SYSTEMATIC REVIEW

Whole Body Vibration and Resistive Exercises May Reduce Risk Factors for Fractures in Type I Osteogenesis Imperfecta

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ABSTRACT

There is a scarcity of research on whole body vibration exercise and resistance exercise as a combined program for children and adolescents with type I Osteogenesis Imperfecta (OI). Type I OI is the mildest and most common form, characterized by mild to moderate fragility without bone deformity. The goal of treatment when working with people with Type I OI is to reduce the risk of fractures primarily by increasing bone mineral density. Research has indicated that whole body vibration, by means of mechanical oscillation, and resistive exercise, that creates a tensile force on the bone and musculature, are effective means for increasing muscular strengthening and bone formation and for preventing the loss of bone mineral density. Using the Oxford Level of Evidence, a systematic review of literature was done to determine if whole body vibration and resistive exercise training can reduce risk factors for fractures in children and adolescents with type I OI. Based on the gathered evidence, we surmised that combining whole body vibration and resistive exercises yields greater effects on bone mineral density in reducing risk factors for fractures in children and adolescents with type I OI.

Keywords used: *Osteogenesis Imperfecta, whole body vibration, resistive exercise, bone density, collagen synthesis, fracture, muscle strengthening*

Background

Osteogenesis Imperfecta (OI), often referred to as brittle bone disease, is a disorder that is characterized by increased bone fragility that results in high incidences of fracture.[1,2] It consists of four types. Type I OI is the mildest and most common form of the disorder, which is characterized as mild to moderate fragility without bone deformity. Type II OI is the most severe form manifested as extreme fragility with severe bone deformity. Individuals affected by this type do not have a high survival rate as they are either stillborn or die during infancy or childhood. Type III OI is moderately severe, wheelchair bound by adolescence, and results in bone deformity such as scoliosis, osteoporosis, and short stature. Lastly, type IV OI is milder and is characterized by mild to moderate fragility, bowing of long bones, and a barrel-shaped rib cage.[3,4] Further descriptions of types of OI are found in Appendix (A).

According to several authors,[2,3,4] OI affects approximately thirty thousand to fifty thousand people in the United States or one in every ten thousand to twenty thousand births. It is considered as the most common genetic disorder. It is estimated that children with type I OI experience five to fifteen major fractures before they reach puberty.

Osteoporosis and other conditions with low bone density are common secondary disorders that result from OI.[3] The development of these secondary conditions is due to a decrease in the overall peak bone mass achieved in people with OI at the end of puberty when skeletal maturity has been reached. This change in the structure and composition of the bone reduces its flexibility and ability to absorb energy, consequently causing the bone to become brittle. Once the bone becomes brittle, it can easily be deformed under applied stress, thereby increasing the risk of fracture.

As with osteoporosis, the management of OI is primarily centered on fracture prevention and control. One preventative method for diminishing the effects of osteoporosis and reducing fracture rate is to develop a high peak bone mass during puberty and adolescence.[6] Through prolonged low stress and strain on bone, strength and peak bone mass can be increased.[7] In people afflicted with osteoporosis, whole body vibration exercise (WBVE) and load bearing exercise have been used as effective treatments for stimulating bone strength and increasing the amount of trabeculae, which is found to be diminished in people with OI.[8] Moreover, women with osteopenia who experience vertebral fractures have up to four times the amount of unconnected trabeculae than women who did not experience fracture.[9]

Pathogenesis of Osteogenesis Imperfecta

Mutations, which can be spontaneous or inherited, of the genes that code for type I collagen, the major structural component of tendon, skin and bone matrix, are the cause of OI. Type I collagen, the most common type of collagen due to its presence in all body tissues, is produced by osteoblasts and is predominantly found in bones due to the strong structure. Once the collagen is produced, a matrix surrounds the collagen, calcium is arranged and trabeculae are formed. The structural stability of extracellular matrix is reliant on the cross-linking of collagen fibers, which improve the tensile strength of the collagen.[4] Trabeculae, which are found in much smaller amounts in people with OI, are formed once bone matrix is laid down. The structure of trabeculae including the number, spacing, thickness, connectivity, and distribution determines the strength of the bone, the absorption and release of energy and therefore its capability to resist failure.

The present study is centered on Type I OI, which appears to be the result of low collagen production rather than genetic defects in the collagen.[3,4,9] The rate of trabecular thickening in people with type I OI is decreased, therefore preventing cancellous bone volume from increasing with age, ultimately leading to diminished strength.[4] WBVE and strengthening exercise have been used as effective treatments for increasing the amount of trabecular bone, in addition to stimulating bone strength, increasing bone mineral density and decreasing the loss of muscle mass.

