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Effects of Extracorporeal Shockwave Therapy on Bone Metabolism Markers in Various Musculoskeletal Conditions: A Narrative Review

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Abstract

Several researches have demonstrated the effectiveness of extracorporeal shockwave therapy (ESWT) without surgery to treat various chronic musculoskeletal pathologies. From the current literature, extracorporeal shockwave therapy is one of the rehabilitation modalities that has a potential to be applied on bone to accelerate the healing process. The mechanical stimuli produced by the shockwaves are able to induce physiological responses at the cellular level. Therefore, detecting early changes to the bone may be crucial for certain cases, especially in the pathological conditions. Plain radiography approach requires a long follow-up time to observe the outcomes of the healing process, and biochemical bone markers provide information regarding the effects of treatment earlier than radiography. Several previous studies have reported the effectiveness of extracorporeal shockwave therapy on the mechanical structures of bones. However, evidences regarding the exact dosage of application and effectiveness of extracorporeal shockwave therapy on bone metabolism markers are still lacking. In previous research, diverse methods such as different number of treatment sessions, dosage of shockwave, time of treatment given, sites treated and time to follow-up were employed, and varied outcomes were observed. This review paper will discuss on the overview of bone metabolism markers, the effects of extracorporeal shockwave therapy on bone metabolism markers in musculoskeletal conditions, and the potential mechanism of action of shockwave on bone biochemical markers. The exact mechanisms of shockwave act on bone biochemical markers are still debatable.

Keywords
Shockwave Therapy; Bone Metabolism; Markers

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Introduction

Shockwave is one of the cost-effective modalities to treat various chronic musculoskeletal disorders which commonly require surgical interventions. Managing chronic diseases could increase the long-term treatment costs.[1] Thus, it is not surprising that research in shockwave have been developed in a wide and new spectrum to explore and optimise the usage of this rehabilitation modality.[2,3] Regarding shockwave and bone, most of the current trends of research investigated the effectiveness of extracorporeal shockwave therapy on the mechanical structures of bone such as bone strength,[4] bone mineral density,[5] bone mass[6] and general functions of the structures[7,8] which require a longer follow-up time to observe the outcomes.

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Plain radiography is the gold-standard approach for monitoring certain bone disorders.[9] Nevertheless, biochemical bone markers may provide information regarding the effects of treatment earlier than radiography. Furthermore, in some conditions, plain radiography cannot be used to distinguish bone changes at the early stage.[10] Thus, the measurement of bone metabolism markers, such as osteocalcin, alkaline phosphatase, etc. may be helpful to identify the early changes related to bone tissues.[10,11,12] The bone cells that respond after receiving mechanical stimulation could impose changes to the structure and physiology of the bone, which could lead to acceleration of healing in bone tissue injuries such as delayed tendon-bone healing[13-15] and segmental defects in the bone.[16] Nevertheless, to date, there are a lack of studies investigating the effects of shockwave on bone biochemical markers, its metabolism activity and the potential mechanism of action of shockwave on bone cells.

Bone metabolism markers

Bone metabolism or bone turnover is a dynamic and continuous remodelling process that is normally maintained in balance between resorption of old or injured bone and formation of a new bone. It occurs on the surface of bone at focused sites which are also known as bone metabolism unit (BMU) or bone remodelling unit.[11] Bone remodelling is defined as an active process throughout the skeleton, essential for calcium homeostasis and preserving the integrity of the skeleton through the coupled activity of osteoclasts and osteoblasts.[17] Biochemical markers of bone metabolism can provide more real-time assessment and can be used as indicators of bone resorption, formation and turnover.[11]

