Osteoporosis in Women and Men

Worldwide, lifetime risk for osteoporotic fractures are 30-50% in women and 15-30% in men. [93]. According to WHO, osteoporosis is second only to cardiovascular disease as a leading health care problem. By 2050, the worldwide incidence of hip fracture in men is projected to increase by 310% and 240% in women [94]. Osteoporosis afflicts an estimated one-third of women aged 60 to 70 and two-thirds of women aged 80 or older. Approximately 200 million women worldwide suffer from osteoporosis [95,96,97]. By 2050, the number of hip fractures could rise to 6.3 million from a mere 1.7 million in 1990. Most dramatic increase is expected to be in Asia during the next decade [98]. In white women, the lifetime risk of hip fracture is 1 in 6, compared with a 1 in 9 risk of breast cancer [99]. Vertebral fractures are as frequent in Asian as in white women [100,101], whereas hip fractures are less prevalent in Asians [102]. It is projected that more than about 50% of all osteoporotic hip fractures will occur in Asia by the year 2050 [93, 103]. 85% of wrist fractures occur in women [104]. Nearly 75% of hip, spine and distal forearm fractures occur among patients 65 years old or over [105]. A 10% loss of bone mass in the vertebrae can double the risk of vertebral fractures, and similarly, a 10% loss of bone mass in the hip can result in a 2.5 times greater risk of hip fracture [106]. The combined lifetime risk for hip, forearm and vertebral fractures coming to clinical attention is around 40%, equivalent to the risk for cardiovascular disease [107]. In women over 45 years of age, osteoporosis accounts for more days spent in hospital than may other diseases, including diabetes, myocardial infarction and breast cancer [107].

About 20-25% of hip fractures occur in men. The overall mortality is about 20% in the first 12 months after hip fracture and is higher in men than women [109, 110]. It is estimated that the lifetime risk of experiencing an osteoporotic fracture in men over the age of 50 is 30% [96], similar to the lifetime risk of developing prostate cancer [111]. Vertebral fractures may cause equal morbidity in men and women. Hip fractures in men cause significant morbidity and loss of normal functioning [112]. Although the overall prevalence of fragility fractures is higher in women, men generally have higher rates of fracture related mortality [110, 113]. As in women, the mortality rate in men after hip fracture increases with age and is highest in the year after a fracture [114,115]. Over the first 6 months, the mortality rate in men approximately doubled that in similarly aged women [114]. Forearm fracture is an early and sensitive marker of male skeletal fragility.
fractures in comparison to women [116]. In Sweden, osteoporotic fractures in men account for more hospital bed days than those due to prostate cancer [117]. 30% of hip fractures and 20% of vertebral fractures occur in men [118].

**Osteoporosis in India**

Osteoporosis is highly prevalent in India [119-122]. The life span of an average Indian has also increased and this also contributes to the increased incidence of osteoporosis. Recent data indicate that Indians have lower bone density than their North American and European counterparts [119,123,124]. It is reported that osteoporotic fractures occur 10-20 years earlier in Indians as compared to Caucasians. As regards the burden of osteoporosis in the Indian scenario, 50% women have osteoporosis. A study conducted at Clinical Research, National Institute for Research in Reproductive Health, India to evaluate the burden of osteoporosis among 450 urban healthy women between 25-75 years of age by determining the bone mineral density revealed that only 29% had normal T score16. Data indicates that BMD values in our population were approximately 15% lower than those in Caucasian women [125-129].

Data suggests that the incidence of hip fracture - which is easily picked up by epidemiology studies as those with hip fractures end up in hospitals - is one woman to one man in India, while in places like Australia it is three women to one man. In most Western countries, while the peak incidence of osteoporosis occurs at about 70-80 years of age, in India it may afflict those 10-20 years younger, at age 50-60. But we do not yet know why. According to estimates, there are about 300 million people with osteoporosis in India. I suspect it may be more - over double the population of Australia. The evidence based on ageing population indicates that there may be a 50 per cent increase in the number of people with osteoporosis in India in the next 10 years. So, this is a huge problem in India.