Whole Body Vibration Exercise

Whole body vibration exercise involves the transfer of energy via oscillations from a vibration device to the human body.[10] This type of exercise is often indicated for people who cannot participate in activities or exercises that utilize dynamic movements, such as running or jumping, as a means to prevent muscle atrophy and bone mineral loss.[11,12]

The mechanism of action of WBVE is based on the idea that the frequency of the extrinsic input from the device activates proprioceptive spinal circuits and therefore causes a reflex. When the muscle fiber twitch frequency is reached, the fiber becomes excited and a muscle contraction results, which in turn provides stress on the bone.[13,14]

The benefits of WBVE include increased muscle mass, increased bone formation, and increased metabolism of skeletal muscle and skin.[14] In addition, whole body vibration is a non-invasive, cost and time efficient way to increase bone density and to strengthen muscles.[12] For example, Blizzard and Young conducted a systematic review of literature utilizing 16 studies to determine the effects of WBVE on the prevention of negative effects experienced from prolonged bed rest. Thirteen out of 16 studies exhibited positive effects of WBVE on items such as bone health, postural control, cartilage thickness and strength. In both healthy and osteoporotic people, WBVE was found to preventively reduce muscle atrophy and bone mineral loss.[11]

Similarly, Gusi and colleagues conducted an eight month study on the effects of a low frequency WBV program on bone mineral density and balance compared to that of a walking program in postmenopausal women. The study found increases in balance and bone mineral density at the hip; specifically the femoral neck.[15] Similar findings were reported in other research related to areas of increased bone mineral density. The femoral neck, the spine and the cortical bone of the tibia were found to have the greatest increase in bone mineral density following WBVE. These sites are all common areas of fracture in adolescents with OI.[12,13,15,16]

Resistance Exercise

Like WBVE, resistive exercise has been found to produce gains in bone mineral density and bone strength. In this study, resistive exercise is defined as kinetic movement where resistance is provided by gravity or by an outside source to elicit a muscle contraction. Resistive exercise is often performed in closed chain during weight bearing exercises.[17] In resistive exercise, the bones are loaded by a force that causes stress on the bone that then results in increased bone mass. In addition, it has been established that resistive exercise performed at a young age helps to improve peak bone mass.[6]

Almsted and associates conducted an experimental study where changes in bone mineral density in college-age men and women were examined following twenty-four weeks of resistance training that included squats and deadlifts. Results revealed bone mineral density was increased in the spine and in the femoral neck among young healthy men.[6] Conversely, Van Brussell and associates examined the effects of a low-resistance strength training program for children without utilizing heavy weights. They concluded from this experimental design study that there was an increase in the muscle force generated by the participants who were in the intervention group compared to the control group. This is relevant to children with OI due to the close association between muscle force and bone strength.[18]

Furthermore, Faigenbaum and colleagues published a position statement on youth resistance training that was supported by the National Strength and Conditioning Association. The article reviewed scientific evidence regarding the effects of resistance training on the physiological, psychosocial and anatomical changes experienced in children. It was concluded that under age-appropriate guidelines, children could improve bone health, reduce their risk of injury and improve their body composition.[17]

Whole Body Vibration Exercise and Resistance Training Combined

When WBVE and resistance training were combined, the same benefits experienced by each variable independently were also seen when used together as a program. Ligouri and associates conducted an experimental study design on the effects of a WBVE program incorporating resistance exercise on changes in bone mineral density in college-age men and women. At the end of the 12-week study, there was an increase in the bone mineral density of the spine.[16] Likewise, Verschueren, et al., in their randomized controlled pilot study on post-menopausal women following a combination program of WBVE and resistance training, found similar results of increased bone mineral density. The study compared the effects of a combined exercise training protocol compared to a resistive training protocol alone. At the end of a six-month training program there was a greater increase in hip bone mineral density, improved balance, increased muscle strength and decreased fat mass in the combination exercise group compared to the resistance training group. Increased bone strength in the hip is important because bone mineral density is a good predictor for femur fracture.[13]

When used solely or in combination, both WBVE and resistance training have been found to have many benefits for increasing bone mineral density. It can be argued that the same combined regimen might yield similar benefits for people with type I OI. Currently, there is little literature that explores the effectiveness of a combined WBVE and resistive exercise program in children with type I OI and that utilizes the Oxford Level of Evidence that categorizes different studies based on the type of research design used.

Problem Statement

Before the beginning of puberty, people with type I OI generally experience major and minor fractures that occur mainly in the fingers. After puberty the incidence of fracture tends to decrease, but peaks again after menopause in women.[3] WBVE and strengthening exercise have been used as effective treatments for stimulating bone strength, increasing bone mineral density, decreasing the loss of muscle mass, and increasing the amount of trabecular bone, which is found to be diminished in patients with OI. With the aim of reducing the incidence of fracture in children with type I OI and with the aim of examining the benefits of WBVE and resistance exercise, we decided to conduct a literature search and rank each study using the Oxford Level of Evidence (OLE). Further details of OLE can be found in the methodology section.

