

NEWS

Vibration Therapy: Does It Have a Future in the Bone Field?

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In the most prominent animal study of its time – a 2001 *Nature* “Brief Communications” entitled “Low mechanical signals strengthen long bones” – Clinton Rubin and colleagues reported data from sheep experiments suggesting that high-frequency, low-magnitude mechanical stimulation (LMMS), in the form of vibration applied to the hindlimb, had impressive anabolic effects on bone. This study of adult ewes found that animals who received vibration at a frequency of 30 Hertz and at an acceleration equal to 0.3 g (where g equals the Earth's gravitational field), for 20 minutes per day 5 times a week over the course of a year, exhibited a statistically significant 34% increase in proximal femur trabecular bone density, a similar increase in trabecular volume, a 45% increase in trabecular number, and a 36% decrease in trabecular spacing, compared to control animals.

“It certainly wasn't the first study that suggested that vibrations can be beneficial to bone, but I think it was the most conclusive evidence that had been provided,” says Stefan Judex, an associate professor in the department of biomedical engineering at State University of New York (SUNY)-Stony Brook and a frequent co-author with Dr. Rubin over the years. Dr. Rubin and his team offered their results as evidence that mechanical signals need not be large to produce positive effects on bone. Indeed, the data suggested to them that low-level bone strains produced by the vibrating platform, similar to the low-level bone strains produced from muscle contractions that occur during passive, everyday activities like maintaining posture, could be similarly beneficial; higher impact activities like walking, running or jumping need not be necessary for bone to adapt favorably to mechanical loading.

Since their sheep study, still remembered well by bone experts, Dr. Rubin and colleagues have made similar observations in mouse and rat experiments, and beginning in 2004, the first evidence that LMMS had beneficial effects on human bone entered the scene with the publication of results from small clinical trials. Now, almost a decade after the sheep study and about half a decade since the first human study, larger clinical trials testing the ability of LMMS to improve bone mineral density (BMD) in the elderly, in children with Crohn's disease, and in childhood cancer survivors, among other groups with fragile skeletons, are planned or are underway.

For many bone experts, LMMS, a low-intensity version of whole body vibration (WBV), has ample appeal as a gentle, non-pharmacological approach to improving skeletal health. However, while Dr. Rubin and his team, who have been responsible for most of the work on LMMS, appear confident that LMMS is anabolic, as do some bone experts who haven't been as directly involved with vibration research, many outside observers take a position of agnosticism on this issue, saying that the evidence is too spotty and inconsistent to conclude that LMMS builds new bone. Indeed, they point to recent animal studies that have failed to substantiate an anabolic effect, and also emphasize the flaws in the clinical trial data to date. Furthermore, neither the more skeptical observers nor Dr. Rubin and his collaborators themselves profess to know with any confidence whatsoever how LMMS might build new bone. While a mechanism of action need not be known in order to proceed with clinical development – bone experts point to the clinical development of bisphosphonates, before a solid understanding of their mechanism of action was achieved, as an example of this – to some the current lack of

a mechanism makes LMMS's potential effectiveness seem suspicious. Ultimately, only results from larger, well-designed clinical trials will convince the bone field that vibration will be a viable option for improving skeletal health.

Clinical Trials, Yes, Gold Standard Evidence, No

It was his experience treating elderly individuals unable or unwilling to exercise, and who also took bone drugs that weren't fully effective, that stimulated Douglas Kiel's interest in vibration. "What we do with our seniors is load them up with medications for all their chronic ailments. Osteoporosis drugs have certainly been effective but they haven't really made as big of an impact as we might have thought in the senior population," according to Dr. Kiel, an associate professor of medicine at Harvard Medical School and director of medical research at the Institute for Aging Research, Hebrew SeniorLife in Boston. "So LMMS was very attractive to me as a way of keeping the skeleton healthy without resorting to medications, and enabling people who couldn't exercise fully to have this option." Dr. Kiel is currently running a double-blind, randomized, placebo-controlled clinical trial of LMMS in elderly men and women to test the potential effect of this treatment on bone.

