021$) that indicated the expected gradual pain decrease only in the 5 Hz training condition while pain in the 1.5 Hz training condition was unchanged during the four week training period (Figure 1).

DISCUSSION

Stochastic vibration training can be considered effective^[15] while the metabolic and cardiovascular strain is low^[16]. Evidence increases for positive effects in clinical samples^[17] and athletes^[18,19]. There are, however, few studies on other more representative populations^[15]. Moreover, studies often suffer from methodological flaws that include studies that use randomized allocation of participants to training conditions. In addition, studies often rely on control conditions that consist of waiting groups only, i.e., a vibration training is compared to "doing no training". If the control group includes another training

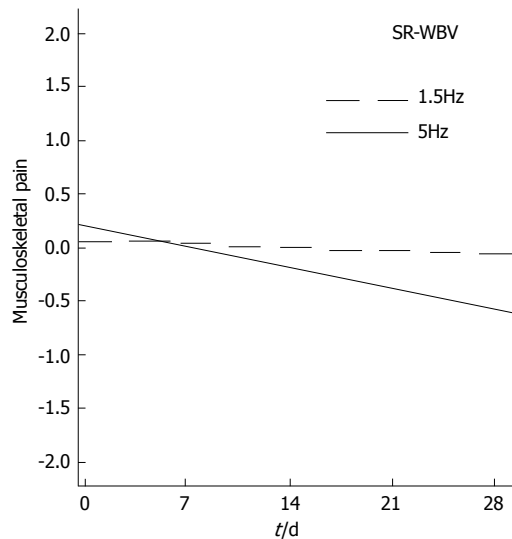


Figure 1 Effect of stochastic resonance whole-body vibration training condition on daily musculoskeletal pain. SR-WBV: stochastic resonance whole-body vibration training.

condition, the training often differs from SR-WBV in many ways, not only stochastic vibration frequency but postures efforts, *etc.* Beside the methodological problem of confounded effects, i.e. the problem to verify stochastic vibration as the only causing the effect and no other feature of SR-WBV that differs from the control training, another problem arises: Participants cannot be blinded in most SR-WBV trials that rely on waiting groups or other trainings, because they easily notice. Therefore, in order to increase the internal validity of RCT, this study includes a control group with “nonfunctional” sham SR-WBV to include the principle of blinding to participants. In this study, following the ACOEM criteria for methodical evaluation of RCTs^[8], participants were blinded with respect to training groups and the study therefore fulfilled a rarely reached qualitative point in evaluation of SR-WBV. The current study included training of healthy young participants without a back pain problem and found reduced musculoskeletal pain in the “functional” 5 Hz training condition but not in the “non-functional” control condition with 1.5 Hz SR-WBV. Noteworthy, the test of SR-WBV showed the difference in training effect using a low frequency of 5 Hz that already is on the lowest level of what training experts expect to be functional^[9]. Thus, SR-WBV was proven effective in a healthy young sample with lowest training effort that was considered potentially valuable before. SR-WBV is also potentially efficient considering the low effort of training (approx. 24 min a week).

The study sample consists of healthy young students. SR-WBV effects are potentially smaller in this sample compared to the overall population. Thus, findings should be replicated in a sample that is representative to the overall population. Further studies should address important research questions like the persistence of training effects.

To the knowledge of the authors, it was the first study examining SR-WBV in a healthy sample using a fully comparable control group including blinded participants. This study indicates that SR-WBV may help to reduce musculoskeletal pain even in healthy young adults. SR-WBV was shown to be a very economic exercise which requires very little effort in terms of infrastructure, time and effort from participants. Promoting SR-WBV might be a way to address people who are not susceptible to conventional exercise.

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COMMENTS

Background

Musculoskeletal pain is common and so far no randomized controlled trial (RCT) tested stochastic resonance whole-body vibration training (SR-WBV) as intervention in young individuals.

Research frontiers

There is need for research on short, economic, and effective training intervention. In this RCT author(s) showed a short SR-WBV to reduce musculoskeletal pain.

Innovations and breakthroughs

The RCT showed benefits were specifically related to frequency of stochastic resonance.

Applications

SR-WBV at work is a promising tool in prevention of occupational musculoskeletal problems.

Terminology

SR-WBV constantly challenges the neuromusculoskeletal coordination to adapt to unforeseeable change.

Peer reviews

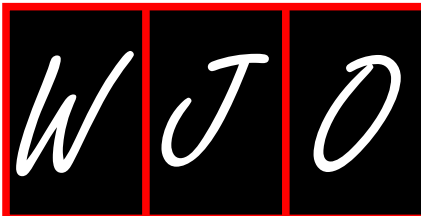
It is interesting and important. A solution of stochastic resonance whole-body vibration that reduces musculoskeletal pain in young healthy individuals is an important point in daily orthopedic practice.

