International Society for Musculoskeletal Shockwave Therapy - ISMST

ISMST

Newsletter

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The ISMST and the ISMST-Newsletter (International Society for Shockwave Therapy) - An international platform for communication and knowledge transfer

Since the end of the 80's, musculoskeletal shockwave therapy has been researched in the field of orthopaedic traumatology, and administered to patients suffering from various sorts of ailments. So it was simply a matter of time before working groups and practitioners' meetings became registered associations and societies. By 1994, national organizations like the German Association for Musculoskeletal Shockwave Therapy (DGST), the Swiss Association for Orthopaedic Shockwave Therapy (SGST) and working groups within the German and Austrian Associations for Orthopaedic and Traumatology (AK 10 of the DGOOC and AK-ESWT of the ÖGO) had been established. Non-German-speaking organizations such as the National Association for ESWT in Italy (SITOD) likewise followed suit. This new technology spread with such explosive force and demonstrating such immense success that an international coordination and communication platform for these organizations soon proved necessary. To this end, the European Society for Shockwave Therapy (ESMST) was founded on 14 June 1997, during the German Orthopaedic Association (DGOT, today the DGOOC) Congress in Vienna, for the purpose of bringing together European researchers and practitioners. Representatives of the management and advisory boards were drawn from all the then existing national organizations.

Immense interest in the technology and the first of many promising publicized results gave impetus for the association to convene on a regular basis. A decision was made for an annual conference, to be held each time in a different country. To ESMST's delight, the personal efforts of its members from the various states helped make these meetings a reality and a success. The list of locations (table) where the association has since met reflects this worldwide resonance. With the ESWT expanding beyond the European border - and Japan, Taiwan and the US on the threshold of becoming active members, the association was renamed the International Society for Shockwave Therapy (ISMST) in London, 1999.

From the inception, the expressive aim was to gather in one place, if possible, all those who are interested in shockwave therapy, in order that the transfer of knowledge not be restricted to national societies and associations or practitioners' groups that specialized in individual devices. With additional applications of this highly successful therapy, the range of healthcare professionals and scientists broaden from accident surgery and orthopaedic to include those in veterinarian medicine, cardiology, sports medicine, dermatology and plastic surgery. The ISMST today has grown to 492 full members, and an additional 81 awaiting membership, from 55 countries (see list, as of 31.12.05).

Well attended from the start, the conferences are marked by lively discourses on the developments of shockwave therapy. While the initial focus of the conferences was on case reports and small serial presentations, the last years have been marked by the rise in scientific standard, exciting clinical trials and spectacular works in fundamental research. This has imbued the conferences with vital impetus and, in turn, greatly influenced research in ESWT clinically as well as animal models. The talks and debates within the congresses and outside the conference halls have powerfully driven developments.

Right from the get-go, the ISMST has sought contact with the industrial sector in order to set itself up as an information clearinghouse and intermediary between research and business. In particular, the continual presence of a platform for manufacturers of devices provides the opportunity for discussion and collaborative development of new technology. The agreement to standardize technical specifications regarding shockwave strengths, frequencies and forms allows for the scientific comparability of studies of various sorts. As all clinical studies must employ unified rules of biometrics, works on shockwave have likewise been standardized by the use of a uniform set of physical parameters.

The ISMST has been able to set up excellent contact to all the national associations - some of which were organized within the ISMST,

thereby facilitating the transfer of knowledge and scientific information as well as the presentation of local activities. The establishment of the ISMST in Vienna during the 1997 German Orthopaedic Congress is the apparent basis for the organization's closeness and intense collaboration with the German-speaking associations. One of the results of this is the cohosting of the 8th International Congress of the ISMST and 5th Joint Meeting of the German-Speaking Societies in Vienna. The collaborative effort with the DIGEST is especially to be highlighted, for example a DIGEST prize worth 3,000 was awarded to the best work done in the field. (Jan Dirk Rompe, Andrea Meurer, Bernhard Nafe, Alexander Hofmann, Ludger Gerdesmeyer: Repetitive low-energy shockwave application without local anesthesia is more efficient than repetitive low-energy shockwave application with local anaesthesia in the treatment of chronic plantar fasciitis).

The good rapport with our partner associations around the world is also affirmed by the activities of the ISMST members and executive members in national organizations. Several national conferences have benefited from the organization's assistance and scientific support (the SITOD Congress in Italy, workshops in Saudi-Arabia, the ONLAT Congress in Columbia, the SBTOC Congress and Training in Brazil, American Ass. of Equine Practitioners in the USA, Argentinean Orthopedic Congress, SFOCAL Congress in France, ASA in Canada). The ISMST has designed a educational and training program to teach and keep physicians around the world regularly up-to-date on the new technology and treatments. (Though financed by the industrial sector, the content matter is completely independent.) These training programs have so far taken place in Sao Paulo, Rio de Janeiro, Naples, Dallas, Monterey, Louisville, Shanghai, New York und Lisbon.

As a result of the development of ESWT in fields like cardiology and dermatology, contact to other disciplines have grown to include not only those that are interested in the musculoskeletal system, but also healthcare professionals who use ESWT to treat circulatory ailments or to stimulate poorly healing wounds to heal.

The exchange of information regarding the congress is also to be found online at www.ismst.com and the conference's website www.shockwavetherapy.org, along with certification and training guidelines and a regularly updated list of literature. The ISMST Newsletter, published since 2005 (available in paper version or to be downloaded from the website), offers up the latest developments in ESWT and fundamental, scientific works and studies.

The association is working towards an established position in information management and knowledge transfer in cardiology and wound healing. We very much hope that every participant at the conferences as well as other events will find this platform - through the association's multidisciplinarity, to be especially stimulating and informative.

In this development we are very happy to see this ISMST-Newsletter, now in the third edition, growing into an international accepted and highly regarded scientific publication.

In this context I will thank the founder and chief editor Paulo Roberto Dias dos Santos from Sao Paulo for his efforts and I wish many more ISMST Newsletters with highly standard scientific articles in the future.

Table: ISMST congresses and presidents:

Event	Year	Place	President	Congress organizer
Founding meeting	1997	Vienna, Austria	Heinz Kuderna	Wolfgang Schaden
1st ESMST Congress	1998	Izmir, Turkey	Heinz Kuderna	Veli Lök
2nd ESMST Congress	1999	London, GB	Heinz Kuderna	Richard Coombs
3rd ISMST Congress	2000	Naples, Italy	Enzio Corrado	Sergio Russo
4th ISMST Congress	2001	Berlin, Germany	Richard Thiele	Richard Thiele
5th ISMST Congress	2002	Winterthur, CH	John Ogden	Beat Dubs
6th ISMST Congress	2003	Orlando, USA	Beat Dubs	John Ogden
7th ISMST Congress	2004	Kaohsiung, ROC	Ching-Jen Wang	Ching-Jen Wang
8th ISMST Congress	2005	Vienna, Austria	Vinzenz Auersperg	Vinzenz Auersperg
9th ISMST Congress	2006	Rio d. J., Brazil	Ana Claudia Souza	Ana Claudia Souza
10th ISMST Congress	2007	Toronto , CN	Robert Gordon	Robert Gordon
11th ISMST Congress	2008	Antibes, France	Roland Hamisultane	R. Hamisultane

MEMBER NATIONS:
Algeria, Argentina, Australia, Austria, Belarus, Belgium, Brazil, Denmark, Cameroon, Canada, Chile, China, Columbia, Costa Rica, Czech Republic, Denmark, Egypt, France, Germany, Ghana, Greece, India, Israel, Iran, Italy, Japan, Jordan, South Korea, Luxembourg, Malaysia, Mexico, Nepal, Netherlands, New Zealand, Pakistan, Portugal, Puerto Rico, Republic of Macedonia, Republic of Slovakia, Saudi Arabia, Singapore, Slovakia, Slovenia, Spain, Switzerland, Taiwan, Thailand, Turkey, Ukraine, UAE, Venezuela, United Kingdom, USA, Venezuela

ESWT in "Bone Vascular Diseases": The Rationale for Treatment and the "Reset Theory"

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Sumary

Recent advances in Extracorporeal Shock Waves Therapy (ESWT) have evidenced the possibility to treat successfully some skeletal pathologies of different origins, but all characterized by bone marrow oedema and eventually osteonecrosis.