Bone formation markers are products of active osteoblasts expressed during different phases of their development and could reflect different aspects of osteoblast function and bone formation. Markers of bone formation can be measured in serum or plasma. Bone formation markers are categorised as by-products of collagen synthesis, i.e. propeptides of type 1 collagen such as Carboxy-terminal Propeptide of Type 1 Procollagen (P1CP) and Procollagen 1 Intact N-Terminal Propeptide (P1NP); osteoblast enzymes, i.e. total alkaline phosphatase (ALP) and bone-specific alkaline phosphatase (BAP); and matrix proteins, i.e. osteocalcin (OC) which is also known as bone-Gla-protein (BGP).[18,19] Bones contain three major minerals, i.e. calcium, phosphorus and magnesium.[20] Thus, calcium and phosphorus are biochemical markers related to bone metabolism.[21] It is known that vitamin D is essential for calcium absorption and maintaining adequate serum calcium and phosphate concentrations. It is also needed for bone growth and bone remodelling by osteoblasts and osteoclasts.[22] Vitamin D deficiency in children and adolescents can impair bone metabolism regulation.[23] In addition, bone morphogenic proteins (BMPs) regulate various growth factors involved in the healing process after bone fracture and promote endochondral bone formation in vivo.[24]

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Bone resorption markers are formed during the bone resorption phase of bone remodelling, which include the by-products of osteoclasts activity released during bone resorption. The bone resorption markers are

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categorised as collagen degradation products; i.e. telopeptides of type 1 collagen (C-terminal such as CTX-1 and CTX-matrix metalloproteinases (MMP)) and serum cross-linked N-telopeptides of type I collagen (NTX-1), hydroxyproline and pyridinium crosslinks such as pyridinoline (PYD) and deoxypyridinoline (DPD); noncollagenous proteins, i.e. bone sialoprotein; osteoclastic enzymes, i.e. tartrate-resistant acid phosphatase and cathepsin K; osteocyte activity markers, i.e. receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG), dickkopf-related protein 1 and sclerostin.[18,19] Bone resorption markers reflect osteoclast activity and / or collagen degradation.[11] High level of bone resorption results in reduced bone density.[25] Markers of bone resorption can be measured in serum or urine.[18] Theoretically, bone turnover can be assessed by comparing the amount of substances that are released during resorption with the amount of substances associated with formation.[11] The increase in the rate of bone resorption, but not reformation creates an imbalance in bone turnover and causing early stage of osteoporosis.[26,27] In general, biomarkers which can be measured for determining the risk of bone fractures are serum calcium, serum phosphorous and 25-hydroxyvitamin D (25(OH) D) levels, bone formation markers i.e. BAP (bone-specific alkaline phosphatase) and osteocalcin, bone resorption markers i.e C-telopeptide and urinary hydroxyproline.[28]

Introduction of previous studies on extracorporeal shockwave therapy and bone metabolism markers

Regarding extracorporeal shockwave therapy on bone metabolism, it has been reported that only a few studies investigated its effects in humans[10,12,29] while the remaining studies used rats as their animal model.[30-35] Animal models are the major tools and helpful for modeling differences in metabolism of bone and bone architecture,[36] which are induced by specific systemic and local factors. Socio-demographic characteristics of the participants or samples enrolled in previous studies are shown in Table 1.

Table 1: Socio-demographic characteristics of the participants/samples enrolled from previous studies

Authors	Age; Mean (Range)	Gender	Participants/Samples
Human studies			
Woelfl et al[29]	Overall: 62 (46-76)	Male = 9 Female = 40	Individuals with normal and low BMD (n=49)
Cacchio et al[10]	Group I (ESWT): 42.8 ± 6.3 Group II (ESWT): 43.1 ± 5.4 Group III (Surgical): 42.5 ± 6.2 Overall: 42.7 ± 5.9	Male = 93 Female = 33	Individuals with a long-bone nonunion (n=126)
Rahim et al[12]	Overall: 20-40; 26.7±5.8	Male = 25	Individuals with ACL tear and underwent primary single autograft hamstring ACLR
Animal studies			
Wang et al[30]	8 weeks	Male = 36	Rats with ACLT osteoarthritic knee (n=36)
Wang et al[32]	10 weeks	Male = 45	Rats with ACLT and MM osteoarthritic knee (n=45)
Wang et al[31]	Not mentioned	Male = 60	Rats with ACLT and MM osteoarthritic knee (n=60)
Hsu et al[33]	4 months	Male = 144	Rats with ACLT osteoarthritic knee (n=144)
Wang et al[34]	8 weeks	Not mentioned	Rats with ACLT and MM osteoarthritic knee (n=56)
Lama et al[35]	Not mentioned	Female = 30	Overiectomized rats (n=30)