Research Question

One of the main focuses of physical therapy for people with OI is on fracture prevention and control, which is achieved by increasing peak bone mass during puberty. Research has indicated that WBVE as well as resistive strength exercise have been shown to increase bone strength. To bridge the gap between Osteogenesis Imperfecta and whole body vibration as well as strengthening exercise and its significant application in the field of physical therapy, specifically in reducing the risk factors in type I Osteogenesis imperfecta, the following research question was formulated: *Would whole body vibrations with resistive exercises compared with resistive exercises alone decrease risk factors of fractures in children and adolescents with type I Osteogenesis Imperfecta?* To facilitate understanding of some technical jargon used in the study, Appendix B defines the terms.

Significance of the Study

Current literature primarily focuses on fracture prevention for people with bone fragility, but not specifically for people afflicted with type I OI. Examining and combining the effects of WBVE with resistive exercise and applying them specifically for the use of fracture prevention in people with type I OI, a current gap may be filled by future research. Specifically, for physical therapists, therapy has often been limited to low impact exercises such as swimming and walking, which do not yield the same increases in bone mineral density that are experienced due to WBVE and resistance exercise. A combination training program might be a possible additional treatment option for physical therapists in preventing future fractures in children with type I OI.

Theoretical Foundation

Type I collagen is produced by osteoblasts and is predominantly found in bones due to the strong structure. Once the collagen is produced, a collagen matrix surrounds the collagen, calcium is arranged and trabeculae are formed. Cross-linking of collagen fibers increases the structural stability of the extracellular matrix and improves the tensile strength of the collagen. Trabeculae are formed once bone matrix is laid down.[4] Resistive exercise and WBVE have been found to produce gains in bone mineral density, bone strength and also decrease muscle mass loss. The mechanism by which these benefits are delivered is by eliciting muscle contraction, which therefore puts a stress on the bone and consequently improves strength of the musculoskeletal system.

Materials and Methods

Different databases were searched: CINAHL, CINAHL Complete, Cochrane, EBSCOHost, Google, Google Scholar, MedlinePlus, PubMed, and SPORTDiscus. Keywords used in the search include: *Osteogenesis Imperfecta, Osteogenesis Imperfecta cause, Osteogenesis Imperfecta and physical therapy, Osteogenesis Imperfecta and whole body vibration, whole body vibration with bone strength, Resistance exercise and bone density, OI low impact therapy, low intensity exercise effect and bone, mechanical loading and bone density, exercise and bone strength*. The keywords and databases utilized from above generated well over 5,000 results. To modify and narrow the search, we used the common Boolean search terms *or* as well as *and*. For example, *Osteogenesis Imperfecta and whole body vibration* generated approximately 1,000 results. To be critical with our literature search, we set the following inclusion criteria to include articles published within the last 15 years, in the English language, with full text articles only. Further, we scrutinized articles that have highest rank or category based on the Oxford Level of Evidence. We found 100 articles that seem to fit with our study. After reviewing the articles, we found 50 articles worth reviewing. However, out of 50 articles, we found 30 studies relevant to the research.

Using the Oxford Level of Evidence (OLE) ranking system, we searched for commonalities among Osteogenesis Imperfecta, whole body vibration, and resistive exercise. [19] Appendix C illustrates the OLE.

Results

To assess the strength of the articles, OLE was used. The table on the following pages summarizes the articles arranged according to level of evidence. These articles are regarded significant in answering the research question.

Discussion

Osteogenesis imperfecta (OI) or brittle bone disease is a disorder that affects collagen synthesis and subsequently results in changes in bone and connective tissue.[4] Children being affected by OI have

Article Title	Author	Date Published	Level Of Evidence	Purpose	Conclusion
Current and emerging treatments for the management of osteogenesis imperfecta	Monti, E, Mottes, M, Fraschini, P, Brunelli, PC, Forlino, A, Venturi, G, Doro, F, Perlini, S, Cavarzere, P, Antoniazz, F.	2010	5	To look at current and emerging treatments for OI.	Bisphosphonates are the current standard of medical management care for OI.
Osteogenesis Imperfecta	Brusin, J.H.	2008	5	To provide background information on OI pathology and relate this to medical imaging techniques.	Type I is a result of lower than normal collagen, not mutated collagen. Majority of OI type I patients develop secondary osteoporosis- possibly extrapolation from post-menopausal studies
OI Section--Pathology Book	Goodman, C. C., & Fuller, K. S.	2009	5	To provide background information on the pathophysiology of bone, muscle, connective tissue, and OI.	Background info
Changes in Bone Mineral Density in Response to 24 Weeks of Resistance Training in College-Age Men and Women	Almstedt, H. C., Canepa, J. A., Ramirez, D. A., & Shoepe, T. C.	2011	1	To elucidate the ideal frequency, intensity, duration, and mode of resistance training necessary to optimize bone health.	A 24 week resistance training program including squat and deadlift increases BMD in healthy young men-especially at the spine. The same results were not seen in women

