Emerging Approaches in the Prevention of Osteoporosis

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Interstitial fluid flow is essential for maintaining bone integrity. Simple, non-invasive approaches which enhance skeletal muscle pumping and thereby ensure sustained interstitial flow through bone have the potential to prevent and treat osteoporosis.
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Introduction

Osteoporosis is characterized by long-term loss of bone tissue. While the bone tissue that remains is normal and fully capable of repairing itself, the effective strength of the skeleton is reduced by the loss, leading to increased risk of fracture following even minor trauma. The most common sites of osteoporotic fractures are those composed principally of trabecular bone, namely, the distal radius, spine, and femoral neck. Osteoporosis is a common occurrence in the aged, usually resulting from slow progressive bone loss, but rapid bone loss can occur during the menopause, extended bed rest, cast immobilization, or extended exposure to microgravity. While inhibitors of bone resorption are commercially available, as well as at least one anabolic agent, a pharmacologic approach is neither an appropriate nor a cost-effective approach for young and otherwise healthy men and women, who are looking for an osteoporosis prevention strategy that can be utilized over extended time periods. Indeed, recent reports suggest that the extended use of bisphosphonates to prevent bone resorption may lead to serious long-term complications (Bamias et al., 2005; Migliorati et al., 2005; Woo, Hellstein, & Kalmar, 2006).

In order to understand the new directions being pursued in the development of preventative strategies for osteoporosis, it is necessary to understand the driving forces behind bone adaptation.

It has long been observed that larger animals have larger bones, and so it was only natural to hypothesize that adaptation processes are directed toward placing bone mass appropriately within the skeleton to the mechanical loading forces placed on the skeleton during day-to-day activities (Wolff, 1892/1986). In this context, osteoporosis is primarily viewed as a physiologic adaptation to an altered environment, that is, an adaptation by changes in the pattern of mechanical loading of the bone tissue. Indeed, numerous animal studies in which bone tissue can be loaded in a controlled manner have shown that mechanical loading of the skeleton can lead to new bone formation. However, investigations specifically addressing the link between mechanical loading and bone mass have shown that there is actually little correlation between mechanical load distributions in bone tissue and bone mass distributions. These results indicate that the bone adaptation is probably not due to the direct influence of mechanical loading but to some phenomenon coupled to the mechanical loading process. Understanding this underlying process is critical, as increased mechanical loading of the skeleton in humans has very little effect on bone adaptation processes. Numerous clinical studies have shown that while high levels of physical activity may be capable of significantly affecting bone mass in the skeleton of children, exercise regimens can produce, at best, only modest increases in bone mass, either in young adults (Jones, Priest, Hayes, Tichenor, & Nagel, 1977; Snow-Harter, Bouxsein, Lewis, Carter, & Marcus, 1992) or in the elderly (Hoshino et al., 1996; Smith, Gilligan, McAdam, Ensign, & Smith, 1989).

Bone Adaptation and Fluid Flow

Though mechanical loading, per se, does not appear to significantly affect skeletal adaptation, the nutritional and hormonal support that is tenuously associated with mechanical loading does have a profound influence on the maintenance of bone tissue. While oxygen and low-mass nutrients can diffuse from the capillaries directly to the cell population of even sparsely vascularized tissues such as bone, large proteins are diffusion limited and so are reliant on fluid flow in the tissue for transport to the cells (Montgomery, Sutker, Bronk, Smith, & Kelly, 1988). These large proteins are being continuously extravasated from the capillaries along with interstitial fluid. The flow of this interstitial fluid through the bone tissue is therefore critical to the integrity of bone cells, and, correspondingly, to the maintenance of bone mass. The extravasation of interstitial fluid is primarily dependent on transmural pressures (i.e., the difference between capillary and tissue pressures), but it can also be influenced by pressure gradients developed by the mechanical deformation of bone tissue during exercise. It is this process that provides the link between mechanical loading and bone adaptation. However, as intensive exercise generally represents a small fraction of the daily activity of most individuals (Fritton, McLeod, & Rubin, 2000), the contributions of capillary pressures and tissue pressures can be expected to dominate interstitial fluid flow in bone.