Approximately 1.6 million hip fractures occur each year worldwide, the incidence is set to increase to 6.3 million by 2050 [130] Currently, there is an increasing incidence of hip fractures in the developed cities in Asia. 1 out of 4 hip fractures occur in Asia and Latin America. The number of hip fractures will increase from 1 to 2 by 2050 [131]. Burden of osteoporosis in the general population is expected to increase and is becoming a heavy financial burden [132]. The annual incidence rate of osteoporotic fractures in women is greater than the combined incidence rates of heart attack, stroke and breast cancer. More women die of osteoporosis fractures than of breast and ovarian cancer put
together [133]. The incidence of hip fracture is 1 woman to 1 man in India [134]. According to WHO, 1 out of 8 males and 1 out of 3 females in India suffers from osteoporosis, making India one of the largest affected countries in the world [135]. There are about 300 million people with osteoporosis in India. Evidence based on ageing population indicates that there may be a 50% increase in the number of people with osteoporosis in India in the next 10 years [136].

**Bioelectromagnetics and Its Application in Skeletal Disorder**

Bioelectromagnetics is the study of the interaction between non ionizing electromagnetic fields (extremely low frequency, \( \text{ELF} \leq 300 \text{ Hz} \)) and biological systems [137-139]. Experimental therapies have been emerging for a variety of medical conditions, such as non-union bone fractures, skin ulcers, migraines and degenerative nerves. Pulsed electromagnetic fields have been used as therapeutic agents over the last 40 years, following convincing evidence that electric currents can accelerate bone formation [140]. Electromagnetic-field stimulation gained credibility as a therapy of bones diseases. A similar observation has been made for cartilage, whereby electrical stimulation of chondrocytes increased the synthesis of the major component of cartilage matrix, known as proteoglycans [141].

A subset of ELF electromagnetic fields, i.e., pulsed electromagnetic fields (PEMF), displays frequencies at the low end of the electromagnetic spectrum [142], from 6 Hz to 500 Hz. Another characteristic of PEMF waveforms is their rate of change. High rates of change (e.g., Teslas/second) are able to induce significant biological currents in tissues, thereby enabling them to have greater biological defects than waveforms of lower rates of change, if the biological effect is dependent on the magnitude of the induced current [147].

This section reviews principally the experimental and clinical results correlative to the applications of electromagnetic fields on bone diseases. Extremely low frequency fields are non-ionizing and athermal (defined as either inducing no significant heating of the tissue) or thermal heating below the naturally occurring thermal fluctuations in tissue [138]. The waveforms associated with PEMFs can be asymmetric, biphasic and quasi-rectangular or quasi-triangular in shape [142]. However, most ELF sources of electromagnetic stimulation produce a sinusoidal waveform [137]. In 1979, the United States Food and Drug Administration (FDA) approved both quasi-rectangular and quasi-triangular waveforms as safe and efficacious forms of treatment of disorders associated
with fractures [142]. Specific types of low-level EMFs (electromagnetic fields) have the ability to produce specific biological responses, depending on the parameters (e.g., magnitude, frequency and waveform) of the field [138]. Intermittent use of PEMF stimulation has been shown to produce superior outcome responses to continuous use [143].

There are two methods in which PEMF stimulation can be non-invasively applied to biological systems: capacitive and inductive coupling. Capacitive coupling does not involve any contact with the body. In contrast, direct coupling requires the placement of opposing electrodes in contact with the skin surface surrounding the tissue of interest [143]. For example, if PEMF therapy is desired for the long bone or one's right arm, the opposing electrodes would be placed on the skin on either side of the right arm, surrounding the bone of interest.

Inductive coupling does not require the electrodes to be in direct contact with the skin. Rather, the time-changing magnetic field of the PEMF induces an electric field (Faraday's Law of Induction), which, in turn, produces a current in the body's conductive tissue [243-146].

Pulsed electromagnetic field stimulation - used as a treatment for conditions such as non-union bone fractures, failed joint fusions, and congenital pseudoarthroses - has yielded success rates of 70% to 95% in prospective and double-blind studies. Treatment times ranges from 20 minutes to 8-10 hours per day, depending on the condition to be treated and the field parameters used [147]. There is no discomfort or known risk associated with this stimulation. It is non-invasive, and the cost of medical treatment is substantially reduced relative to the costs of surgery [138,142,143, and 147]. The presence of implanted metals does not appear to affect the therapeutic ability of the PEMF exposure [146]. Furthermore, PEMF therapy is simple to use [147]: no surgical procedure is required; the PEMF stimulation can be performed in an office setting. There are no known complications, no anesthetic is required, and the length of treatment is comparable to bone-grafting procedures. However, these advantages of PEMF stimulation are qualified by the cooperation of the patient [148]. Specifically, the patient must sometimes use the PEMF stimulation device for 10 hours a day[149].