BMD = Bone mineral density
MM = Medial meniscectomy
ACLT = Anterior cruciate ligament transected
ACLR = Anterior cruciate ligament reconstruction
ESWT = Extracorporeal shockwave therapy

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These previous studies demonstrated that shockwave could stimulate changes in bone metabolism markers in the serum level which contribute in normalising bone mass in the low bone mineral density individual,[29] healing of long bone non-union,[10] stimulating osteogenesis and regression of osteoarthritis of the knee,[30-33] in which the outcome is dependent on the number of therapy sessions[32] and the sites treated.[31,34] Lama et al[35] also reported that extracorporeal shockwave therapy alone or combination with raloxifene could produce anti-osteoporotic effects. The research methodology and main findings of the effectiveness of shockwave therapy on bone metabolism markers in previous studies are summarized in Table 2.

In the aforementioned previous studies, there were differences in the number of treatment sessions, dosage of shockwave prescribed, time of treatment given, sites treated and time to follow up, and varied outcomes were observed. For instance, bone metabolism markers produced significant changes as early as two months post-treatment in the human study by Cacchio et al[10] However, no significant changes were found in bone metabolism markers after a one year follow up in the human study by Woelfl et al[29] Besides, in rats, noticeable significant changes in bone metabolism marker were found as early as two weeks post-treatment in Hsu et al[33] However, the significant changes were only observed at 12 weeks in Wang et al[31] and Wang et al[32] animal studies. The details of the previous studies on extracorporeal shockwave therapy and bone metabolism markers are discussed in the subsequent sections.

Extracorporeal shockwave therapy (ESWT) on bone metabolism in fracture

A randomised controlled trial study has been conducted to investigate the influence of ESWT on bone turnover markers in individuals with normal and low bone mineral densities (BMD) during fracture healing.[29] A single, high energy extracorporeal shockwave therapy with 0.55mJ/mm^2 and 3000 shocks was applied immediately after surgery to the intervention group. After one year, the serum levels of bone turnover markers including bone alkaline phosphatase (BAP), c-telopeptide of type I collagen (β-CTX), serum band 5 tartrate resistant acid phosphate (TRAP5b), as well as vitamin D3, parathyroid hormone (iPTH) showed no significant changes. However, it was found that ESWT could improve the serum levels of bone turnover markers in patients with low BMD compared to individuals with normal BMD. Therefore, it was recommended by the authors to apply ESWT as one of the treatment options in low BMD patients with fractures.

Extracorporeal shockwave therapy (ESWT) on bone metabolism post anterior cruciate ligament reconstruction

A quasi-experimental study done by Rahim et al[12] found that shockwave therapy had no significant effect on osteocalcin, human cross-linked C-telopeptide of type 1 collagen (CTX1), calcium, and phosphorus postoperatively. However, six sessions of shockwave therapy elicited the highest serum calcium level at week 12 post-operatively among all the study groups. In the study, the application of ESWT was administered to the participants once a week for three weeks (started at week 7) in the 3ESWT group. Meanwhile, for the 6ESWT group, the application of ESWT was administered to the participants once a week for six weeks (started at week 7). Total energy used is 0.18 mJ/mm^2 for the 6ESWT group meanwhile for the 3ESWT group, half of the dosage i.e. 0.09 mJ/mm^{2}was used. ESWT was administered at 500 shocks, 1.5 bar, once per week for either 3 or 6 weeks. The authors speculated that the dosage prescribed in this study might be inadequate to generate significant positive changes on bone formation and resorption markers.