Joint loading modality: its application to bone formation and fracture healing	Zhang, P. P., Malacinski, G. M., & Yokota, H. H.	2008	2	Explains the novel joint loading modality and discusses two of its potential underlying mechanisms as well as possible clinical applications.	Joint loading is effective for inducing bone formation along the length of the entire long bone regardless of distance from loading. CT imaging showed that knee loading accelerated closure of wound and increased speed of the remolding process.
Effect of 6-Month Whole Body Vibration Training in Hip Density, Muscle Strength, and Postural Control in Postmenopausal Women: A Randomized Controlled Pilot Study	Verchueren, S.M.P., Roelants, M., Delecluse, C., Swinnen, S., Vanderschueren, D., & Boonen, S.	2004	1	To look at effect of WBV on Hip Density, Muscle Strength, and Postural Control in Postmenopausal Women.	Isometric and Dynamic strength of knee extensors increased in WBV and Resistance groups but declined in the control group. Total hip bone mass density increased in the WBV group but did not change in the RES or control groups. The WBV group also had improved recovery of balance after ballistic abduction of arms.

Insights into Material and Structural Basis of Bone Fragility from Diseases Associated with Fractures: How Determinants of the Biomechanical Properties of Bone are Compromised by Disease	Chavassieux, P., Seeman, E., and Delmas, P.D.	2007	5	To provide a foundation of information on the structure and make-up of bone and the effect of metabolic bone disorders on the make-up resulting in bone fragility and increased fractures.	OI characteristics: decreased bone mass, bone formation, bone resorption, number of trabeculae, and cortices thickness.
Effects of whole-body vibration exercise on human bone density-systematic review	Rehn, B., Nilsson, P., & Norgren, M	2008	2	To systematically review nine randomized studies to determine the effects of whole-body vibration exercise on human bone density.	WBVE may be a promising training alternative for improving bone density in individuals who cannot participate in regular exercise regimens
Whole Body Vibration Training is Osteogenic at the Spine in College-Age Men and Women	Ligouri, G. C., Shoepe, T. C., & Almsted, H. C.	2012	1	To evaluate the osteogenic potential of WBV training with dynamic exercise at improving bone health in young individuals, thereby optimizing peak bone mass development and lowering future risk of osteoporosis.	Dynamic exercise performed on a WBV platform may be osteogenic. Increases in BMD at the lateral and posterior-anterior view of the spine may be due to the high level strain caused by dynamic exercises on the platform

The effects of Different Resistance Training Protocols on Muscular Strength and Endurance Development in Children	Faigenbaum, A. D., Westcott, W. L., Loud, R. L., Long, C.	1999	1b	To compare and evaluate response of a low-rep heavy load versus a high-rep moderate load training program on children.	1 set of high rep-moderate load may be more beneficial than 1 set of low rep-heavy load.
Physical Training in Children with Osteogenesis Imperfecta	Van Brussel, M., Takken, T., Uiterwaal, C., Pruijs, H., Van Der Net, J., Helders, P., & Engelbert, R.	2008	1	To study effects of a physical training program on exercise capacity, muscle force, and subjective fatigue levels in patients with mild to moderate OI.	Significant improvement in aerobic capacity was found after 3 months of training in children with OI.
Osteogenesis imperfecta: Anthropometric, skeletal and mineral metabolic effects of long-term intravenous pamidronate therapy	Vallo, A.; Rodriguez-Leyva, F.; Rodriguez Soriano, J.	2006	3	To look at the effects of long-term intravenous pamidronate therapy.	Intravenous pamidronate therapy reduces the annual fracture incidence in children with OI and allows for normal growth. The effects seemed to peak after 2 years of therapy showing bone mass gain was either sustained or it declined.
"Vibration As An Exercise Modality: How It May Work and What It's Potential May Be"	Rittweger, J.	2010	1	To provide information regarding the physical principles of vibration exercise.	WBV counteracted fatigability of knee extensors during isometric contractions. Multiple negative, unintended consequences highlighted as it relates to WBV exercise

Congenital and metabolic disorders leading to fracture	Borland, S., and Gaffey, A.	2012	5	To review congenital and metabolic causes of fractures, specifically osteogenesis imperfect and congenital pseudoarthrosis	Early diagnosis of these conditions can greatly affect the outcome. There is no firm evidence from which to base management recommendations on due to the rarity of these disorders. Further studies need to be conducted, however IV biophosphates are now being turned to as a preventative measure against fracture.
Effects of whole-body vibration exercise on prevention of the negative effects of prolonged bed rest	Blizzard, R. R., & Young, J. L.	2010	2	To systematically review literature that studies the effects of WBVE on prevention of the negative effects of prolonged bed rest.	In young healthy males and females, WBVE appears to be a hopeful and safe intervention for muscle strength, and size in the lower body, and for bone density.