Larger clinical trials like Dr. Kiel's are necessary to convince the bone field that it should pay more serious attention to LMMS because there have only been a handful of clinical trials of LMMS thus far, and the results from those trials have not produced the kind of evidence that proponents of evidence-based medicine find compelling. For instance, one of the most widely cited studies is a 2004 trial published in *JBMR*. This study, a 1-year, prospective, randomized, double-blind, placebo-controlled trial examined the effects of LMMS in 70 postmenopausal women with a mean age of 57 years. This study did not find any statistically significant differences in BMD between subjects who received vibration and controls who stood on placebo devices. Rather, it was only a subgroup analysis that found that subjects in the

highest quartile of treatment compliance who were lighter in weight did exhibit a statistically significant benefit; such individuals exhibited a 0.18% gain in BMD compared to a 3.17% loss of BMD in patients receiving the placebo, for a relative benefit of treatment of 3.35% greater BMD over the course of the study.

Two other clinical trials cited often by experts also provide suggestive but still rather unconvincing evidence. In a trial published in 2006, investigators studied 48 young women, aged 15-20 years, who had low BMD and at least one previous fracture. Subjects who received vibration exhibited a statistically significant 2.1% increase ($p=0.025$) in trabecular bone in the lumbar vertebrae, and a 3.4% increase ($p<0.001$) in cortical bone in the femoral midshaft, while control subjects did not exhibit changes in those measures. However, this study was not a randomized trial as subjects were assigned to the treatment or control group based on where they lived, nor were the subjects blinded since vibration machines were installed only in the homes of those who received vibration. In addition, whether the results in these younger subjects would apply to postmenopausal is uncertain. Likewise, in another clinical study published in 2004, 20 children, aged 4-19 years (mean age of 9.1 ± 4.3 years) with mobility-limiting disabling conditions such as cerebral palsy and muscular dystrophy, who received LMMS exhibited a 6.3% increase in volumetric trabecular BMD of the proximal tibia while those who stood on placebo devices exhibited a decrease of 11.9%, resulting in a net benefit of treatment of 17.7% ($p=0.0033$). However, this double-blind, randomized, placebo-controlled trial was only a very small pilot trial, and, again, whether the results would apply to elderly individuals is unclear.

There are in fact a handful of additional small studies examining the effects of vibration at much higher acceleration levels, in excess of 1 g, on bone. However, these studies, which have examined the effects of the Galileo[®], Power Plate[®] and other high-acceleration devices, have produced inconsistent results, with some finding changes in BMD and others unable to

document effects on bone. "Whole body vibration may be a promising technique, but the evidence is not strong enough to conclude that it is effective for bone loss or osteoporosis," according to Laurence Vico, based on her literature review of the effects of vibration on skeletal and other tissues published in 2008 in *Ageing Research Reviews*. Dr. Vico, director of the bone tissue biology lab at Université Jean Monnet in St-Etienne, France, is planning clinical studies to address these questions. She believes that new techniques like high-resolution peripheral quantitative tomography (HR-pQCT) should complement studies that have thus far only used DXA, in order to gain a more precise understanding of potential alterations of bone that may result from vibration treatment.

Part of the reason why clinical studies may have produced inconsistent findings is that there are numerous vibration parameters, and clinical studies have used different combinations of these parameters, with some studies not even explicitly specifying all of them. Indeed, one can speak of vibration in terms of its direction, that is, whether the vibration is vertical such that, when a person stands on the platform, vibration is applied to both feet at the same time, or whether the vibration is applied in an oscillatory, side-alternating fashion, like a see-saw. But vibration is also applied at a particular frequency measured in Hertz, a particular amplitude measured in millimeters, and a particular acceleration measured in gravitational units. How long the vibration is applied is another parameter, as is the subject's body position on the vibrating platform. With so many variables used inconsistently across studies, perhaps it is not surprising that studies have produced mixed results, and in addition, comparisons between studies become difficult to make.

Less Is More...Or Is It?

Of all the parameters of vibration, the one that generates the most debate is acceleration or magnitude (the latter term is often used interchangeably with acceleration). Devices used in studies of LMMS have generally provided an

acceleration of about .3 g, while the Galileo device and similar ones can go well beyond 1 g. Dr. Rubin, lead author of the *Nature* sheep study, professor and chair of the department of biomedical engineering, and director of the Center for Biotechnology, at SUNY-Stony Brook argues adamantly that lower magnitudes are far more preferable to higher ones because of safety concerns. "The key question that is true for any therapy or potential therapy is, 'Is it safe'? I think the higher-magnitude devices put the skeleton at risk, particularly if it's a frail skeleton as in the elderly or the young," says Dr. Rubin. In expressing his concerns about the safety of high-magnitude vibration, Dr. Rubin is very quick to volunteer an acknowledgment that he has a conflict of interest in this regard, as he has founded a company that makes the vibrating platforms that produce LMMS. However, he believes that the evidence for the efficacy of LMMS versus that for higher-magnitude vibration supports his case. "The studies that are done on the higher-magnitude devices do not show orders of magnitude greater benefit than what we see with the lower-magnitude devices, so why put yourself at risk in the first place?" Dr. Rubin asks.