Studies performed over the last 4 decades have clearly demonstrated the importance of interstitial fluid flow in the formation and maintenance of bone mass. In the mid-1960s, Keck and Kelly (1965) first demonstrated that increased bone growth was associated with increased venous pressure. These observations led to investigations of interstitial flow in bone, and the demonstration of lymphatic vessels in bone directed from the marrow to the periosteal surfaces (Seliger, 1970). Subsequently, it was shown that high venous pressures encouraged bone formation in the absence of any change in blood flow (Kruse & Kelly, 1974), and also that high venous pressure was associated with increased venous filtration (Li, Bronk, An, & Kelly, 1987). The influence of increased venous pressure and increased filtration has been confirmed more recently using the rat hindlimb suspension model of microgravity (Bergula, Huang, & Frangos, 1999).

Numerous additional studies have lent support to the theory that blood flow and interstitial fluid flow are critical to the maintenance of bone mass. Colleran and associates (Colleran et al., 2000) showed that decreased blood flow to the limbs results in decreased cancellous bone formation as well as reduced periosteal bone. McDonald and Pitt Ford (1993) demonstrated that an important effect of mechanical loading was the significant alteration of blood flow in bone. Perhaps one of the most important clinical observations regarding the role of venous pressure and filtration was made by Issekutz and colleagues (Issekutz, Blizzard, Birkhead, & Rodahl, 1966), who demonstrated in a population of young men that bed rest resulted in substantially elevated urinary calcium secretion and that no form of supine exercise regimen was capable of inhibiting this calcium loss. However, just six periods of quiet standing for 30 minutes per day returned urinary calcium to normal levels. These study results are consistent with the premise that the influence of gravity (hydrostatic pressure effects) on the fluid within bone is sufficient to increase capillary filtration and interstitial flow, allowing bone mass to be maintained.

The proposition that interstitial flow may be a critical factor in the maintenance of bone mass is also consistent with the distribution of bone loss in disuse, whether due to aging, bed rest, or passive inactivity. Bone loss does not occur to any degree in the thorax or cranial regions of the skeleton, where blood pressure and/or gravity can sustain a normal filtration rate, and skeletal muscle pump activity combined with gravity can maintain interstitial fluid return via the lymphatic system. However, at sites where interstitial flow is limited, due to either a lack of adequate filtration or inadequate return, loss of bone mass is commonly observed.

Maintenance of bone mass, in summary, requires adequate filtration and transport of nutrients and growth factors through the bone tissue. Adequate filtration, correspondingly, requires high capillary pressures, which are normally produced by the influence of gravity during upright stance. In addition, sustained fluid transport through bone requires effective venous and lymphatic return, which serves to maintain low tissue pressures. Venous and lymphatic return, at least in the periphery of the body, is mediated primarily by skeletal muscle pumping, an often ignored physiologic function. Developing strategies to prevent bone loss, therefore, requires an understanding of how gravity influences fluid flow in the human, and how effective circulation is maintained through skeletal muscle pump activity.

Fluid Flow in Humans

Gravitational Effects on Circulation

The pumping action of the heart is sufficient to sustain blood circulation for individuals in the supine (or prone) position, but it is not sufficient when an individual is upright.

When humans are in a supine posture, the peak blood pressure generated by the heart is approximately 100 mmHg throughout the large arteries. Conversely, venous pressures in the supine position range from slightly negative at the right atrium to no more than 15 to 20 mmHg in the peripheral veins. Therefore, the driving pressure from the lower limb vessels back to the heart is only about 20 to 25 mmHg. A pressure of 25 mmHg is equivalent to approximately 25 cm (10 inches) of water, meaning that venous pressure in the supine position is sufficient to raise blood about 25 cm above the lowest point in the body. For most individuals, this pressure is adequate to return blood to the heart when an individual is lying down.