Multiple vibration displacements at multiple vibration frequencies stress impact on human femur computational analysis. (Journal of Rehabilitation Research & Development	Ezenwa, B. & Han Teik, Y.	2011	3	To examine the effects of stress dispersion on a model of a femur with and without multiple vibration displacements at multiple vibration frequencies(MVDMVF). The results were then compared to the stresses sustained during jogging, walking and stair climbing to determine a safe frequency for the elderly and osteoporotic populations.	The stress levels from MVDMVF were found to be significantly higher on the femur than without the MVDMVF. Specifically MVDMVF produces stress similar to that of stair climbing and walking but less than that of jogging. MVDMVF is safe for use in the elderly and those with osteoporosis who ambulate independently.
Low-frequency vibratory exercise reduces the risk of bone fracture more than walking: a randomized controlled trial	Gusi, N., Raimundo, A., & Leal, A.	2006	1a	To compare the effects of an 8 month low 12.6 Hz frequency WBV exercise program using a reciprocating platform with a walking program on balance and bone mineral density, both of which are factors of fractures, in healthy postmenopausal women.	An 8 month WBV program using a low frequency and reciprocal vibrating plate increased balance and hip BMD in postmenopausal women when compared to a walking exercise program. They inferred that balance and hip BMD are two significant determinants in bone fractures.

Clinical risk factors but not bone density are associated with prevalent fractures in prepubertal children	Ma, D., & Jones, G.	2002	3	To investigate whether or not maternal peak bone mass, physical activity, exposure to sunlight, breastfeeding in early life, maternal smoking during pregnancy, and inhaled corticosteroids in the previous year were associated with prevalent fractures.	Ten percent of children had prevalent fracture particularly in the upper limbs. The mechanism of most fractures were originated from low-energy in the home falls. Older children who participated more in sports, who had corticoid steroid use in the previous year, and who were less breastfed had higher incidence of fracture. None of these findings were statistically significant except for the breastfeeding finding. Clinical risk factors for fracture may be more important than BMD alone in assessing fracture risk in prepubertal children.
Effect of 8 month vertical whole body vibration on bone, muscle performance, and body balance: A randomized controlled study	Torvinen, S., Kannus, P., Sievanen, H., Jarvinen, TA., Pasanen, M., Kontulainen, S., Nenonen, A., Jarvinen, TL., Paakkala, T., Jarvinen, M., & Ilkka Vuori	2003	1a	To assess the effects of an 8-month WBV intervention on bone, muscular performance, and body balance in young and healthy adults.	No effect on mass, structure, or estimated strength of bone at any skeletal site- but did increase vertical jump height.

Preliminary results on the mobility after whole body vibration in immobilized children and adolescents	Semler, O., Fricke, O., Vezyroglou, K., Stark, C., & Schoenau, E.	2006	4	Effects of WBV training sessions (Daily therapy sessions with 3 cycles each with Cologne Standing-and-Walking-Trainer (a Galileo WBV- system) supplemented by a tilt-table	All patients demonstrated increased muscle force and increased mobility after the 6 month intervention
A fracture risk assessment model of the femur in children with osteogenesis imperfecta (OI) during gait	Fritz, J. M., Guan, Y., Wang, M, Smith, P.A., & Harris G. F.	2009	3a	To determine the risk factors or fractures and stresses put on a femur model for a patient with OI and to determine how clinical gait analysis data can analyze fracture risk.	The authors concluded that their fracture risk assessment model using gait analysis and von Mises stresses was a helpful way to predict risk factors for fractures in patients with osteogenesis imperfecta.
Effect of whole body vibration training on mobility in children with cerebral palsy: a randomized controlled experimenter-blinded study	Lee, B., & Chon, S.	2013	1	Effect of WBV training exercise	WBV has beneficial effects on helping children with CP gain mobility and the ability to walk via increased muscle thickness of muscles associated with gait- soleus and tibialis anterior.

increased risk for fractures due to bone fragility leading to skeletal deformities.[5] Fracture risk in general results from a combination of both bone-dependent and bone-independent factors.[20] Specific to OI, these dependent factors can include bone geometry and material properties.[23] Independent factors are not specific to effects on the bone but the individual in general.

In a randomized controlled trial, Gusi et al. argued that major determinants of bone fractures include falls, bone fragility, loss of balance, and decreased lower limb strength.[15] While type I OI presents with less common fractures than other types of OI, it is the third most common type of the disorder to experience fractures.[5] Similarly, in a randomized controlled trial, Almstedt et al. posited that to prevent osteoporosis [a disease similar to OI] that has increased fracture risk, it is essential that an individual build peak bone mass during growth and young adult life.[6] While other treatments such as bisphosphonates have been found to be effective in reducing bone fractures in children and adolescents with OI by inhibiting the reabsorption of bone and increasing bone mass, effects have been shown to peak at two years and are either maintained or decline thereafter.[21] A research review, using the OLE to rank the literature, had been conducted to determine if the combination of whole body vibration and resistive exercise would decrease the risk of fractures in the population of adolescents with type I OI by increasing the bone mineral density and improving muscle strengthening. The following sections have been identified as common themes from the reviewed literature.