Until few years ago, for some of these pathologies, therapeutic options were uncertain and for some other ones the unique curative solution was surgical therapy.

On the basis of some clinical and experimental data from the literature, the authors outline the importance, not only to treat precociously all those skeletal diseases characterized by "bone vascular disturbances" and altered local bone turnover (in order to avoid a possible and irreversible worsening), but also discuss the rationale for considering ESWT a powerful not-pharmacologic tool to normalize local heightered bone metabolism ("Reset Theory"). From this point of view, ESWT seems to have also a potential value of therapeutical intervention before positive radiographs are obtained.

Rewiew

The presence of bone marrow oedema may be associated with a wide range of focal bony lesions, including malignant, benign, non-neoplastic causes and traumas as well.

We cannot consider bone marrow oedema as a distinct clinical entity, but, more likely, as a uniform pattern of reaction in bone and its vascular supply to various external or internal disturbances (1). According to some of the authors, the widely used term of bone marrow oedema should be replaced by "ill - defined signal intensity" or "oedema - like MR imaging abnormality" (2).

The causes of bone marrow oedema are mostly unknown, although probably of multifactorial and different origins; it has been recently established that, generally, as the volume of bone marrow oedema increases relative to the size of the underlying lesion, the probability that the underlying lesion is benign is increased (3).

Characteristically, bone marrow oedema can accompany many painful entesopathies and tendinopathies in sports medicine: in these pathologies, MR is the only imaging technique that allows direct evaluation of bone marrow edema, by using the fat suppressed T2-weighted or STIR images; moreover, the extent of bone marrow oedema can reflect the biomechanics of trauma (4) and be considered a typical manifestation of "overuse" (5).

Although the clinical significance and natural history of bone marrow oedema is still a matter of debite (4), due to the possibility to assess many of these musculoskeletal injuries by MR scans, this early overuse reaction needs to be raised, to allow preventive and therapeutic options to be considered to reduce the incidence of this stress response producing limb pain syndromes (6).

Moreover, bone oedema occurs in various forms of inflammatory and non-inflammatory arthritis and probably represents a cellular infiltrate within bone. It is common in early rheumatoid arthritis and is associated with erosive progression and poor functional outcome. Histopathological studies suggest that a cellular infiltrate comprising lymphocytes and osteoclasts may be detected in subchondral bone and could mediate the development of erosions from the marrow towards the joint surface. There is emerging evidence from animal models that such an infiltrate corresponds with MR bone oedema, pointing towards the bone marrow as a site for important pathology driving joint damage in rheumatoid arthritis (7).

According to some of the authors, if no persistent clinical response is achieved, these imaging methods may help to predict future erosiveness and help in clinical therapeutic decision making (8).

Recently, it has been recognized also the importance to detect bone marrow oedema in "bone stress injuries", that, for example, are rarely being diagnosed in patients with sensory neuropathy, most likely because they may be silent in terms of pain (diabetic patients). Load-related pain is considered a key feature of any "bone stress injury", a symptom, which may be partially or completely absent in subjects with sensory neuropathy (loss of protective sensation) (9).

In diabetic patients with polyneuropathy, symptoms of "bone stress injuries" of the foot are atypical, in that there is load-related swelling, rather than load-related pain. Immediate diagnosis, and treatment with off-loading, can lead to a restitutio ad integrum like in non-neuropathic patients. Delayed cessation of overuse, however, may cause irreversible joint and bone damage ("Charcot foot") (9).

In all these skeletal bone pathologies, characterized by bone marrow oedema at the MR scans, although of different origins and clinical settings, it seems to emerge the concept that precocious detection and earlier treatment may avoid worsening of the clinical pictures and irreversible modifications at the tissue level.

This concept of earlier detection and treatment of bone marrow oedema is even more important in many other bony diseases, that, although less common, if not promptly recognized and adequately treated, can produce persistent osteoarticular degeneration.

We refer to all skeletal pathologies, whose main characteristic is bone marrow oedema, namely: Bone Marrow Edema Syndrome of the Hip (BMESH) (also called transient osteoporosis or regional osteoporosis of the hip), other transient bone marrow oedema syndromes, regional migratory osteoporosis, shifting bone marrow oedema or some other ones, whose bone marrow oedema can be associated to osteonecrosis (as, for example, in true avascular osteonecrosis).

Bone Marrow Edema Syndrome of the Hip (BMESH) is a new, non - traumatic recently described syndrome, characterized by disabling joint pain. In general, it seems a self - limited disease, characterized by normal radiographs and typical BME pattern of the femoral head on MR scans, with complete spontaneous resolution within 3 - 9 months, (10)

There is significant confusion concerning the nomenclature and pathophysiology

of "BMESH": transient (regional) osteoporosis, migratory osteolysis, idiopathic or regional osteoporosis, algodistrophy (11). MR is the most sensitive and specific means of early diagnosis, due to the presence of an "inflammatory pattern" (dark in T1 and white in T2).

The existence of marrow oedema seems to be strongly associated with the occurence of pain (12, 13).

Etiology still remains unclear, although different pathological noxiae have been advocated: thromboemboli, impairement of venous return and local hyperemia (vasomotor disturbances), injuries to the vessel wall (vasculitis), altered lipid metabolism and subchondral fat embolism, decreased fibrynolisis (10) and abnormal activation of Regional Acceleratory Phenomenon (RAP) (14).

Today, multifactorial transient bone ischaemia is regarded to be the main etiological factor (10).

Angiographic studies evidenced that the nutrient arteries to the femoral head can be dilated and the femoral head perfusion increased, thus suggesting a role in vasomotor response for the pathogenesis of this clinical entity. From this point of view, BMESH might be considererd as a reversible process after temporary ischaemia of the femoral head. (13)

Bone biopsies taken from patients affected by BME, demonstrated that bone was alive (they showed no features of avascular osteonecrosis or

osteoporosis); most strickly changes were found at the marrow level (with accumulation of fluids, fat cell fragmentation and fibrovascular tissue); there were also seams of osteoid lined by osteoblasts, with irregular woven bone formation and mild inflammatory changes. All these features (BME, bone marrow necrosis and active repair) may be considered as expression of increased bone turnover, in an attempting to react to a pathological stimulus (perhaps hypoxia) (10, 11, 14). Moreover, an increase in interstitial fluid is an expression of bone marrow oedema, which, if uncorrected, may lead to necrosis with local collapse of bone (11).