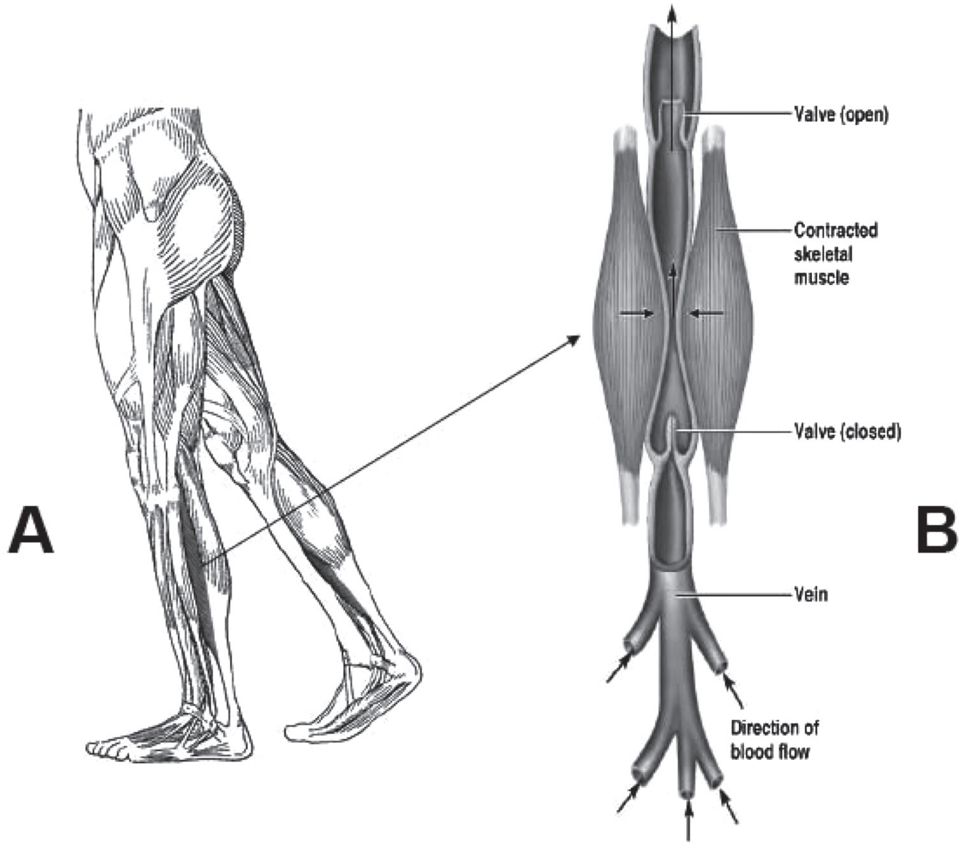
However, when humans assume an upright posture, the pressures in the circulatory system change dramatically. For example, when standing, the heart is about 1200 to 1500 cm above the feet. Venous pressures of 25 mmHg are clearly incapable of returning blood to the heart during standing; and indeed, even upright sitting would experience diminished venous return in the absence of a supplemental pump that is capable of significantly increasing venous pressures.

Role of Skeletal Muscle Pumping in Maintaining Fluid Flows

Venous return from the extremities during upright posture is accomplished in humans by skeletal muscle activity. In the legs, this "muscle pumping" is predominantly the result of calf muscle contraction synergistically assisted by competent venous valves (Figure 15.1). The role the calf muscles play in driving blood back to the heart against the force of gravity has given rise to the term "second heart." In returning this venous blood, the calf muscle pump (in particular, the soleus muscle) also serves to maintain arterial blood pressure during upright posture. In the absence of adequate calf muscle pump activity, blood sequestration into the lower extremities can be substantial. Even in healthy individuals, a shift to upright posture typically leads to a 10% blood volume shift of 7 ml/kg, or 300–600 ml, into the lower extremities (Sheperd, 1966). This "loss" of blood volume results in inadequate cardiac refilling and therefore decreased cardiac output per the Frank-Starling mechanism (Rowell, 1993).

Additionally, skeletal muscle pumping is essential for lymphatic return from the lower limbs. Upper body lymphatics can drain back to the subclavian vein by gravity-driven flow, and the thoracic region drains during respiratory motion. But the lower limbs lack any explicit lymphatic pump, and so lymphatic fluid return is completely dependent on skeletal muscle activity. While it is widely believed that interstitial fluid extravasated from capillaries is reabsorbed at the venous end of the capillaries, it has been well established that, under normal conditions, capillary flow is unidirectional—from vessel lumen to interstitium—with lymphatic drainage removing filtered interstitial fluid (Zweifach & Intaglietta, 1966). This is not an insubstantial amount of fluid, as has been shown through studies of serum volume changes during a shift in posture. Lymphatic return amounts to approximately 3 liters per day when an individual is supine, or roughly an amount equal to the entire serum plasma volume in an adult. However, the volume of this flow is greatly influenced by the increased hydrostatic forces created by gravity when an individual is upright. For example, up to 20% of serum fluid leaves the vascular system through extravasation within 30 minutes of attaining an upright stance (Hagan, Diaz, & Harvath, 1978). This fluid largely pools in the interstitial

Figure 15.1



Soleus muscle in synergy with unidirectional valves promotes venous and lymphatic fluid return. In the absence of soleus muscle contraction, blood tends to pool in the legs, resulting in increased venous pressure, while diminished lymphatic return results in peripheral edema and swelling

spaces of the lower limbs unless it is taken up by the lymphatic system. Inadequate lymphatic return, therefore, results in substantially increased interstitial fluid pressures. These high tissue pressures serve to inhibit extravasation from the vascular supply with a corresponding loss of nutrient delivery to the dependent tissues.