When considering the use of PEMF stimulation as a clinically therapeutic agent, are the health risks associated with exposure to such stimulation. While evidence for carcinogenic effects of magnetic fields is small, and there is no evidence supporting the direct damage of DNA by electromagnetic fields, there is some support that magnetic
field stimulation could act as a co-carcinogen in combination with a known genotoxic and/or non-genotoxic carcinogen. There is greater support for the possibility of teratogenic and reproductive effects of ELF magnetic fields [137]. Despite the ongoing debate over the safety of PEMF exposure, it is generally believed and accepted that brief exposure to the fields is safe. Nevertheless, there are still warnings for those with known cancers, those who are pregnant, and those with permanent pacemakers to avoid exposure sessions [143].

To date, the only FDA approvals for the use of PEMF stimulation for clinical treatment are for therapeutically resistant problems of the musculoskeletal system, such as delayed-union bone fractures, failed joint fusions, and congenital pseudoarthroses [150]. Several cellular mechanisms, including increases in growth factors, have been implicated as the possible causes of success from PEMF stimulation. For example, fracture non-unions, failed joint fusions, and congenital pseudoarthroses are thought to be healed via increases in mineralization [142], angiogenesis, collagen production, and endochondral ossification that result from PEMF stimulation. Congenital pseudoarthroses also show decreased osteoclastogenesis following PEMF therapy [147].

**Bone Repair**

Bone repair requires the cooperation of specific bone cell types: osteoblasts and osteoclasts. Osteoblasts are involved in the formation of bone, while the main function of osteoclasts is bone resorption. Generally, these cell types are in normal balance, and the amount of bone is kept constant. When a fracture occurs, osteoblasts and osteoclasts work together to quicken the healing process. However, sometimes healing is not at an optimum level and non-union results. These types of fractures require an additional stimulus, such as pulsed electromagnetic-stimulation, to assist in the healing process [151].

Pulsed electromagnetic-field stimulation has been shown to have an effect on bone repair via a number of different mechanisms. Firstly, PEMF has been shown to stimulate calcification of the fibro cartilage in the space between the bony segments. Secondly, the increase in blood supply that arises due to PEMF's effects on ionic calcium channels have been implicated as a source of improved bone healing. Thirdly, PEMF has been suggested as having an inhibitory effect on the resorptive phase on wound repair, leading to the early formation of osteoids and calluses [152,153]. A fourth mechanism by which PEMF is thought to have an effect on bone repair is through its influence on increasing the rate of bone formation by ostcoblasts [151].
The degree to which PEMF stimulation is effective is dependent on several factors, including anatomic location, associated surgery, patient age, disability time, date of treatment initiation, adherence to treatment protocol, and infections. In general, non-unions in young adults are more easily stimulated to heal than those in older adults and stimulation has been found to be more effective if initiated within two years of onset of the original fracture [149].

Non-union fractures are those fractures in which healing does not occur within six months of injury. These fractures represent 3% of all long-bone fractures, and result in a tremendous amount of discomfort and pain. The use of PEMF stimulation as a treatment for non-unions has been very successful, with success rates reaching 80% [143,148]. The amount of time required prior to having this treatment prescribed is slowly being reduced from its original requirement of nine months following injury. Furthermore, the successful results obtained from this treatment have prompted discussions of the use of these fields for treatment of ordinary fractures. It is anticipated that PEMF stimulation on ordinary fractures would reduce the amount of time that a cast must be worn [143].

The first study to report successful application of PEMF stimulation was conducted by Bassett et al. Using 43-beagle dogs with surgically produced bilateral fibular osteotomies, these researchers were able to demonstrate a non-invasive acceleration of the repair process in the dogs following 28 days of exposure to low-frequency, low intensity PEMFs (2 mV/cm, 1.5 ms, 1 Hz, biphasic; or 20 mV/cm, 0.15 ms, 65 Hz, biphasic). The 65 Hz PEMF was more effective in improving healing (i.e., producing new bone tissue) than the lower-frequency field [154,155].