We agree with some of the authors in the literature, that BMESH and related syndromes can represent not a distinct disease but eventually an early reversible subtype of non - traumatic osteonecrosis (ON) (15, 16).

BME can also accompany true ON, generally in the painful phases of the disease (at different joint districts) and oedematous changes are premonitory lesions of osteonecrosis in subchondral areas as well (**FIGURE 1**) (17, 18).

Fig. 1

BME has been recently recognized in fact to be an important pathogenetic and prognostic factor in degenerative osteoarticular diseases.

It has been described that a spectrum of changes occurs in the subchondral zone, seen with MR scans in patients with osteoarthritis (OA), as "bone marrow oedema pattern" (19, 20, 21), and that the first structural finding identified to have a correlation with pain seems to be right bone marrow oedema (18, 22).

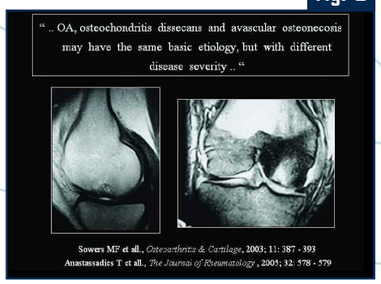
From the histological point of view, in degenerative joint diseases the subchondral region shows reactive enhanced vascularization and heightered local bone metabolism (23). In particular, angiogenesis and inflammation are closely integrated processes in OA and may affect disease progression and pain (24). Vasculature is accompanied by nerves, Substance P mediated, as identified in erosion channels and osteophytes: this offers evidence why articular remodelling is perceived painful; in particular, compressive forces and hypoxia have been postulated to stimulate these new nerves (24).

It is recognized, nowadays, the importance of hemodynamic factors in the development of OA: changes in hemodynamics (in combination or due to overloading) lead to changes in the physicochemical enviroment of the cells, by which subchondral bone formation and bone removal are controlled (21).

BME in degenerative osteoarticular diseases have been described to have spontaneous complete resolution in 0.5 % of the cases, while a percentage of 5 - 9.8 % decreasing and 18.8 - 40 % increasing exstension with time (25, 26). Resolution of pain generally coincides with the disappearance of bone marrow oedema (27) and subchondral bone marrow abnormalities have been shown to be predictors of radiogaphic progression in OA, while reduction in the extent of bone marrow abnormalities is associated with a decrease in cartilage degradation (26), thus confirming that MR alterations may reflect early changes of degenerative disease (2).

Considering that OA, osteochondritis dissecans and avascular osteonecosis may have the same basic etiology, but with different disease severity (23, 28), once again, precocious recognition and prompt treatment could have a key role in preventing worsening and irreversible tissue degeneration (**FIGURE 2**).

Fig. 2



Although not so clear until now the pathogenesis, from the general point of view, what seems to be common to all these main skeletal pathologies, characterized by the presence of bone marrow oedema (alone or related to avascular osteonecrosis and osteochondropaties) is a local "vascular disturbance" related to increased bone turnover (strickly correlated also from the biological point of view). Older pathological works on subchondral bone need to be revisited in view of the prominence recently given to subchondral bony lesions, identified by MR, that probably develop as a result of biomechanically induced bone resoprtion (23).

Prolonged or exaggerated activation of Regional Acceleratory Phenomena (RAP) has also been advocated in the progression from focal osteoporosis and bone marrow oedema to avascular necrosis, due to a preexisting structural bone damage (14).

RAP was firstly described by Frost in early 1980, as increased local bone turnover (or remodeling), with persistent activation of resorbing osteoclasts (OC) and reparative phenomenons (29), that, under local, metabolic, or biomechanical altered microenviroment (as it is postulated to be in avascular osteonecrosis and osteochondropaties), may lead also to irreversible tissue damage (osteoarticular degeneration).

It is well known since a long time that ON, if conservative therapies fail, leads to OA, with irreversible tissue degeneration.

It is known as well, that bone marrow oedema strongly correlate with necrotic volume and has been considered the most significant risk factor for worsening of hip pain, for example. A large necrotic volume of 30% or more may be the second useful indicator for predicting future worsening of hip pain (30).

Moreover, higher grades of articular cartilage defects are associated with higher prevalence and greater depth and cross-sectional area of subchondral bone marrow oedema (31) and subchondral cysts develop in pre-existing regions of subchondral bone marrow edema-like signal (32).

According to all above considerations, as for bone marrow in sports medicine and arthritic pathologies, also in "bone vascular diseases", the target of therapy seems to be bone marrow oedema.

From the point of view of therapeutical options, since BME and related syndromes can have a self - relieving course, in the literature, there are not yet general guide - lines and the argument is still under debate, although new strategies seem to have recently emerged.

Against BMESH, for example, other than simply unload and physical therapy, or symptomatic drugs, until few years ago, surgical bone core decompression was still a higly recommended procedure, due to the possibility of immediate pain relieve after surgery and average duration of symptoms reduced, by core decompression, from 6 months to 2 months (15).

More recently, Iloprost (IP), a vasoactive substance (prostacyclin stable analogue) has been described to be effective in relieving bone marrow oedema syndromes.

Disch, for example, described the possibility to arrest the spread of necrosis, by reducing the oedema. Iloprost can influence the flow equilibrium towards absorption, and regulation of endothelial function may prevent the recurrence of oedema, by improving the flow characteristics of the blood (11).

Different mechanisms could describe the action of Iloprost; in particular, enhancement of fibrynolisis, increase in red cells deformability, down - regulation of leucoyte adhesion molecules, inhibition of proinflammatory cytokines production, partial inihibition of polimorphonucleates and limphocytes adhesion to endothelial cells, attenuation of the inflammatory response, through modulation of cellular interactions, could be suggested as a potential mechanism of action of IP, when used for the treatment of pathological conditions, characterized by endothelial activation (33).

Intravenous IP has been proposed also as a novel therapy for the treatment of post-transplant distal limb syndrome (PTDLS). PTDLS is a benign but disabling complication in the first year after renal transplantation, characterized by bilateral, often incapacitating pain in the feet and or knees on motion and a significant rise in alkaline phosphatase levels on laboratory evaluation. On MR, bone marrow oedema of the affected bone regions can be demonstrated. IP led to prompt pain relief, thus being a promising therapeutic concept leading to a quick relief of symptoms without relevant side effects (34).

In any case, we have to consider that IP can have some collateral effects, like: nausea (21%), temporary increase of pain (21%), flushes and local erythema in the site of injection, hypotension and arrythmia (thus not indicated for cardiopatic patients) (11).

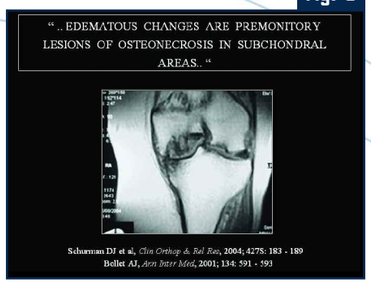
A recent cross - sectional study suggests also an association between antiresorptive treatments (oestrogen and bisphosphonates) and improved symptoms and/or decreased bone marrow anormalities (35). The most wide application of the antiresorptive treatments is in osteochondropaties, where improved symptoms of OA and decreased bone marrow anormalities have been described (35, 36).