Role of Skeletal Muscle Activity in Maintaining Bone Mass

From the above discussion, it should be evident that the maintenance of adequate interstitial fluid flow across the bone tissue is essential for preventing the loss of bone mass that leads to osteoporosis. In order to sustain this interstitial flow, two conditions must be met:

1. An individual must spend a significant portion of the day upright, so as to maximize the hydrostatic pressure on the circulatory system. The gravitational

force operating on the circulatory system ensures high capillary pressures, which lead to high levels of fluid extravasation from the blood supply, thereby providing the nutritional support necessary to maintain bone mass.

2. The extravasated fluid must be cleared from the tissue surrounding the bone and returned to the circulatory system. If this fluid is not removed, increased tissue pressure (edema) will preclude further interstitial flow, resulting in loss of nutritional support to the tissue and bone atrophy.

For young, healthy individuals, maintaining an upright posture for a significant fraction of the day is not usually an issue, though this factor can be an insurmountable hurdle in the prevention of osteoporosis in the elderly or in bed rest patients. However, ensuring that an individual has sufficient calf muscle pump activity to maintain low tissue pressure and thereby permit sustained interstitial fluid flow through the bone tissue can be more problematic. Even for an individual in good health, age-related changes in the musculature can result in the conversion of the critical Type IIA (fast twitch oxidative) muscle fibers in the soleus into Type IIB (fast twitch glycolytic) muscle fibers, which are unable to sustain continual contraction. Osteoporosis preventative therapy, therefore, becomes a matter of training up the soleus to improve calf muscle pump function. Numerous approaches are currently being pursued for achieving effective calf muscle pump stimulation. These include training based on physical activity regimens, functional electrical stimulation, and reflex-mediated micro-mechanical stimulation of the calf muscles.

Skeletal Muscle Pump Stimulation and Bone Health

Physical Activity

Physical activity is widely accepted as a successful preventative strategy for a wide variety of conditions. Perhaps best documented are the beneficial influences of exercise on the cardiovascular system, and the ability of exercise to assist type II diabetics in regulating serum glucose levels. Both of these outcomes can be achieved by increasing the activity of any of the voluntary muscles, and so strenuous exercise of many forms has been found to be beneficial for these conditions.

However, developing a physical activity regimen capable of enhancing calf muscle pump activity presents a somewhat greater challenge, in that the dominant muscle of the calf muscle pump, the soleus, is largely an involuntary muscle. While the soleus can be voluntarily contracted, this muscle typically fires autonomically when the individual is either sitting or standing in order to maintain balance and posture. Correspondingly, exercises focused on balance and postural control, such as T'ai Chi Chuan, have recently emerged as potential exercise modalities capable of inhibiting bone loss. T'ai Chi Chuan is a unique form of physical activity, characterized by a high demand for neuromuscular coordination, low velocity of muscle contraction, low impact, and minimal weight bearing (Figure 15.2). In a case-controlled study in postmenopausal women ($N = 17$), T'ai Chi exercise was found to significantly reduce the rate of trabecular bone loss in the tibia (Qin et al., 2002). More recently, the effectiveness of T'ai Chi Chuan in slowing

Figure 15.2

An illustration of postural movements in T'ai Chi Chuan. T'ai Chi Chuan is an ancient Chinese martial art technique that involves deep diaphragmatic breathing and relaxation, with many fundamental postures that flow imperceptibly and smoothly from one to the other through slow, gentle, and graceful movements. The benefits of T'ai Chi Chuan are improved muscle strength, flexibility, postural balance, and neuromuscular coordination, reduced fall risks, and improved bone density

bone loss has been demonstrated in a larger prospective study (Chan et al., 2004). In this controlled study of 132 women (mean age: 54±3.5 years), regular practitioners of T'ai Chi Chuan saw a three- to four-fold reduction in their rate of bone loss. In addition to preventing bone loss, T'ai Chi Chuan has the benefit of improving muscle strength, flexibility, and neuromuscular coordination, and thus of reducing fall-related fracture risks in the elderly population (Lane & Nydick, 1999).