Non-Unions

Bassett, Pilla, and Pawluk [156] reported the first account of a therapeutic benefit of ELF PEMFs in humans. These researchers reported that PEMF stimulation (75 Hz) on surgically resistant non-unions led to osteogenesis as a result of the therapy. Twenty-five of the 29 patients in the study displayed radiographic evidence of bone formation following one month of stimulation. Furthermore, these researchers were able to prevent several individuals who were recommended for amputations from these painful and debilitating procedures.

Following the success of Bassett et al. [156], further research was conducted investigating PEMF stimulation on fracture healing. Heckman et al. [149], for example, reported a 64.4% success rate in 149 patients who used PEMF stimulation to treat non-
unions. For patients, who maintained intensive use of the stimulation for three months, effectiveness was seen in 85% of patients. Frykman et al. also reported success of PEMF stimulation. These researchers reported an 80% success rate among 44 patients with non-unions of the scaphoid (a small bone in the wrist joint) treated with PEMF stimulation, and advocated PEMF stimulation as an alternative method for treating non-union scaphoid fractures when long-arm cast treatment proves ineffective [148]. This finding was replicated in 1997 in a case study of a 12-year-old boy with a non-united carpal scaphoid fracture who was successfully treated with PEMF stimulation, such that union of the fracture was established following treatment [157]. The use of PEMF stimulation appears to be effective and a reasonable choice of treatment among individuals suffering from non-unions [149].

A more recent reporting by Traina et al. [146] of the successful application of PEMF exposure for the treatment of non-unions claimed a 74% healing rate, with age of patient, site of fracture, type of non-union, and presence of infection as significant factors influencing the results. The presence of infection of the bone tissue or surrounding soft tissue was previously reported to not have an effect on the treatment outcome [146].

The early success of PEMF treatment of non-unions was not replicated in every study. For example, PEMF stimulation (0.3 T/s burst waveform, 15 Hz) was not shown to be defective in the treatment of un-united tibia fractures at 12 months post-injury. Specifically, Barker et al [158] found that five of the nine patients in the active treatment group, relative to five of the seven patients in the placebo group, displayed united fractures at the end of the 24-week experiment. These data suggest the need for further research; yet, this study included only 16 patients, and so there was very little statistical power to detect a significant difference. Also, the induced electric fields were much lower in this study than in the original work by Basset [156].

**Congenital Pseudoarthrosis**

Pulsed electromagnetic-field stimulation has also been shown to have clinical efficacy for the treatment of congenital Pseudoarthrosis [152]. This treatment modality aims at bone consolidation, as well as prevention of re-fracture and misalignment of the bones involved [146]. Specifically, PEMF (8 T/s, 20 pulses repeated at 15 Hz) stimulation, along with immobilization of the fractured area, was found to have an 80% or greater success rate for Type I and Type II lesions (gaps less than 5 mm wide) for which no operations had yet been performed. Type III lesions (lesions which are atrophic, spindled,
and had gaps in excess of 5 mm wide) were not as responsive to PEMF stimulation, displaying a 7% success rate in response to treatment that included only PEMF, and an overall 19% success rate for treatments that also included operations. The lesion types were declined according to the lesion's appearance on X-ray photographs [152]. The success of treatment of congenital pseudoarthrosis with PEMF stimulation was outstanding since in the past, amputation was the most frequent outcome for this disorder [142].

**Osteotomies**

Pulsed electromagnetic field stimulation has been shown to have an additional use in bone repair. Treatment of osteotomies (misaligned bones) in guinea pigs with PEMF therapy (15 HZ, 200 is unipolar pulse, 1.8 mT, 3 T/s) has resulted in increased new bone growth in the gap caused by the osteotomy relative to placebo group animals, where loose connective tissue filled the osteotomy sites. This study provides implications to humans about the possibilities of using PEMFs to quicken craniofacial healing [153]. However disapproval of PEMF stimulation was provided by De Haas et al. [159], who found that recently osteotomized long bones of rabbits given PEMF stimulation experienced a quicker initiation of the healing process, but did not have a significantly reduced time for solid union, relative to control rabbits.