A decreased prevalence of OA subchondral lesions has been reported in elderly women treated with alendronate and oestrogen and a reduction of symptoms in those treated with bisphosphonates (23); in particular, nitrogen - containing bisphosphonates demonstrated more significant therapeutic effects (36). Ibandronate, for example, a potent nitrogen-containing bisphosphonate, whose efficacy in the management of postmenopausal and corticosteroid-induced osteoporosis has been proven, has also been emploied for bone marrow oedema syndrome relief (37).

In recent years, a number of important mediators of disease progression have been identified and these represent potential therapeutic targets for slowing or reversing the pathogenesis of OA (38); in particular, it has been postulated that drugs affecting bone metabolism might alter the progression of OA, thus revealing an increased level of interest in subchondral bone as a therapeutic target (36).

Since the early 2000 years, ESWT other than for inflammatory diseases of soft tissue and bone healing disturbances, has been proposed as a valid therapeutic options for "bone vascular disorders". While it was emerging the concept that ESWT may act as a potential option for aseptic ON (39, 40), (although successful rate is inversely related to the extent of tissue damage), first reports were proposed about the possibility to treat successfuly also BMESH and algodystrophic syndromes (41) (**FIGURE 3**). Due to the time-course of pain relief and the final positive results, it may be postulated that ESWT may have a prostacyclin - mimetic, vasoactive effects, when an ischaemic or noxious stimuli induce a loss of local bone homeostasis (42, 43).

Fig. 3



It has been described in the literature also the possibility to successfully treat ON of the femoral heads in Systemic Lupus Erythematous (SLE). The follow-up at 3 years showed no pain on activities for daily living. MR showed substantial reduction in bone marrow oedema and no further collapse of the lesions. Radiographs and MR showed no change in the staging of the disease. ESWT provided beneficial effects for hips affected by ON in patients with SLE. This novel treatment modality resulted in significant pain relief and functional improvement of the hip and reduction in bone marrow oedema. It appeared that ESWT might have the potential to curtail the progression of the disease (probably related to BME) and to delay the need for total hip arthroplasty in the very young patients contracted with SLE (44).

Recently, ESWT has been also proposed in the application of osteochondropaties characterized by BME, other than osteochondral lesions (45, 46) (**FIGURE 4**): also for these pathologies, BME disappearance (within few months) correlated with pain relieving (43) (**FIGURE 5**).

While it is known the osteogenic potential of ESWT, both in vivo and in vitro (47), the mechanism by which this acoustic stimulation may be effective also in relieving bone marrow oedema (and eventually reducing increased local bone turnover) still remains in the field of speculation, although many clinical

evidences and some other experimental data from the literature seem to suggest intriguing hypothesis, about the possibility to induce Nitric Oxide (NO) production for regulating altered local bone omeostasis.

Fig. 4

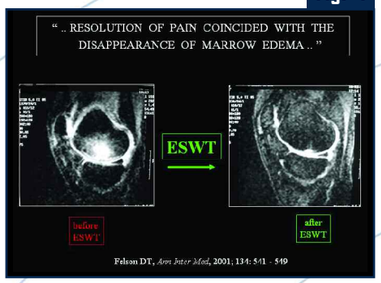
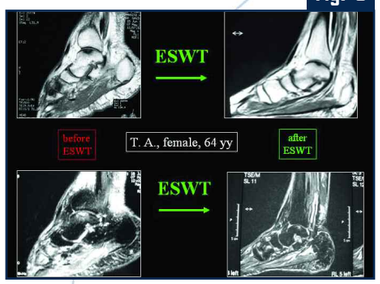


Fig. 5



Firstly, the therapeutical action of ESWT is very similar to those obtained after IP administration, whose mechanism of action on endothelium has been previously described.

Secondly, bisphosphonates with an NO - donor group are more active in pain and BME relieving, when administered for osteochondropaties. From the experimental point of view, the new class of bisphosphonates (BPs) containing nitrooxy NO-donor functions proved to display affinity for hydroxyapatite. Injection of (99m)Tc-labeled derivatives 11 and 18 into male rats showed a preferential accumulation of the compounds in bone as compared to blood and muscles. The products were found to inhibit the differentiation of pre-osteoclasts to functional osteoclasts induced by receptor activator of NF-kappaB ligand (RANKL), through a prevalent NO-dependent mechanism (48).

BPs are an important class of antiresorptive drugs used in the treatment of bone diseases, including osteoporosis. Although their mechanism of action has not been identified at the molecular level, there is substantial evidence that BPs can have a direct effect on osteoclasts by mechanisms that may lead to osteoclast cell death by apoptosis. BPs can also inhibit proliferation and cause cell death in macrophages in vitro: it has been recently suggested that the mechanism by which BPs inhibit bone resorption may involve osteoclast apoptosis. Induction of macrophage apoptosis by BPs in vivo may also account, at least in part, for the anti-inflammatory properties of BPs as well as the ability of BPs to cause an acute phase response (49).

Some experimental studies on rats seemed to show that NO donated by organic nitrates, including nitroglycerin, may protect against bone loss associated with oestrogen deficiency, thus suggesting that organic nitrates may thus be beneficial in conditions where bone turnover is compromised such as in osteoporosis (50).

Thirdly, bone remodeling reflects an equilibrium between bone resorption and formation and all pathological conditions due to heightened bone turnover are characterized by local increase in OC number and activity (29).

The OC is unique in its ability to resorb bone, controlled by the main circulating inhibitor, calcitonin, in association with locally produced modulators. NO is an important member of the latter group; it is produced by the vascular endothelium (and nervous system) and is involved in both neurotransmission and the regulation of blood pressure. This autocoid is also a potent inhibitor of osteoclast function by stimulating guanylate cyclase, with a consequent increase in cyclic GMP. The abundance of NO-producing endothelial cells in bone marrow and their proximity to osteoclasts suggests that marrow endothelial cells may play a physiological role in the regulation of osteoclastic activity (51).

NO is a multifunctional signaling molecule and a key vasculoprotective and potential osteoprotective factor; it regulates normal bone remodeling and pathological bone loss in part through affecting the recruitment, formation, and activity of bone-resorbing osteoclasts (52). It can be considered a powerful inhibitor of bone resorption: a direct demonstration of its production is therefore strong evidence for a role in modulating osteoclast function (53).

It is well known since a long time that NO produces rapid osteoclast detachment and contraction in vitro, and this effect is accompanied by a profound inhibition of bone resorption. Since NO also influences behaviour of the osteoblast, the bone-forming cell, in vitro, a similar effect in vivo might imply a general influence on bone remodeling (54). More in details, the local expression of receptor activator of nuclear factor-kappaB ligand (RANKL) and osteoprotegerin (OPG) in bone determines the entry of monoblastic precursors into the osteoclast lineage and subsequent bone resorption. The effect of NO to decrease the RANKL/OPG equilibrium should lead to decreased recruitment of osteoclasts and positive bone formation. Thus, drugs and conditions that cause local increase in NO formation in bone may have positive effects on bone remodeling (55).

NO has emerged also as a potent regulator useful in alleviating oestrogen deficiency bone loss: some experimental studies suggest in fact that NO donors can be an alternative pharmacological strategy for regulating bone resorption (56).

Addition to the prednisolone structure of a chemical moiety (linker+nitric ester), that releases NO species, yielded a novel glucocorticoid (nitro-prednisolone or NCX-1015) with enhanced anti-inflammatory activities. This is the prototype of a new class of glucocorticoids, the nitro-steroids, endowed with enhanced anti-inflammatory properties and reduced bony side effects. These and other experimental observations may prompt the assessment of the clinical impact of the nitro-steroids on rheumatoid arthritis and inflammatory bowel disease (57)

In other words, accordingly to many of the authors, we can consider that NO is a strong protective agent in regulating bone turnover (52, 53, 58, 59, 60).