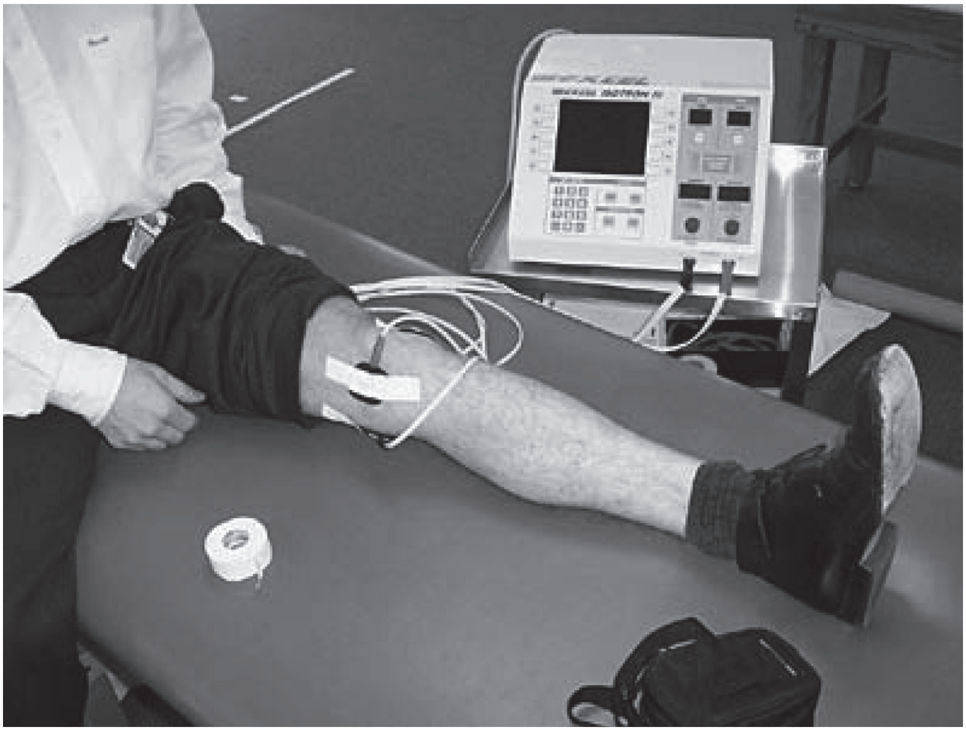
T'ai Chi Chuan is easily learned and can be practiced throughout one's lifetime. However, like all exercise programs, it requires that an individual set aside significant time each day to perform the exercises. In Asian societies where T'ai Chi Chuan is linked to other cultural values and activities, high levels of compliance are observed, but it is unclear to what extent T'ai Chi Chuan could become broadly practiced by populations in Western cultures.

Functional Electrical Stimulation

Electrical stimulation of muscle (Figure 15.3) is a widely used technique directed to both enhancing intrinsic muscle function and training up muscle so that it can function normally in the absence of external stimulation (Langzam, Nemirovsky, Isakov, & Mizrahi, 2006; Paillard, Noe, Passelergue, & Dupui, 2005). Common application areas include stroke rehabilitation, bladder stimulation, phrenic nerve pacing, and neuroprosthetics (Peckham & Knutson, 2005). In addition, a major focus of electrical muscle stimulation is in the treatment of patients with spinal cord injury (SCI), who commonly experience extensive muscle as well as bone atrophy below the site of injury. One objective of these studies has been to determine whether electrical muscle stimulation can assist in preventing further bone loss in these patients or even serve to augment bone mass.

There is compelling physiologic evidence to suggest that direct electrical muscle stimulation should be effective in influencing bone mass. One complication of lower limb muscle atrophy is severe orthostatic hypotension, as the loss of lower limb muscle activity also eliminates any muscle-pumping activity (Claydon, Steeves, & Krassioukov, 2006). In a study of six chronic and acute SCI patients, electrical stimulation of muscles in the lower limbs was found to significantly improve diastolic and systolic pressure, indicative of the ability of such stimuli to activate the muscle pump (Sampson, Burnham, & Andrews, 2000). Consistent with this observation, several studies have demonstrated that electrical stimulation can prevent bone loss and even increase bone mass in the lower limbs in SCI