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Events Calendar 2011

January 16-20, 2011
Combined 4th International
Conference of the Saudi Orthopaedic
Association & SICOT Trainee Day,
Abha, Saudi Arabia

January 24-27, 2011
7th Middle East Orthopaedics
Conference 2011, Dubai International
Convention Centre, Dubai,
Saudi Arabia

January 28-30, 2011
National Orthopedic Conference
2011, San Francisco, California,
United States

February 15-19, 2011
American Academy of Orthopaedic
Surgeons, San Diego, CA,
United States

February 16-20, 2011
2011 Annual Meeting of the American
Academy of Orthopaedic Surgeons,
San Diego, CA, United States

February 19, 2011
Pediatric Orthopaedic Society of
North America Specialty Day, San
Diego, CA, United States

March 09-11, 2011
Annual London Imperial Spine
Course, London, United Kingdom

March 21-25, 2011
31st Caribbean Orthopaedic
Meeting, Anse Marcel, Saint Martin

March 28-April 02, 2011
The Association of Children's
Prosthetic-Orthotic Clinics 2011
Annual Meeting, Park City, UT,
United States

April 01-04, 2011
Ain Shams 2nd Orthopaedic
intensive course (Orthopaedics from
A to Z), Cairo, Egypt

April 20-22, 2011
IMUKA 2011: Masterclass in
Arthroscopy and Related Surgery,
Maastricht, Netherlands

May 11-14, 2011
2011 POSNA Annual Meeting,
Montreal, Quebec, Canada

May 12-15, 2011
84th Annual Meeting of the
Japanese Orthopaedic Association,
Yokohama, Japan

May 15-19, 2011
8th Biennial ISAKOS Congress
(International Society of
Arthroscopy, Knee Surgery and
Orthopaedic Sports Medicine), Rio
de Janeiro, Brazil

May 25-28, 2011
16th Pan Arab Orthopedic
Association Congress & 27th
SOTCOT Congress, Tunis, Tunisia

June 01-04, 2011
12th EFORT Congress in cooperation
with the Danish Orthopaedic
Association (European Federation

of National Associations of
Orthopaedics and Traumatology),
Copenhagen, Denmark

June 08-12, 2011
2011 ABJS Annual Meeting
(Association of Bone and Joint
Surgeons), Dublin, Ireland

June 15-18, 2011
11th Annual Meeting of the
International Society for Computer
Assisted Orthopaedic Surgery,
London, United Kingdom

July 07-09, 2011
66th Annual Meeting of the
Canadian Orthopaedic Association,
St. John's, Newfoundland and
Labrador, Canada

July 13-16, 2011
18th International Meeting on
Advanced Spine Techniques,
Copenhagen, Denmark

July 22-24, 2011
Sri Sathya Sai International
Orthopaedic Conference- 2011
On Pelvis And Lower Extremity
Trauma", Sri Sathya Sai Institute
of Higher Medical Sciences,
Prasanthigram, Puttaparthi, Andhra
Pradesh, India

July 25-28, 2011
2011 Update in Orthopaedics, Grand
Wailea Hotel Resort & Spa, Wailea,
Maui, Hawaii, United States

September 06-09, 2011

SICOT 2011 XXV Triennial World
Congress, Prague, Czech Republic

September 13-16, 2011
BOA/IOA Combined
Meeting(British Orthopaedic
Association & Irish Orthopaedic
Association), Dublin, Ireland

September 14-17, 2011
23rd SECEC-ESSSE Congress
(European Society for Surgery of
the Shoulder and the Elbow), Lyon,
France

September 14-17, 2011
46th SRS Annual Meeting &
Course (Scoliosis Research Society),
Louisville, Kentucky, United States

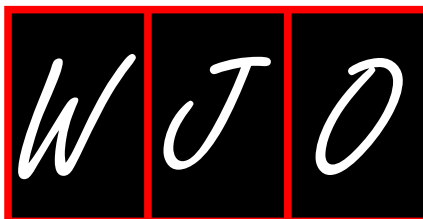
September 15-18, 2011
2011 World Congress on
Osteoarthritis, San Diego, California
92167, United States

September 21-23, 2011
HIP IMPROVEMENTS AND
PROCEEDINGS, Toulouse, France

October 25-28, 2011
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November 7-11, 2011
86ème Réunion Annuelle SOFCOT,
Paris, France

December 12-15, 2011
EOA 63rd Annual International
Conference, Cairo, Egypt



INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

World Journal of Orthopedics (World J Orthop, *WJO*, online ISSN 2218-5836, DOI: 10.5312) is a monthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 245 experts in orthopedics from 30 countries.

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Maximization of personal benefits

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. So, to realize these desired attributes of *WJO* and create a well-recognized journal, the following four types of personal benefits should be maximized. 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. (1) 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; (2) 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; (3) 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; and (4) 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. 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.

Aims and scope

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Columns

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In press

- 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

Organization as author

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

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- 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]

Volume with supplement

- 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]

Issue with no volume

- 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:10.1097/00003086-200208000-00026]

No volume or issue

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

Books

Personal author(s)

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

Conference proceedings

- 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

Conference paper

- 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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Write as mean \pm SD or mean \pm SE.

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Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *v* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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