Whole Body Vibration and Its General Effects

Whole body vibration exercise has been shown to prevent muscle atrophy and bone mineral loss and may be a vital alternative for people, such as individuals with OI, who may have difficulty participating in traditional dynamic training.[11,12] An experimental controlled design by Ligouri et al. found that dynamic exercises, or exercises involving concentric and eccentric muscle contractions, performed on a whole body vibration plate have been shown to increase bone density in the lumbar spine for healthy college students.[16] Likewise, Verchueren and associates conducted a randomized controlled pilot study, which demonstrated that whole body vibration training has been shown to increase knee extensor strength, improve balance recovery, and increase total hip bone mass density. Furthermore, Rehn and colleagues performed a systematic review, which showed that there was an increased bone density in the lower back and lower extremities for postmenopausal women.[8,12] All of these findings of strength, balance, and bone mass density are major risk factors in fracture. Therefore, improving these may lead to decreased fractures for individuals.[15]

Lee and Chon performed a randomized control, experimental blinded study that demonstrated that whole body vibration interventions have also shown increases in muscle thickness for people with cerebral palsy, which is also an immobilizing disorder comparable to OI.[14,22] In a preliminary study, a whole body vibration intervention involving a Cologne Standing-and-Walking Trainer consisting of a Galileo WBV- system and tilt-table demonstrated decreases in spasticity and improved functional motor patterns in children with cerebral palsy. It also increased mobility and lower extremity force in four children with OI.[14]

Whole Body Vibration Effects on Bone Mineral Density

Whole body vibration works by causing muscle fibers to contract energy on attached bone as well as by providing mechanical vibration to put stress on human bone.[13] Semler et al. found that WBV improves muscular coordination of high frequency contractions of opposing muscles which in turn improves power for those that are motor impaired. It is also shown that people with OI have improved force development in lower extremities and improved overall mobility.

Numerous studies have shown significant increases in bone density, especially to the hip, femoral neck, and areas of high trabecular bone content.[8,12,13,15,16] For instance, Ligouri and associates found that with whole body vibration exercise, bone mineral density increased in the lateral and posterior-anterior view of the spine, respectively, due to the amount of trabecular bone in those areas.[16] Ezenwa and Han Teik, and Gusi et al. showed increases at the femoral neck in their respective studies. Moreover, Rehn et al. found increased bone mineral density in the trabecular bone of the femur.[12,13,15] Verchueren and associates demonstrated no changes in BMD in the total body or lumbar spine but did find local changes of BMD in the hip.[8]

It is significant to note that previous studies argued the importance of femoral neck bone mass density as a predictor of femoral fractures, which is common in OI.[13] Long bone fractures in the lower extremities, specifically the femur, are the most common and likely bone to fracture in the OI population.[5] In their case controlled study, Fritz et al. found the highest risk of fractures occur during mid-stance and the loading response of gait where areas of high stress are on the lateral and medial aspect of the femur at the mid diaphysis.[23] Building and maintaining bone mass density, especially specific to this area, is important for preventing fractures in the OI population.

Resistive Exercise Effects

A form of treatment at maintaining or increasing bone density is resistance training.[8,12] Load bearing exercise, aerobic training, and strength training allow the bone to accommodate to changes in mechanical loads to preserve and even increase bone density.[8] According to Rehn et al., similar results to WBV exercises have been found with resistance and weight-bearing regimens having the same duration of treatment time. [12] On the other hand, high intensity aerobic, resistance training, and strenuous load bearing have been found to cause an increased risk of fractures and injury for individuals with osteoporosis.[8] Due to the similarity of the pathology with osteoporosis, high intensity resistance training may not be an appropriate intervention.

Lower impact exercises including swimming, biking, and walking are not as effective at increasing bone due to ground reaction forces during these exercises only being equivalent to zero to two times an individual's body weight.[6] Resistive exercises performed were found to have variations within the research. Specific to children in a prospective control trial, Faigenbaum et al. showed that both low repetitive heavy resistance exercise and high repetitive moderate resistance exercises demonstrated strength gains in leg extensor muscles.[17]

Almstedt et al. found increases in bone mineral density (BMD) in healthy young men by having participants perform exercises such as squats, leg extensions, stiff legged deadlifts, seated heel rises, planks, bench press, seated rows, seated dumbbell press, standing barbell curl, french press, shoulder shrugs and abdominal crunches.[6] Ligouri et al. used whole body vibration in addition to squats, lunges, still-leg deadlifts, stationary lunges, push-up holds, bent-over rows, and jumps on and off the platform, with progression to the addition of heel and toe raises as well as resistance bands.[16] Similar exercises were used in Verchueren's study on a vibration platform including static and dynamic knee extension, squats, deep squats, wide stance squats, one-legged squats, and lunges.[8] In a study about physical training in children with OI, Van Brussel et al. found that low-resistance strength training might be best for this population from a randomized control trial.[18]