While there has been much study of the adverse effects of exposure to occupational vibration, very little is known about how various combinations of vibration amplitudes and frequencies used to benefit bone are transmitted to the body. A recent *JBMR* study by Harri Sievänen and colleagues addressed this issue. Dr. Sievänen and his collaborators placed accelerometers on the skin of the ankle, knee, hip and lumbar spine of four healthy male volunteers and measured how different combinations of amplitudes and frequencies were transmitted by vertical vibration to the skeleton. They found that, depending upon the amplitude and frequency of the vibration, the actual peak accelerations measured at the skin could be much greater than the peak accelerations measured at the vibrating platform, and expressed concern about applying accelerations greater than 1 g to frail skeletons.

While the low accelerations from LMMS vibrating devices may be advantageous

from a safety perspective, they may be disadvantageous from an efficacy perspective; critics wonder whether .3 g will be enough to stimulate an anabolic response. Some recent animal studies published in the *Journal of Orthopaedic Research* have found that, in fact, it wasn't. Indeed, in recent experiments by Matthew Silva and colleagues that examined the effects of LMMS in adult, aged mice, an anabolic effect could not be documented. "We were disappointed that we couldn't find a positive effect. We found some small changes, but overall there was no benefit," according to Dr. Silva, a professor of orthopedic surgery at Washington University in St. Louis, Missouri. Likewise, in another recent study by a group from the Netherlands, no anabolic effects on trabecular or cortical bone could be observed when adult ovariectomized rats were subjected to .3 g of LMMS.

Moving Forward Without a Mechanism of Action

Such recent, negative findings raise an obvious question for which no-one who has been involved with vibration research, nor anyone who has observed its progress from afar, can give anything close to a definitive answer: is there a viable mechanism by which LMMS could stimulate the skeleton? Nobody doubts that the skeleton responds to mechanical loading; the question rather is how large the mechanical loads need to be. In this regard, speculation about a mechanism of action is just that: speculation. "There are a number of ideas out there, but I don't think there is substantial evidence for any of the hypotheses," Dr. Judex says.

There is agreement that, because the acceleration produced by LMMS is so low, direct strain of the bone matrix is likely not a viable mechanism responsible for the effects of LMMS on bone. However, one possibility is that byproducts of direct strain are involved, and so perhaps LMMS works by causing fluid flow, small amounts of which then affect the osteocyte, the cell type thought to mediate the skeleton's response to mechanical loading. This is a hypothesis that is entirely unconvincing to Charles

Turner, a professor of biomedical engineering at Indiana University-Purdue University Indianapolis. "[LMMS] is basically non-existent as a mechanical signal to the osteocyte, because the osteocyte requires the bone to deform, and these signals just don't deform the bone," according to Dr. Turner, a bone biomechanics and mechanotransduction expert who asserts that there is "almost no evidence of vibration efficacy in bone."

Another potential mechanism that has been proposed has nothing to do with mechanical loading and bone strain. Rather, Dr. Rubin and Dr. Judex have proposed that potentially acceleration per se could explain the purported effects of vibration on bone. In this scenario, the weight-bearing that occurs during LMMS and that mechanically loads the skeleton is not necessary; simply shaking a bone would be enough to produce an anabolic response. This idea emerged from experiments where LMMS was delivered to the tibia of an anesthetized mouse lying on its back; essentially the mouse leg was simply being shaken back and forth, without the involvement of weightbearing. "We were still able to find an osteogenic response, which shows that matrix deformation is not really necessary," according to Dr. Judex. Somehow, according to this new theory that Dr. Judex concedes is purely speculative, acceleration or deceleration itself affects the cells within the bone matrix; perhaps the nucleus of cells within the matrix moves back and forth as the tibia is moved back and forth. If true, this would offer interesting clinical possibilities: non-weight bearing skeletal sites like the distal radius, as well as fragile skeletons that could not withstand weight-bearing, such as those belonging to patients with spinal cord injuries, could be targeted. However, in additional experiments from Dr. Silva's group that attempted to test this hypothesis, no consistent bone anabolic effects could be found using a model of vibration that minimized bone deformation.