Also exercise promotes positive bone remodeling, through controlling cellular processes in bone: it has been described that mechanical strain differentially regulates eNOS and RANKL expression from osteoprogenitor stromal cells in a magnitude-dependent fashion. Some data suggest in fact that physiologic levels of mechanical strain may coordinately regulate eNOS and RANKL in a manner leading to positive bone remodeling (61).

Based on the above mentioned importance of NO in mantaining normal bone turnover, as one of the biochemical product by application of ESWT on endothelial cell cultures seem to be NO, due to a stimulatory effect on endothelial NO-Synthase (eNOS) (62, 63, 64), we hypothesized that main target of this therapy, in those skeletal diseases characterized by vascular disturbances and/or altered local bone homeostasis, may be specifically endothelium.

We can postulate that mechanical stimulation of bony tissue (induced by ESWT and perhaps transduced by eNOS activation and NO production), may exert a tissue protective effect, thus normalizing heightened bone metabolism, primarily inhibiting increased local OC activity, like a sort of "Reset Mechanism" (we name it the "Reset Theory") (**FIGURE 6**). Moreover, as persisting bone marrow oedema can be related to a worsening prognosis and development of osteoarticular degeneration, by stimulating local production of NO (probably by eNOS activation), we may positively interphere on altered local bone turnover, thus inducing a "protective" effect on the progression of many bone and cartilage degenerative diseases (42, 43).

From this point of view, ESWT (actually avoided of clinical side effects) seems not only to be a powerful not pharmacologic and not invasive tool for normalizing bone metabolism, but also to have a potential value of preventive and therapeutical intervention before positive radiographs are obtained (**FIGURE 7**).

Fig. 6

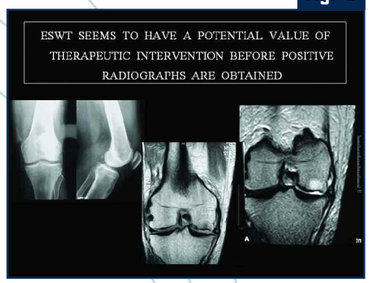
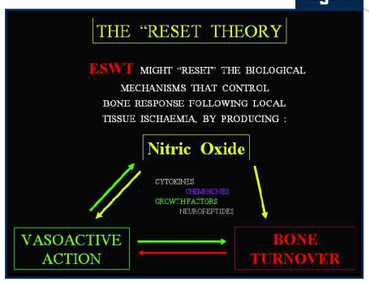


Fig. 7



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Tendinosis of the Shoulder and Related Entities Treated with ESWT. Histopathological and Clinical Correlation

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Introduction

The use of shockwaves in different medical entities has been steadily increasing since 1981 (the first application in Urology), despite the fact that bio-molecular action or responses of diseased human and animal tissues to SW have not been explained in detail. Perhaps the main reason is due to the fact that, to date, we do not know all the possible sequences of events in acute and chronic inflammation, so lacking this data, we are unable to define exactly how the properties of shockwaves act on tissues. A histological feature in Tendinopathy of Shoulder Rotator Cuff is the coexistence of acute and chronic inflammation acting simultaneously so that when SW are applied, we can induce a new "state of flogosis" which in many instances results in resolution of the patient's complaint and imagenologic studies, demonstrates reparation of the specific medical disorder upon which shockwaves have been clinically demonstrated to be useful.

Recent studies of cell and matrix mechanotransduction have suggested possible means of actions of SW in tissues, shedding light on the relationship between "pressure and living tissue response", which could confirm the basis for using SW in particular medical situations (1, 2, 4, and 6).

Patients and Methods

Between December 2003 and June 2005, 90 patients with shoulder pain and dysfunction

were diagnosed by x-rays and sonography. Twenty-five patients showed Tendinosis, 15 showed Tendinosis with intramural tears up to 5 mms and 50 showed Calcifying Tendinosis (65 female, 25 male, mean age = 58 yrs.). All of patients had shoulder complaints for more than 6 months with no previous surgical procedure in the affected shoulder and had received various treatments for pain including NSAIDs.

Twelve patients showed "Frozen Shoulder" and received a short course of oral corticoids and PT immediately after SW application.

For evaluation VAS and ROM were used comparing the normal shoulder at 12 and 24 weeks follow-up. SW treatment was applied using an Orthospec (Medispec) device, and 4000 pulses with an energy flux density of 0.33 mJ/mm2 were applied in a single session.

For histological comparison 10 samples were collected from other patients that underwent surgical procedure for the same diagnosis, and in five of them we applied SW immediately before surgery. All biopsies for light microscopy included tendon and chondral-bone samples from the areas of reinsertion and were treated under habitual techniques for theses tissues, using H-E, Masson Trichrome and Toluidine Blue stains /techniques (3).

Results

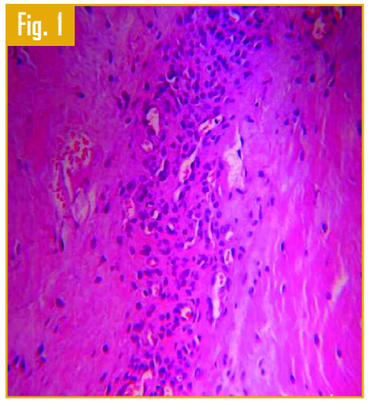
At 24 weeks, 70% of the patients were declared "successes" because they were: pain free; progressively decreasing their use of NSAID`s; returning to normal sleep; and improving their ROM (63 patients). Sonography showed resolution of calcified tissues, healing of intramural tears and less tendinopathic aspect of the rotator cuff. Twenty percent of the patients were declared "partial successes" (8 of them with Frozen Shoulder) and 10% were declared "failures".

Thirteen patients (14%) opted for surgical resolution and biopsy (tendon samples and chondral-bone samples) of their condition none resolved by SW.

Histopathological Results

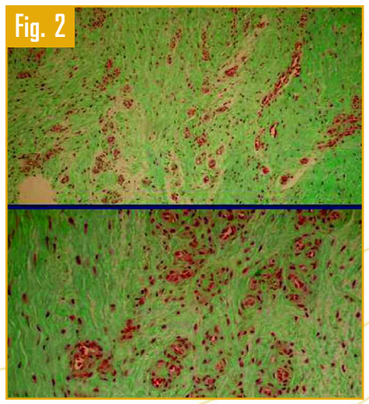
With usual stains tendons showed a consistent hypervascularization characterized by hypertrophic neo-blood vessels and new cellularity with fibro-connective repair (**fig.1,2**), also seen in the edge of tendinopathic intramural tears. Theses changes were distributed randomly through normal and tendinopathic areas of the tendon, and resident blood-vessels appeared undisturbed. The cellularity accompanying neo-blood vessels include round cells resembling those of erythropoietic origin (**fig.3**), and a precise distinction was shown between those cells repairing the matrix tendon and round cells.

Fig. 1



Tendinopathic SW-treated biopsy taken at 20 weeks. Strong neo-vascularized tendon area with fibro connective repair surrounded by diffuse tendinosis areas.