Parameters of Whole Body Vibration and Resistive Exercise Together

Decreased bone density is a risk factor for hip fractures. Therefore, training, such as whole body vibration and resistive exercise that increases this bone density, could possibly benefit people afflicted with OI by reducing their risk for fractures.[8] There is a variation in the research for parameters used with whole body vibration. Ward et al. found that high-frequency, low amplitude vibration increased trabecular bone density in children with neuromuscular disease.[14] Studies under our systematic review showed ranges in frequency used from 10-130 Hz equaling that number of repetitions per second.[8,11,12,13,15,22,24]

Research has shown that a frequency of 30-40 Hz is beneficial for bone density,[22] but many studies averaged between 15-60 Hz.[11,15] Gusi et al. found that a frequency of 10-15 Hz would be effective in decreasing bone loss in the hip and would be gentle for a frail population.[15] For example, one study divided frequency into specific effects with 10-26 Hz for balance and gait, 27 Hz for speed, and 30-40 Hz for balance in stroke patients and aging adults.[22] Ezenwa and Han Teik have argued vibration devices that provide multiple vibration input frequencies, encompassing all muscle fiber twitch frequencies, will enhance intact muscle group recruitment more than a single-frequency alternative.[13] It will provide more benefit during vibration training, and a frequency of 20-130 Hz would encompass both slow and fast twitch muscle firing.[13]

Other studies used various amplitudes ranging from 0.7 to 9mm (with the average being around 2-4 mm),[11,12,15,22] magnitude ranging from .2-10g,[11,12,24] and types of plates varying between vertical or lateral displacements.[15] For instance, Rehn et al. found a range from 0.7 to 4.22 mm amplitude and 0.2 to 10 g magnitude in his review.[12] Additionally, Blizzard & Young showed positive effects with amplitude 3.5-4 mm and acceleration from .3-.5 g by performing a systematic review.[11] Finally, Verchueren et al. demonstrated positive effects on specifically hip BMD using a vertical displacement plate, a low amplitude of 1.7-2.5, and a high frequency of 35-40 Hz.[15]

Summary

With research indicating possible benefits from whole body vibration training, it also presents a less invasive, inexpensive, and efficient alternative form of treatment for individuals with OI[21] with no or very few negative side effects reported.[12,15] Preliminary research has been done on treatment interventions to decrease the risk of fractures for individuals with OI and on whole body vibration interventions to increase bone density, improve strength and balance, and improve mobility. However, there is still further research that needs to be done on which specific parameters and exercises performed in combination with whole body vibration would be most beneficial to individuals with OI to decrease the risk of fractures.

Conclusion

Based on the reviewed literature and the use of OLE, we found that overall, whole body vibration combined with resistance exercise will provide benefit to individuals with Type I OI by increasing bone density through mechanical stimulation and muscle contraction tensile forces, hence improving strength, mobility, and balance. All of these factors play a role in decreasing the risk of fractures, especially those that frequently occur in the femur and hip. This research is vital in providing information for treatment intervention for populations that have an increased risk of fracture rate, such as those with OI.

The general effects of whole body vibration from the research have shown to prevent muscle atrophy and bone mineral density, improve strength and balance, and even further improve BMD in areas of the hip and spine. Other effects that have been shown in research include increasing muscle thickness and functional motor patterns and decreasing spasticity in children with CP. Specific to children with OI, research has also shown increases in mobility and lower extremity force due to WBV.

Research has demonstrated that the direct effects of WBVE on bone mineral density are due to a combination of muscle contraction causing a tensile force and mechanical vibration, both of which load the bone. Increases in BMD have been found especially in areas of high trabecular bone content in the hip and femoral neck. This is important to note due to the femur area being at risk for fractures because of its high stress levels and is important to note because the femur is the most commonly fractured bone in children with OI.

Resistive exercise has many positive effects found throughout research. It allows for strength gains and due to load bearing exercise, it can preserve and even increase bone density. However, in a frail population like those with OI, traditional dynamic heavy resistance may be too intense and put these individuals at risk for further injury. Low impact exercise, on the other hand, may not be effective enough to produce increases in BMD. Throughout the research, there is a wide variety of exercises used but is mostly focused on squatting, deadlifts, heel raises, and leg extensor exercises. Low resistance physical strength training for children with OI is recommended by the research for the most part.

Parameters for an intervention of WBV and resistance exercise together vary greatly throughout the literature. Overall, high frequency and low amplitude is recommended. While an average of 15-60 Hz was found in the study, the parameter ranged from 10-130 Hz. Studies found that in general, 30-40 Hz may be effective for bone density increases. Amplitude ranged from .7-9 mm with averages being between 2-4 mm throughout studies, and magnitude ranged from .2-10 g. Studies also showed variations between the use of vertical or lateral whole body vibrating plates.