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Table 2: Summary of the research methodology and main findings of the effectiveness of shockwave therapy on bone metabolism markers in previous studies

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Authors	Aims/ Purposes	Study groups	Type of shockwave machine	Sedated	Treatment onset	Dosage / sessions	Bone metabolism marker parameters	Findings
Human studies								
Woelfl et al[29]	To investigate the influence of ESWT on bone turnover markers in individuals with normal and low BMD during fracture healing	A control and an intervention group	Duolith Storz Medical Ag (Tägerwilen, Switzerland).	Yes	Immediately after surgery	0.55mJ/mm², 3000 shocks (once)	BAP, β-CTX, TRAP5b, Vitamin D3, iPTH	1. After one year, the serum levels of bone turnover markers including BAP, β-CTX, TRAP5b, vitamin D3, iPTH showed no significant changes. 2. ESWT could improve the serum levels of bone turnover markers in patients with low BMD compared to individuals with normal BMD.
Cacchio et al[10]	To investigate the response of bone turnover markers to ESWT in the management of long bone non-unions in human	ESWT groups: (Group I and Group II), and a surgical group (Group III)	Dornier Epos Ultra lithotripter; Dornier Medizintechnik, Wessling, Germany and Modulith SLK; Storz Medical, Tagerwilen, Switzerland	Yes	Not mentioned	Group I: 0.40 mJ/mm² Group II: 0.70mJ/mm², 4000 impulses (4 sessions, once a week for 4 weeks)	Osteocalcin and bALP	1. 76% of the participants healed completely 2. Serum osteocalcin and bALP concentrations were significantly higher in the healed group compared with the non-healed group during the first 2

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								months after ESWT treatment.
Rahim et al[12]	To investigate the effects of three or six sessions of low energy ESWT on bone metabolism markers in individuals who had undergone post anterior cruciate ligament reconstruction.	The groups were physiotherapy without ESWT (control), three sessions of ESWT combined with physiotherapy (3ESWT), and six sessions of ESWT combined with physiotherapy (6ESWT) groups.	ShockMaster 300, GymnaUniphy, Germany	No	Started at week 7 post ACLR in intervention groups	6ESWT Group: 0.18 mJ/mm^2 once per week for 6 weeks. 3ESWT Group: 0.09 mJ/mm^2, once per week for 3 weeks. 500 shocks, 1.5 bar.	Osteocalcin, CTX1, Calcium, and Phosphorus	1. Shockwave therapy had no significant effect on bone resorption and formation markers postoperatively. 2. Six sessions of shockwave therapy elicited the highest serum calcium level at week 12 post-operatively among all the groups.
Animal studies								
Wang et al[30]	To investigate the effects of ESWT on OA knee in rats	A control, and two intervention groups	OssaTron orthotriptor (Sanuwave, Alpharetta, GA, USA)	Yes	At 12th weeks after ACLT	0.18 mJ/mm^2, 14kV, 800 impulses (once)	Serum Osteocalcin, ALP	1.Serum osteocalcin level was significantly higher in ACLT plus ESWT group compared to the ACLT alone group. 2. No significant changes were found in serum alkaline phosphatase.
Wang et al[32]	To investigate the effects of different number of ESWT sessions in OA knee in rats	A control, a surgical, and three intervention groups	OssaTron orthotriptor (Sanuwave, Alpharetta, GA, USA)	Yes	One week after knee surgery	0.22 mJ/mm^2, 14 kV, 800 impulses	Serum Osteocalcin	1. Serum osteocalcin level was significantly decreased in rats with ACLT and MM without ESWT, and in rats with