A third speculative hypothesis is that LMMS works by affecting not cells in the bone matrix but rather cells in the bone marrow. This idea had its start with a 2007 *PNAS* paper where Dr. Rubin, Dr. Judex and

colleagues found that mice that had received LMMS had less fat in the torso than non-vibrated animals. Based on this work, the authors have hypothesized that vibration pushes mesenchymal stem cells to follow an osteoblastic instead of an adipocytic differentiation pathway. However, while many experts are intrigued by the data, they say it is far too early to tell whether this stem cell hypothesis is correct, and some are downright skeptical, arguing that vibration affects so many different systems in the body that it quite possible that numerous confounding variables, such as effects of LMMS on hormones, may account for the data.

Bone or Muscle (or Something Else)?

Regarding a mechanism of action, another hypothesis is that LMMS has little to do with bone. "If you are studying vibration, you should be concentrating on muscle efficacy and prevention of falls. Vibration may actually show anti-fracture efficacy in the long run without having any significant bone effects," according to Dr. Turner. Agreeing with this sentiment is Dr. Sievänen, an author of the *JBMR* study mentioned earlier examining how vibration is transmitted to the body. "In many cases, falling is the root cause of these fractures, and vibration training has beneficial effects on muscle performance and balance. This effect is quite consistent and observed in many randomized controlled trials, whereas the effects on bone are less convincing, although promising."

Dr. Turner suggests a potential mechanism where standing on a vibration platform causes one to feel out of balance. As a consequence, the postural muscles that allow a person to stay standing and avoid falling are stimulated. Ultimately, through this proprioceptive mechanism, the net result is an increase in muscle strength and an improvement in balance. Whether LMMS is sufficient to act on muscle and balance, or whether higher magnitudes will be necessary, is unclear. In the clinical study of LMMS in young women with low BMD mentioned earlier, in a per protocol analysis, high compliers (i.e., those who stood on the vibrating platform for at least 2 minutes per

day) exhibited a statistically significant 7.2% greater mass in the total paraspinal musculature compared to a pooled group of controls and low compliers. Because of these results, as well as results from bed rest studies showing beneficial effects of vibration on muscle and balance, Dr. Kiel will be assessing muscle, falls and balance in his clinical trial.

In addition to muscle, balance and proprioception, vibration experts note that WBV may also have effects on the endocrine system, as well as on the vascular system, effects that could potentially explain some of the effects of WBV on muscle and the skeleton. That so many different physiological systems have been implicated underscores an added complexity to the vibration research arena: the vibration parameters that may be effective in producing beneficial or adverse effects on one system may differ from those affecting other systems. "We have evidence now to suggest that vibration may be beneficial as a whole, but with the effects that we see in the different organ systems – in the bone, in the muscles, in the nervous system, in hormones, in tissue perfusion – it is very likely that different systems react differently to different frequencies of vibration and different magnitudes as well" according to Jörn Rittweger, a physiologist at the German Aerospace Center's Institute of Aerospace Medicine in Cologne, Germany who focuses his research on the acute effects of vibration. Thus, the potential for vibration to affect so many different systems in the body highlights the need to better understand the various parameters of vibration, particularly magnitude and frequency.

The Appeal of Vibration

Vibration, as a therapeutic modality, has much in its favor. Its guiding principle – that the skeleton responds to mechanical stimuli – is a fundamental tenet of bone biology that few would dispute. In addition, the idea of a non-pharmacological solution to the problem of weak bones holds much appeal, especially for elderly patient populations for whom bisphosphonates have limitations. One of the limitations of bisphosphonates for

all patient populations is that they work primarily just on bone. Thus, the potential for LMMS to work on many different tissues in addition to bone adds further to its appeal, as it offers a multi-dimensional approach to what is in fact a multi-dimensional disease where not only bone but muscle, balance, and falls, all come into play.

Yet, despite this potential, it is an open question whether LMMS will ever be a viable way to treat low bone mass, as the most basic questions in the vibration field remain unanswered. Will an acceleration of .3 g

actually be enough to stimulate bone or muscle? If higher accelerations are necessary, will the vibration be safe enough to recommend for frail populations? Which vibration parameters are ideal, and for which specific physiological systems? Most of all, how does vibration work – is vibration primarily a muscle story? An osteocyte tale? A stem cell saga? A combination of all three? Experts will be looking to clinical trials for answers about vibration, which despite its promise, has a highly uncertain future in the bone field.