Limitations

We limited our research to type I Osteogenesis Imperfecta because this is the mildest and most common form of the disease. Our main focus of research was on children and adolescents due to the higher incidence of fracture before puberty in these populations. OI type I patients are generally discouraged from performing high risk, high impact activities. Because of this, activities on the WBV machine were limited to resistive, moderately low-impact exercises to emphasize safety and bone strengthening. Another limitation in our research was lack of extensive information on pediatric and adolescent closed and open chain strengthening protocols as well as whole body vibration research for these populations.

Future Directions

While this review provides a solid foundation, it is essential that future research be done to determine the most beneficial protocol with this intervention for individuals with OI. Whole body vibration and resistance exercise can be an intervention that provides decreased risk of fracture for this population, possibly leading to an overall higher quality of life and increased health. It is important to note that this intervention of whole body vibration and resistance exercise should be used as a preventative measure for these individuals, especially in adolescence since this is the age that they are most prone to fractures. Because of the variation in so many components of this intervention, further research should be done to determine what would be the safest and most beneficial protocol for individuals with type I OI. Further research should focus on specific benefits for this population on the reduction of fractures with whole body vibration and resistive exercise.

While preliminary research has been done to show that whole body vibrations with strengthening exercises, when compared with standard strengthening exercises, could possibly reduce fracture occurrence in patients with type I OI, more research needs to be conducted to determine specific protocols for strengthening exercises and whole body vibration parameters that would be beneficial to this population. The variation in parameters of frequency, amplitude, number of sessions, session duration, intervention time, exercises, and protocols in available research proves that more studies are required to determine a more defined protocol that would include specific frequencies, amplitudes, and magnitudes, the most beneficial type of plate, and detailed exercises and repetitions. More evidence needs to be found to determine if this intervention would be beneficial for increasing bone density, maintaining bone density, achieving specific benefits, and achieving the ability to reduce the risk of fractures for these individuals long term in order to provide them with the best possible quality of life while being safe enough to not cause any increased harm.

Research has been conducted for many associated populations with conditions comparable to OI and conducted on outcomes of whole body vibration treatments such as mobility and muscle gains. However, the question still remains regarding what specific resistive exercise and whole body vibration treatments help with fracture reduction in individuals with OI. This question can thus guide research for further studies.

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Appendix A: Classification of Osteogenesis Imperfecta

Type	Severity	Features
I	Mild	Low incidence of fracture, without bone deformity
II	Perinatal Death	Fractures present at birth, respiratory failure, bone deformity
III	Severe	Often do not live into third decade of life, multiple fractures, bone deformity
IV	Moderate	Variable fractures, bone deformity, barrel shaped rib cage
V	Moderate	Variable fractures, intraosseous membrane ossification
VI	Moderate to severe	Fractures and fish scale histology
VII	Moderate	Fractures and deformities of the limbs
VIII	Moderate	Fractures and deformities of the limbs
*Adapted from Borland, et al. (2012); Goodman, et al. (2009) [4,5]		

Appendix B: Terms and Definitions (To facilitate the understanding of some technical terms, the following are defined)

- *Bisphosphonates*- a group of pharmaceutical agents that prevent the reabsorption of bone and can reverse the loss of bone[4]
- *Bone Mineral Density (BMD)*- the amount of mineral material in gram/square centimeter of bone[4]. It is often measured by dual energy x-ray absorptiometry or DEXA
- *Collagen*- a protein that provides and maintains the structure and strength for all tissues in the body[4]
- *Fracture*- a break in the bone that presents as a discontinuation of the bone resulting in a wide variety of seriousness and complexity[4]
- *Osteogenesis Imperfecta (OI)*- an uncommon genetic disease in which there is a defect in the production of normal collagen affecting connective tissue such as bone; it is also known as brittle bone disease[4]
- *Osteoporosis*- a pathology in which the bone structure is porous resulting in decreased bone mass that can increase the risk of damage and fractures to bone[4]
- *Resistive exercise*- kinetic movement in which resistance is provided by gravity or an outside source used to cause muscle contraction often performed in closed chain during weight bearing[17]
- *Whole body vibration*- a motorized stimulus that vibrates at a certain frequency causing the body to shake[12]

Appendix C: Oxford Centre for Evidence-based Medicine Levels of Evidence

Level	Therapy/Prevention, Etiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centers	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical center	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies

3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009.

Notes: Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because: EITHER a single result with a wide Confidence Interval OR a Systematic Review with troublesome heterogeneity. Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
† Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
‡ See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§ Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§ By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
†† An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡ Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
††† Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
†††† Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.

*** By poor quality prognostic cohort study we mean one in which sampling was biased in favor of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
**** Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 - 5 years chronic)