								ACLT and MM which received ESWT three times a week for 3 sessions of treatments. 2. No significant changes in osteocalcin level was observed in control rats with sham arthrotomy without ACLT or MM, and received no ESWT. 3. Serum osteocalcin level was significantly increased in rats with ACLT and MM, which received ESWT once a week for one session of treatment, and in rats with ACLT and MM, which received twice a week for 2 sessions of treatments.
Wang et al[31]	To investigate the site-specific effects of ESWT in osteoarthritis of the knee in rats.	A control, a surgical, and three intervention groups	OssaTron (Sanuwave, Alpharetta, GA, USA)	Yes	One week and twelve weeks after knee surgery	0.219 mJ/mm^2, 800 impulses, 14 kV	Serum Osteocalcin	1.Serum osteocalcin level in all the treated groups was significantly higher compared with the non-treated group at 12 and 24 weeks.
Hsu et al[33]	To investigate the effects of ESWT	A control, a surgical, and an	Not mentioned	Not mentioned	Not mentioned	0.18mJ/ mm^2, 800 impulses, 4Hz	OPG, ALP, MMP13	1. Significant increase of bone formation

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	on joint tissues in early osteoarthritis of the knee in rats	interventi on group						markers, i.e. OPG, and ALP, as well as MMP13 which is also known as bone related genes, at 2 weeks post extracorporeal shockwave therapy compared with the non-treated group.
Wang et al[34]	To investigate the best target site of OA knee for ESWT in the initiation of osteoarthritic changes of the knee in animal model	A sham, a control, and five interventi on groups.	OssaTron (Sanuwave, Alpharetta, GA, USA)	Yes	One week after the surgery	0.22 mJ/mm2, 800 impulses (once)	Serum Osteocalcin	1. Application of ESWT to the medial tibial subchondral bone is a more effective therapy for OA knee than lateral tibia and femur condyles of the knee joint. 2. ESWT on subchondral bone significantly regulated bone remodeling through osteogenesis biomarkers, i.e. osteocalcin at 12 weeks post shockwave treatment. 3. Osteocalcin significantly influenced the level of molecular expression in different locations of ESWT application.

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								4. ESWT regulated the bone volume and porosity in subchondral bone, as well as correlated with the expression of osteocalcin from various locations.
Lama et al[35]	To evaluate the modulation of serum parameters and tissue markers of bone resorption and bone formation in ovariectomized rats after repeated SW therapy, alone or in combination with raloxifene	A sham, a control, and three intervention groups	Duolith SD1-Storz Medical AG, Tagerwilen, Switzerland	Yes	16 weeks after the surgery	0.33mJ/mm^2, 3Hz, 1000 shocks (5 sessions, one session/ week for 5 weeks)	ALP, RANKL, osteoprotegerin and iPTH	1.Serum parameters involved in bone remodeling, i.e. ALP, RANKL, osteoprotegerin and iPTH that altered by ovariectomy were restored by ESWT alone and combination of ESWT with raloxifene.

β-CTX= c-telopeptide of type-I-collagen
ACLT=Anterior cruciate ligament transection
ESWT=Extracorporeal shockwave therapy
ACLR = Anterior cruciate ligament reconstruction
BAP= Bone specific alkaline phosphatase
RANKL=Receptor activator of nuclear factor kappa-B ligand
CTX1=Human Cross-Linked C-telopeptide of Type 1 Collagen
TRAP5b= Serum band 5 tartrate-resistant acid phosphate
iPTH= Intact parathyroid hormone
MM=Medial meniscectomy
OA=Osteoarthritis
MMP13=Matrix metallopeptide 13
OPG= Osteopontin
BMD=Bone mineral density
ALP=Alkaline phosphatase
bALP=bone alkaline phosphatase

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Extracorporeal shockwave therapy (ESWT) on bone metabolism in non-union

Cacchio et al[10] have investigated the response of bone turnover markers to ESWT in the management of long bone non-unions in humans. The shockwave treatment consisted of four sessions of extracorporeal shockwave therapy, i.e. once a week for four weeks with 4000 impulses and 0.40 mJ/mm^2 energy flux density (EFD). Their study found that out of 34 patients, 26 patients healed completely. However, no bone tissue response was found in the remaining eight patients after ESWT treatments. They also found that the osteocalcin and bone alkaline phosphatase (bALP) concentrations were significantly higher in the healed group compared with the non-healed group during the first two months after ESWT treatment. Therefore, the authors speculated that insufficient dosage used might be the underlying factor that led to the poor

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bone tissue response in the non-healed group. Besides, they suggested that osteocalcin and bALP could be used to predict the bone tissue response to extracorporeal shockwave therapy in the treatment of patients with femoral or tibial non-unions, as radiography was not able to distinguish the differences at the early stage.