Fig. 2



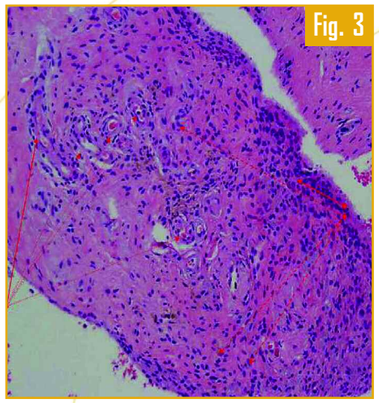
Tendinopathic treated biopsy; in 1, resident blood vessels appear normal with sin gle endothelial linning (arrows); in 2, clumps of neo-vessels surrounded by active hyper cellularity with fibroconnective aspect repair. (4000i/0.33mJ/mm2, biopsy at 16 weeks.)

In some fields of chondral bone samples of treated patients we could identify the same reaction, including numerous hypermuscularized

neo-blood vessels surrounded by impressive hypercellularity, a finding which had eluded us in our previous histological work (5) (**fig.4**). During the histological revisions we could find no signs of cell necrosis, anaplasia or displasia in the treated tissues. None of the tendinopathic control material showed any of the changes observed in SW treated samples.

Discussion

It is significant to note the same reaction in tissues with quite different acoustic impedance. Possibly it is indicative that SW have " target areas " from which similar responses arise. To find neo-blood vessels crossing the area in different directions along resident undisturbed blood vessels following the axis of the collagens and fibroblasts rows is indicative of a "cell reservoir" responding promptly to SW and probably inducing a coherent tissue reaction (**fig.4**).



Biopsy taken at 16 weeks after SW treatment .On the left, red arrows indicate neo vascularization and on the right shows the presence of "round cells" indistinguishable from plasma cells or mast cells.

Chondral-bone biopsy in treated patient, biopsy taken at 10 weeks. Of significan ce, the presence of hypermuskularized active neo-vessels with new cellularity, resem bling those found in soft-tissue response to SW. The comparison with common remode ling subchondral bone areas offers great differences between blood-vessel quality and number and the profusion of the cellular aspect.

One aspect that we observed during the analysis of the material is the appearance of "round cells", quite similar to mast cells and plasma cells. They are indicative of "acute flogosis" thus we surmise that the probable effect of SW is to induce a new inflammation over a "chronic inflamed tissue", creating a new opportunity to resolve the anomalous conditions using the normal ontological repair mechanism.

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Shock waves hit cardiac muscle: extracorporeal cardiac shock wave therapy proves safe and beneficial in patients with chronic ischemic heart disease

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The Society of Shock Wave Treatment in Cardiology has not been formed yet, but the growing number of original papers published in cardiology journals on extracorporeal shock wave (ESW) therapy of ischemic heart disease indicates that cardiologists recognize well their main problem. Indeed, epidemiological studies show increasing incidence of post-ischemic heart failure in the general population followed by growing number of hospital admission related to the exacerbation of its symptoms. New treatment options, that could inhibit or retard the progression of the disease and heart remodeling, would save numerous patients and reduce the need for heart transplantation. Shock waves seem to offer great hope with their extracorporeal use in patients with ischemic heart disease.

Two recent clinical studies reveal the positive effects and clinical safety of ESW therapy in patients with severe coronary artery disease. In the study by Fukumoto et al.1 nine patients with over 12 months of history of stable angina pectoris, with no indications for percutaneous coronary intervention or coronary artery bypass grafting, have been treated by ESW applied under echocardiographic guidance to the ischemic regions of the heart 3 times during one week, 200 shots/spot, 0,09 mJ/mm2 at 20-40 spots each time (Modulith SLC, Storz Medical, Kreuzlingen, Switzerland), repeating the procedure after 1, 3 and 6 months. The therapy improved perfusion, evaluated by dipiridamole stress thallium scintigraphy, specifically in the ischemic areas of myocardium. This effect was associated with the reduction of symptoms from III to II CCS class in 55,5% of the patients (III to I in one case) and the reduction in the use of nitroglycerine that persisted over 12 months of follow-up. The group of Khattab et al.2 enrolled at their institution ten patients with similar characteristics (CCS class III or IV despite the maximum tolerated pharmacological therapy) and subjected them to 9 sessions of ESW (3 cycles) over 3 months at the same energy (0,09 mJ/mm2). The overall results raise even more enthusiasm, with 75% success defined as an improvement of angina symptoms to become CCS class II or less and a substantial reduction of ischemia in the treated myocardium at follow-up tomograms.

The enthusiasm generated by the results of the first clinical studies may be dampened by the low number of patients, lack of randomization and placebo group. The first problem should be overcome with time, but the solution of the latter may be hampered by the ethical problems and technical obstacles. The therapy, although not described by the patients as painful, is associated with the feeling of compression on the chest that may be difficult to mimic without the application of shock waves in order to eliminate the placebo effect.

As is often the case with the new life saving therapies that enter the clinic long before their action is fully understood, also the mechanisms of the cardiac ESW treatment remain merely a hypothesis. Recent findings, however, shed light on the possible effects of shock waves on cardiac tissue. In a rat model of chronic hind limb ischemia, which mimics the clinical setting of patients with chronic ischemia, the tissue preconditioning with low energy SW improved recruitment of circulating endothelial progenitor cells following enhanced local expression of chemoattractant factors, such as vascular endothelial growth factor (VEGF) and stromal cell-derived factor-1.3 Other convincing results from in vitro studies indicate that the vascular effects of SW application are mediated through enhanced expression of VEGF receptors and nitric oxide.4, 5 But the presence of the cardiac resident stem cells that can give rise to new cardiomyocytes, endothelial cells and smooth muscle cells in the adult heart, suggests that more than just a neovascularization is involved in the restoration of heart function after chronic ischemia. In fact, the application of SW on cultured cardiac primitive cells, isolated from human hearts with post-ischemic cardiopathy, enhanced their differentiation and maturation, without causing their apoptosis (authors' observations, manuscript under revision). Again, the auto- and paracrine action of induced by SW expression and release of growth factors seem to be responsible for the observed results. The effects of cardiac ESW therapy emerging from basic science research and from first clinical experience are summarized in the table below.

At this stage of the investigations drawing conclusions must be done carefully, nevertheless the cardiac SW therapy seems effective in ameliorating symptoms and reducing ischemia in the treated myocardium. Moreover, tissue preconditioning with shock waves followed by cellular therapy (injection of autologous stem or progenitor cells into coronary vessels or damaged myocardium) may improve homing, survival and differentiation of cells through the stimulation of synthesis and release of growth factors in the chronically ischemic tissue. Further studies are needed to identify the patients and protocols most appropriate for the cardiac SW therapy, nonetheless it is reasonable to state that the new chapter of regenerative medicine will definitely have shock waves as one of protagonists.