Figure 15.3



Functional electrical stimulation of muscles employed to enhance and train intrinsic muscle function. Evidence supports the concept that electrical stimulation can be effective in maintaining bone mass, but this approach suffers from the discomfort and inconvenience of use. (Image used with permission from the John Hopkins University Arthritis Unit)

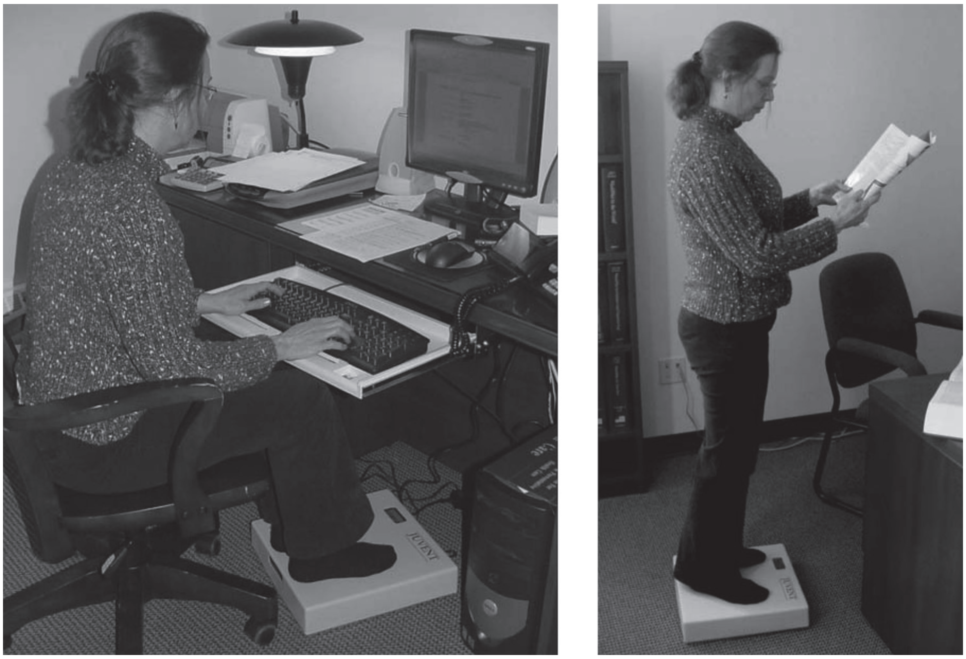
patients. Belanger and colleagues (Belanger, Stein, Wheeler, Gordon, & Leduc, 2000) reported that stimulation of the quadriceps muscle for 1 hour a day, 5 days a week, over 24 weeks, significantly increased bone mass in the proximal tibia and distal femur. Eser et al. (2003) showed that electrical muscle stimulation for 30 minutes a day, starting immediately after the onset of muscle paralysis, slowed the rate of bone loss in the tibia by 50%. Similarly, in a crossover trial, electrically stimulated cycling activity was able to reverse bone loss in the distal femur and proximal tibia, demonstrating that sustained stimulation was necessary to maintain the bone mass (Chen et al., 2005). However, a more recent study indicates that these effects may be limited to the more distal aspects of the limbs. Clark et al. (2006) addressed the effect of lower limb muscle stimulation on bone mass in the proximal femur and lumbar spine, and while they were able to show a beneficial effect of the stimulation on tibial bone mineral density, no effect was observed at the proximal femur or lumbar spine, where osteoporotic fractures most frequently occur.

Clinical results for SCI patients suggest that, at least conceptually, direct electrical stimulation of the musculature may have potential as a means to prevent bone loss. However, electrical stimulation is not conveniently applied, can be painful, and often leads to rapid muscle fatigue, factors that may significantly limit its applicability as a long-term prevention strategy for osteoporosis.

Mechanical Stimulation

As a means of bypassing the complications of direct electrical stimulation of muscle contraction, investigators have recently begun pursuing the concept of using reflex-mediated pathways to trigger muscle activity indirectly. Stimulation of a muscle such as the soleus can be readily achieved through such an approach, as it is fundamentally a postural muscle and hence receptive to a wide variety of somatosensory inputs. For example, mechanoreceptors on the plantar surface, such as the Meissner's Corpuscles, provide feedback on body position when standing, and correspondingly, are linked to the soleus muscle through short-loop reflex arcs. Micromechanical stimulation of the plantar surface stimulates the cutaneous mechanoreceptors, which subsequently initiate calf muscle contraction. Stimulus amplitudes of no more than 20–30 microns are sufficient to stimulate the cutaneous receptors in young adults when applied in the optimal frequency range for these receptors (40–60 Hz), though receptor sensitivity does decrease with increasing age (Inglis, Kennedy, Wells, & Chua, 2002). This strategy has been implemented in a device that can be placed in front of a chair, or under a desk, so that the user can readily obtain calf muscle pump stimulation essentially continuously, in either the home or the workplace (Figure 15.4a and 15.4b).