Extracorporeal shockwave therapy (ESWT) on bone metabolism in osteoarthritis (OA) of the knee

In a previous animal study by Wang at al[30] application of ESWT to the osteoarthritic knee after anterior cruciate ligament transection (ACLT) showed regression of OA of the knee in rats. They observed that serum osteocalcin level was significantly higher in ACLT plus ESWT group compared to the ACLT alone group. Additionally, no significant changes were found in serum alkaline phosphatase. The ESWT was administered once in 12 weeks with the dosage of 800 impulses at 14kV. The authors mentioned that regression of osteoarthritic knees after ESWT was supported by the changes in biomarkers of bones at 24 weeks. Their findings also demonstrated that bone formation markers, i.e. serum osteocalcin were more sensitive than serum alkaline phosphatase after receiving stimulation by the shockwave.

As an extension to the abovementioned study by Wang at al[30], the effects of different number of extracorporeal shockwave therapy (ESWT) sessions in OA knee in rats were investigated by Wang at al[32]. The ESWT treatments consisted of the application of 800 impulses of shockwave at 14 kV, i.e. equivalent to 0.22 mJ/mm^2 with a different number of sessions. It was found that bone formation markers of osteocalcin level were significantly decreased in rats with ACLT and medial meniscectomy (MM) without ESWT, and in rats with ACLT and MM which received ESWT three times a week for three sessions of treatments. However, no significant change in osteocalcin level was observed in the control rats with sham arthrotomy without ACLT or MM, and received no ESWT. This study also found that osteocalcin level was significantly increased in rats with ACLT and MM, which received ESWT once a week for one session of treatment, and in rats with ACLT and MM, which received twice a week for two sessions of treatments. The changes of osteocalcin level have been demonstrated at week 12 of this study. The results obtained reflected that the osteocalcin level in osteoarthritis of the knee in rats was related and affected by the number of ESWT treatment session.

A study done by Wang at al[31] showed that ESWT resulted in site-specific effects in osteoarthritis of the knee in rats. Sixty rats were divided into five groups. Group I was the control which received sham surgery without ACLT and medial meniscectomy (MM), and without ESWT. Group II received ACLT, MM and without ESWT. Group III received ACLT, MM and ESWT at the distal of femur. Group IV received ACLT, MM and ESWT at the proximal tibia. Meanwhile, group V received ACLT, MM and ESWT at the distal femur and proximal tibia. Each extracorporeal shockwave therapy session consisted of 800 impulses at 14 kV, i.e. 0.219 mJ/mm^2 energy flux density. It was found that one of the subchondral bone remodelling biomarkers, i.e. serum osteocalcin level in all the treated groups were significantly higher compared with the non-treated group at 12 and 24 weeks. Thus, it was speculated that ESWT could lead to improvement in subchondral bone remodelling including osteogenesis in ACLT induced-OA changes of the knee. This study also proved that the effects of ESWT were consistent when application was at the distal of femur or proximal of the tibia. In addition, no additive effects were noted when both areas, i.e. distal of femur and proximal of tibia were treated simultaneously.

Another animal study has been conducted by Hsu at al[33] to investigate the effects of extracorporeal shockwave therapy on joint tissues in early osteoarthritis of the knee in rats. It was found that 800 impulses at 0.18mJ/mm^2 with the frequency set at 4, resulted in a significant increase of bone formation markers, i.e. osteopontin (OPG), and alkaline phosphatase (ALP), as well as matrix metallopeptidase 13 (MMP13)

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which is a bone related gene, at two weeks post extracorporeal shockwave therapy compared with the non-treated group. It was speculated that ESWT has potential to regulate the biological functions of osteoblasts in the treatment of early OA of the knee. Thus, it is believed that ESWT could enhance osteogenic factors reflecting local stimulation of bone formation.