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Table 1. **The effects of cardiac ESW treatment emerging from basic research studies and clinical experience.**

Clinical effects	Biomorphological and functional effects	Cellular effects
• better physical activity tolerance (lower CCS score) • reduced use of nitroglycerin • possible reduction of hospitalizations and need for heart transplantation	• improved myocardial perfusion • improved contractility and ejection fraction • possible inhibition of pathological heart remodelling	• increased number of endothelial cells per myocyte • upregulation of growth factors and cytokines expression • activation of progenitors and precursors of cardiac cell lineages

Extracorporeal shockwave therapy (ESWT) for the treatment of chronic bone and soft tissue infections

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Abstract

Extracorporeal shockwave therapy (ESWT) has been applied successfully to treat aseptic non-unions and multiple other orthopedic disorders. However, infections have always been considered a contraindication for ESWT due to the assumed risk of bacterial spreading and exacerbation of infection. In this regard, experimental data are now available disproving these assumptions and even demonstrating antibacterial efficacy of extracorporeal shockwaves. Furthermore, results of animal studies and clinical investigations have shown ESWT to significantly improve bone and soft tissue infections. Based on the available data, the exclusion of patients with local musculoskeletal infections from ESWT has to be reconsidered. Nevertheless, further clinical data are necessary to provide evidence for the efficacy of ESWT in chronic musculoskeletal infections.

Introduction

Extracorporeal shockwave therapy (ESWT) has become increasingly popular in orthopedics for the treatment of bone and soft tissue pathologies. In spite of the excellent results reported in level 1 evidence studies for the treatment of standard indications like enthesiopathies (proximal plantar fasciitis, calcifying tendonitis of the shoulder, tennis elbow) or non-unions of fractures [1-6], infections have always been considered a contraindication for ESWT due to a possible risk of exacerbation of infection and bacterial spreading with subsequent bacteremia and sepsis [7,8]. Although the risk of treating an infected site with extracorporeal shockwaves has never been studied in a controlled experiment, single cases of secondary infections after treating infected kidney stones with ESWT have been published [9-12]. Furthermore, contradictory data exist on transient bacteremia after ESWT of kidney and gallbladder stones and the requirement of antibiotic prophylaxis during treatment of infected stones [13-19]. In this regard it has been hypothesized that bacterial spreading after shockwave fragmentation of kidney stones is attributable to lesions in the mucous membrane after clearance of sharp stone fragments rather than directly caused by the shockwaves.

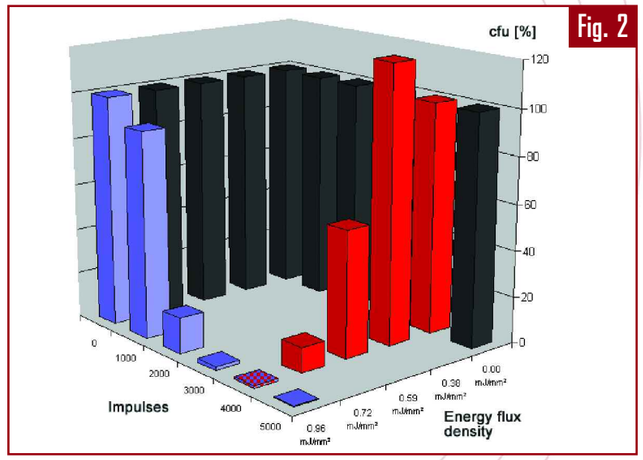
Recent publications of in vitro, animal and clinical investigations have provided substantial new information on the effect of ESWT on bacteria and infected bone and soft tissue, and the exclusion of patients with local musculoskeletal infections from ESWT has to be reconsidered.

ESWT and bacteria: in vitro data

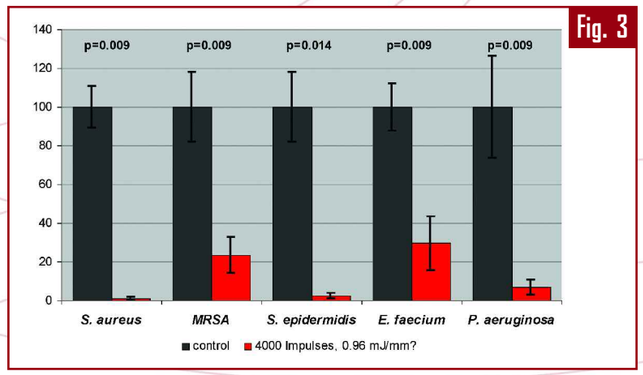
Several publications have examined the effects of shockwaves on human cells and bacteria. Results of in vitro studies are summarized in table 1. While complex interactions are already known for human cells - such as an increased transfer of molecular markers to the cells and a more intensive gene transfer in tumor cells, few studies with conflicting results were available on the interaction with microorganisms. Stoller and Workman were first to study the effect of extracorporeal shockwaves on the microbiological flora of urinary calculi [20]. In vitro fragmentation of clinically isolated deposits occurred either purely mechanically or with ESWT (up to 1000 impulses), followed by an analysis of the bacterial flora. The authors were unable to identify any antibacterial effect as a result of the shockwaves. The same result was obtained by Kerfoot et al. with a variety of bacterial strains in suspension treated with up to 4000 impulses [21]. In contrast, Reid and coworkers pointed to a significant bactericidal effect of extracorporeal shockwaves on suspended bacteria in urine [22]. The antibacterial effect of ESWT was neutralized by embedding bacteria in agar and calcium carbonate crystals for the simulation of struvite stones. Finally, Von Eiff et al. were able to demonstrate that a certain impulse count was necessary as a minimum threshold value in order for extracorporeal shockwaves to have an antibacterial effect [23]. In suspension, the growth of Staphylococcus aureus was reduced by more than 3 logarithmic levels with 350 impulses or more. However, no antibacterial effect was observed with fewer impulses. Complete disinfection was even achieved in the majority of sufficiently treated samples.

Since results significantly depended on experimental set-up, and studies did not allow comparison due to different test set-ups, media and energy levels (given in "kV"), we developed a standardized experimental model (**Fig. 1**) and systematically investigated the influence of energy flux density (ED), impulse rate and growth medium on bacterial survival in vitro. Antibacterial efficacy of ESWT was demonstrated for all tested pathogenic bacteria [24]. Our results with Staphylococcus aureus in suspension (NaCl or CAMHB growth bouillon) further demonstrated that bacterial killing by ESWT was clearly energy-dependent, and both the applied impulse rate as well as the administered ED of the single shocks influenced bacterial survival [25]. An increase in impulse counts continuously decreased bacterial growth, and a reduction of bacterial growth by more than 99.5 % was achieved after the application of 5000 shocks (0.96 mJ/mm² in NaCl, **Fig. 2**). Bacterial killing was significantly reduced if the tests were carried out in bacterial growth medium (CAMHB) [26].

Standardized test set-up for the reproducible investigation of shockwave effects on bacteria in suspension. The arrow indicates the test probe located within the shockwave focus.



Influence of impulse rate and energy flux density (ED) on the growth of Staphylococcus aureus *ATCC 25923. Increase of impulse counts significantly reduced the number of colony forming units (CFU). An increase of ED initially promoted bacterial growth (0.38 mJ/mm²), higher ED significantly decreased bacterial growth.*



Antibacterial effects of 4000 impulses of focused shockwaves with an ED of 0.96 mJ/mm² on different bacterial strains in suspension.

Similarly, bacterial killing was also enhanced with an increase in ED (**Fig. 2**). The antibacterial effect of ESWT was again stronger in NaCl at 21°C compared to growth medium (CAMHB) and 37°C. However, impulses of lower ED in the range of 0.38 mJ/mm_ were not followed by bacterial killing, but by a promotion of bacterial growth up to 120% (NaCl, 21°C) or even up to 219% under growth promoting conditions (CAMHB, 37°C). Shockwaves of higher ED again demonstrated significant antibacterial potency [25, 26].