Figure 15.4



Reflex-mediated, calf muscle pump activation can be achieved through plantar stimulation either the seated or standing position. A small electromagnetic actuator is sufficient to provide a 20-30 micrometer displacement to the plantar surface that stimulates cutaneous mechanoreceptors, which subsequently initiates calf muscle contraction. The lack of any direct attachment to the subject allows convenient use and so may have potential as a long-term bone loss preventative strategy.

Studies utilizing this technology have shown that calf muscle pump activation can be readily enhanced. Stewart, Karman, Montgomery, and McLeod, (2004), using plethysmographic techniques, have shown that plantar stimulation can increase lower limb blood flow by close to 50% during upright tilt, while increasing pelvic flow by 35% and even thoracic flow by 20%. In addition, plantar stimulation was shown to almost double lymphatic return pressure. Using cardiovascular monitoring techniques, plantar stimulation has also been shown to significantly enhance venous return from the lower limbs, resulting in reversal of orthostatic hypotension and orthostatic tachycardia (Madhavan, Stewart, & McLeod, 2005).

Consistent with these observed effects on lower limb muscle pump activity, sustained plantar stimulation has been shown to significantly increase lower limb muscle strength in postmenopausal women (Russo et al., 2003). Torvinen et al.(2003) have shown a similar result for lower leg strength in an 8-month study of 56 young adult men and women in the 19–38 age group.

Correspondingly, these effects on the musculature have been observed to affect bone density over the long term. In children, effects of plantar stimulation have been reported as early as 6 months after the start of use (Ward et al., 2004). In adults, a longer duration use appears to be necessary to observe a substantial effect on bone density. In a 1-year-long, randomized, controlled study of postmenopausal women, daily use of plantar stimulation was effective in preventing bone loss in a dose-dependent manner (Rubin et al., 2004). Women who utilized plantar stimulation for 18 minutes a day or more experienced no loss of bone density in the femoral neck, as compared to a 2.1% loss in the control group. Similarly, in the lumbar spine, highly compliant subjects experienced only a 0.1% loss of bone density over the year, versus a 1.6% loss in the control group.

These preliminary results, combined with the ease of use of this technology, suggest that this technology may, in the near future, form the basis of a convenient, noninvasive, nonpharmacologic means to prevent or reduce age-related bone loss and osteoporosis.

Concluding Remarks

Over the past several decades, physiologic studies have identified interstitial fluid flow as being a dominant factor in the regulation of bone mass. Ensuring adequate interstitial flow through bone tissue must be an essential goal in any long-term strategy for preventing osteoporosis. Sustaining high levels of interstitial fluid flow requires extended periods of upright posture in combination with effective skeletal muscle pumping activity. Because age-related changes in the postural musculature of people commonly result in degradation of skeletal muscle pumping activity, explicit techniques need to be developed to regain this lost function.

Here, we have reviewed three techniques currently under development. Balance-oriented exercise programs, such as T'ai Chi Chuan, appear to be capable of preventing bone loss, but they require a commitment level from the individual that may be very difficult to achieve. Sustained electrical stimulation of the musculature has been shown to reverse bone loss, but it can be painful and may not find wide acceptance beyond subpopulations with a very high fracture risk. An alternative approach that has more recently been proposed is reflex-mediated muscle stimulation.

Micromechanical stimulation of the plantar surface has been shown to significantly enhance calf muscle pump activity by activating mechanoreceptors on the surface of the foot, which trigger soleus (calf) muscle contractions through a reflex arc. This technology has been shown to significantly increase venous and lymphatic return from the lower limbs, enhance blood flow to the lower limbs, and prevent bone loss in postmenopausal women. Convenience of use may lead to wide acceptance of this technology. More importantly, however, the success of this technology has served to refocus attention on the importance of maintaining skeletal muscle pump activity in the goal of preventing of bone loss and osteoporosis.

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