A study carried out by Wang at al[34] validated that the application of ESWT to the medial tibial subchondral bone is a more effective therapy for OA knee than lateral tibia and femur condyles of the knee joint in rats. Apart from that, this study found that ESWT on subchondral bone significantly regulated bone remodelling through osteogenesis biomarkers, i.e. osteocalcin at 12 weeks post shockwave treatment. Their study also found that osteocalcin significantly influenced the level of molecular expression in different locations of ESWT application. They observed that ESWT regulated the bone volume and porosity in subchondral bone, as well as correlated with the expression of osteocalcin from various locations. The EWST was applied one week after surgery with the dosage of 800 impulses at 0.22 mJ/mm^2 energy flux density. The treatment areas mentioned were medial of tibia, lateral of tibia, lateral of femur, lateral of tibia and femur, and medial and lateral of femur.

Extracorporeal shockwave therapy (ESWT) on bone metabolism in osteoporosis

Lama at al[35] reported that repeated sessions of extracorporeal shockwave therapy alone and combination of extracorporeal shockwave therapy and raloxifene are beneficial to promote bone formation and suppress resorption in ovariectomised rats. They found that the serum parameters involved in bone remodelling, i.e. alkaline phosphatase, receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin and osteoblast proliferation (PTH) that were altered by ovariectomy were restored by extracorporeal shockwave therapy alone and combination of extracorporeal shockwave therapy with raloxifene. In their study, 16 weeks after surgery, 0.33mJ/mm^2 with 3Hz and 1000 shocks was applied at each treatment session. The treated group received five sessions of extracorporeal shockwave therapy, i.e. one session per week for five weeks. Changes in serum parameter could be observed at week 6 post extracorporeal shockwave therapy. The authors speculated that shockwave managed to produce anti-osteoporotic effects with extracorporeal shockwave therapy alone or combined with raloxifene. The authors also postulated that the mechanisms of these effects can be a result of the increase of bone formation and the reduction of bone resorption.

Conclusion

Based on the aforementioned previous studies, it seems that individuals may respond differently to shockwave although similar dosage was prescribed. The dosage used might be insufficient for certain patients and may need to be modified to obtain effectiveness. In other words, shockwave may not be appropriate to be prescribed in one fixed dosage, and providing a range may be more appropriate for obtaining positive outcomes. Besides, some of the studies found that bone metabolism markers can be the indicators for healing in non-union patients and bone mass in low bone mineral density patients. One of the studies demonstrated that osteocalcin is more sensitive than alkaline phosphatase after shockwave treatment. Meanwhile, based on an animal study, more than two treatment sessions for two consecutive weeks at certain dosages were unsuitable to be prescribed, as they resulted in decrement in the serum osteocalcin level. Furthermore, shockwave treatment showed site specific effects for osteoarthritis in rats, as the positive changes could only be seen at the particular areas treated. Nevertheless, through the observation of bone metabolism markers, the initial changes at cellular level can be detected as early as two weeks post treatment in the animal studies and two months post intervention in human studies. Almost all the collected articles showed significant changes in bone metabolism markers after shockwave treatment. Only one research found no significant effects on bone biochemical markers. This might be due

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to the follow up time being one-year post treatment, which was extended too long after the intervention period. Based on this review, initial alteration in bone metabolism markers is beneficial to detect the early changes in the bone at a cellular level. Thus, it is believed that through bone metabolism markers, potential positive outcome of extracorporeal shockwave therapy can be predicted earlier than radiology outcome after the treatment sessions. However, the exact mechanisms of shockwave act on bone biochemical markers are still debatable. A few speculations have been highlighted based on the previous studies' outcomes; nevertheless, they still needed to be validated. Thus, it is concluded that future studies are warranted to explore and validate the published study findings.

Commented [h20]: Answering the Reviewer B. This is our conclusion based on our review.

Declaration of Competing Interests

There is no actual or potential conflict of interest in relation to this article.

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