We summarize that available data from in vitro studies clearly demonstrated energy-dependent antibacterial effectiveness of shockwaves. Furthermore it has to be recognized that shockwaves might also stimulate bacterial growth under certain conditions that allow optimized bacterial multiplication. Taken the complexity of chronic infections with reduced microcirculation, tissue edema, local necrosis, abscess formation, inflammatory processes, and impaired local immune response into account, in vitro models only provide limited information and in vivo studies are necessary to adequately assess effects of ESWT on infected tissue.

ESWT and infections: in vivo data

Since infections have always been considered a contraindication for ESWT, in vivo data on the interaction of shockwaves with infected tissue are very limited. Nevertheless, ESWT is increasingly applied to treat chronic wound problems and difficult-to-heal skin lesions like venous ulcerations. Since chronic wounds have to be considered colonized by bacteria, chronic wounds have to be regarded an "infection model" for ESWT. Schaden and coworkers reported the results of treating skin lesions with planar shockwaves in a last year's issue of the "ISMST Newsletter" and observed an overall complete healing rate of 74%; only 7% of patients responded with a wound closure of less than 50% area and had to be considered failures [27]. Furthermore, no systemic or local side effects of ESWT were reported.

In another clinical study, Schaden investigated ESWT in both aseptic and septic non-unions, and observed a healing rate of 77% for both types of non-union without any complications due to shockwave treatment [28]. The results are limited since the author did not provide data on the state of infection (history of infection or ongoing active infection); nevertheless, consolidation rates of 77% in septic non-unions are definitely encouraging.

The first controlled study evaluating local and systemic effects of ESWT applied to infected bone was carried out by our group in the rabbit model of chronic osteomyelitis [29]. Chronic bone infections were induced by injecting sodium morrhuate and Staphylococcus aureus into the proximal tibia of New Zealand white rabbits. The avoidance of a foreign body as well as the bone sclerosis induced after the injection of sodium morrhuate helped to optimally mimic bone conditions in chronic osteomyelitis and septic

non-unions. After establishment of chronic osteomyelitis, planar ESWT was applied twice to the infected target area (1500 impulses at each session; energy flux density = 0.3 mJ/mm²). An untreated group of similarly infected animals served as a control. Signs of bacterial spreading were not detectable after ESWT, neither in blood cultures nor in histological analyses of representative organs. Clinical parameters as well as laboratory values also remained unchanged after ESWT. Of particular interest, histological scores of osteomyelitis were significantly decreased in the ESWT-group compared to the untreated control, thus demonstrating improvement of active bone infection after ESWT. However, S. aureus was still detectable in tissue samples of all animals.

Based on the available in vivo data we conclude that ESWT of infected bone did neither induce bacterial spreading nor worsening of infection. The results further suggest ESWT to be beneficial in the treatment of chronic bone and soft tissue infections.

Discussion

Chronic musculoskeletal infections, especially chronic osteomyelitis and septic non-unions represent a group of disorders that are extremely difficult to treat and challenge both patients and physicians. Since most patients have a history of soft tissue trauma and / or repeated operations, new and non-invasive treatment options are badly required. However, until now septic non-unions and chronic osteomyelitis have been considered a contraindication for ESWT. On the other hand, a myriad of publications is available reporting successful treatment of aseptic non-unions by ESWT, with healing rates up to 90% [6]. Rationales of treating non-unions by ESWT are documented stimulatory effects on bone growth, neovascularization and hyperemia [30-32]. These effects induce healing processes in sclerotic bone, in which vascularization is decreased. Bone sclerosis and vascular insufficiency are also the essential pathologic factors in chronic bone and soft tissue infections. Furthermore, neovascularization and hyperemia could improve access of immune defense and systemically administered antibiotics to the site of infection.

We demonstrated that ESWT did neither worsen active bone infections, nor induce bacterial spreading or sepsis in vivo. The studies demonstrated antibacterial potency in vivo. Furthermore, we were able to exclude negative side effects of treating infected bone. A combined application of ESWT and antibiotics might even be more effective and should be studied in a controlled investigation. Based on the available data presented in this manuscript we hypothesize that ESWT should be made accessible to subjects with septic non-unions, and might even be a therapeutic option in chronic bone infections. These possible new indications should be investigated in future clearly defined and well-controlled studies.

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Table 1. **Current data on the interaction of ESWT with bacteria**

Author	Bacterial strain	Medium	Impulses	Energy	Bacterial Growth after ESWT	Significance
Stoller 1990 [20]	miscellaneous	Urinary calculi	1000	18 kV	no significant difference	Kidney stones could not be disinfected by ESWT
Reid 1990 [22]	P. mirabilis	Urine, Agar, $CaCO_3$	1000 2000 2000	19 kV	55%, no significant difference, no significant difference	Antibacterial effect when treated in suspension; embedding of bacteria in agar and calcium carbonate crystals prevented bacterial killing by ESWT
Von Eiff, 2000 [23]	S. aureus	PBS	1000	20 kV	0.08%	Significant bacterial killing with increased impulse count
Kerfoot 1992 [21]	E. coli, S. aureus, S. faecalis, P. aeruginosa	Suspension	4000	20 kV	no significant difference	Experimental set-up with stiff vials prevented penetration of shockwaves
Gollwitzer, 2004 [24]	S. aureus, S. faecalis, S epidermidis, P. aerusinosa	NaCl	4000	0.96 mJ/mm²	1.1-29.7%	Significant antibacterial effectiveness of ESWT against all tested bacteria
Gerdesmeyer, 2005 [25]	S. aureus	NaCl	0-4000	0-0.96 mJ/mm²	0.1-120%	Energy-dependent killing of bacteria (ED and impulse counts)
Horn, 2007 [26]	S. aureus	NaCl, CAMHB	0-4000	0-0.96 mJ/mm²	0.1-120% 60-219%	Promotion of bacterial growth with low ED in growth promoting conditions; no inhibition of efficacy of gentamicin by ESWT
Horn et al., unpublished	S. aureus, S. epidermidis	bone	4000	0.96 mJ/mm²	1.6-23.8%	Bacterial killing in bone

Instructions for Authors

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Review articles on topics of general interest are welcomed. Reviews should include the specific question or issue that is addressed and its importance for the shockwave therapy community, and provide an evidence-based, balanced review on this topic. The article should include a description of how the relevant evidence was identified, assessed for quality, and selected for inclusion; synthesis of the available evidence such that the best-quality evidence should receive the greatest emphasis; and discussion of controversial aspects and unresolved issues. Meta-analyses also will be considered as reviews. Authors interested in submitting a review manuscript should contact the editorial office prior to manuscript preparation and submission.

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Authors are encouraged to submit articles with interesting case reports with relevant information regarding diagnosis and therapy, unique for shockwave therapy. The articles should be short, accurate and easy to understand, and should consist of the following:

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- A discussion, whereby the clinical consequences are described and the most interesting aspects of the case report.

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Authors are invited to give a description and background information of developments in the field of further diagnostics and clinical tests and methods that are relevant to all aspects of shockwave therapy, training and rehabilitation. It is not necessary to include examples of patients, as in case reports. The articles should be up-to-date, short, accurate, and easy to understand and should contain the following:

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- And introduction with the theme of the article
- A description of the used test method or diagnostic
- A conclusion with the practical relevance and practical tips.

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– **Book:** Perry J. Biomechanics of the shoulder. In: Rowe CR, ed. The shoulder. London: Churchill Livingstone, 1988:1-15.

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