The pulse parameters of a magnetic field as well as its duration of use are important characteristics that have been shown to influence the effectiveness of PEMF stimulation. Matsumoto et al. [160] investigated the bone formation surrounding dental implants inserted into the femur of rabbits, and found that bone contact with the implant was greater among PEMF-treated (100 Hz. rise times of 8 T/s 12 T/s and 32 T/s for 0.2 mT, 0.3 mT and 0.8 mT peak, respectively) animals relative to controls. Among treated rabbits, 0.2 mT and 0.3 mT fields had significantly greater bone contact and bone area than the 0.8 mT-treated femurs. No significant difference was observed for bone contact or bone area for those femurs treated four hours/day as opposed to eight hours/day. Furthermore, it was found that two weeks of exposure had a significantly greater effect than one week; yet, the measured outcomes were not significantly lower at two weeks than they were following four weeks of exposure. This study indicated the need to select the proper magnetic-field intensity, duration, and length of treatment to maximize the outcome [161].
**Hip Arthroplasty**

Hip arthroplasties are required when individuals are suffering from hip problems. A common side effect of such surgeries however is the loosening of the prosthesis that occurs in 15% - 25% of patients within 10 years of the surgery. The successful application of PEMF therapy in orthopedic disorders prompted Konrad et al. [162] to consider its use in a non-blinded, uncontrolled study investigating the treatment of twenty-four patients suffering from aseptic loosening of the hip prostheses. Patients were assessed for levels of pain and hip movements prior to and following exposure to magnetic fields (50 Hz, 5 mT). No patients were randomized to a sham condition. Significant improvements in pain ratings and all hip movements (except for flexion and extension) were noted following exposure sessions in patients suffering from loose hip replacement, but not for those patients suffering from severe pain due to gross loosening of the hip prostheses [162]. This suggests that PEMF therapy may only be beneficial in reducing mild to moderate pain associated with hip prostheses, but not severe pain levels.

**Perthes Disease**

While there have been good results found from the treatment of orthopedic disorders with PEMF, not all diseases or conditions have benefited from such treatment. For example, Perthes' disease a condition in which young children suffer from a temporary loss of blood supply to the femoral head (the ball part of the hip joint) has not been shown to benefit from PEMF stimulation [163]. Twenty-two boys, randomized to either orthosis plus PEMF treatment or sham treatment, displayed no significant differences in treatment durations (an average of 12.5 months for those receiving PEMF versus an average of 12.0 months for those receiving sham). The treatment time was defined as the amount of time required for the upper femoral epiphysis (the top part of the femoral head) to be resistant to the deforming effects caused by weight-bearing. Based on this controlled study then does not appear to be a significant effect of PEMF stimulation on the successful treatment of Perthes disease.

However, there are inconsistencies in the literature with respect to the success of PEMF stimulation in treating diseases associated with the femoral head. For example research investigating the ways in which PEMF stimulation enables repair of the dead bone associated with lack of blood supply to the femoral head, has found that PEMF exposure enables repair of the dead bone by promoting in growth of new blood vessels, while maintaining a balance between the rate of dead bone removal and the formation of
new bone [142]. Vallbona and Richards [140], commenting on studies using EMF stimulation to treat femoral-head necrosis, reported that this form of treatment resulted in successful progression for lesions located in the hips, according to both clinical (80% successes) and magnetic resonance (MR) imaging (76.6% successes) evaluations. The combined clinical and MR imaging success rate was reported as 63.3% for the lesions.

**Joint Diseases**
Pulsed electromagnetic-field therapy has been shown to be effective in treating joint diseases; yet, the degree of its success depends on the specific joint disease in question. Specifically, joint diseases involving only one joint, as well as single traumata (suffering from acute lesions), show significant improvement following PEMF stimulation. In contrast, disorders involving multiple joints (e.g., polyarthrosis, rheumatoid arthritis) are much more resistant to the effects of PEMF stimulation, and show less improvement following treatment sessions. In a large 11-year experimental study, 3014 patients suffering from a joint disease were treated with extremely low frequency, low-intensity sinusoidal magnetic fields (0.6 T/s - 1.2 T/s). Patients were given one 15 - 40-minute session daily for 10 - 15 days to assess the effects of the pulsed magnetic field exposure on healing of the joints and associated pain levels. These patients (except females who were pregnant or menstruating, and individuals who carried a pacemaker) were exposed to the magnetic fields. Control patients (in addition to the 3014 patients) were included and provided with sham treatment. Of the 3014 subjects who received PEMF exposure, 78.8% showed good results (i.e., pain disappearance, 40% - 50% increase in degrees of freedom of the sick joint, maintenance of bone tit for at least three months, decrease in thermal irradiation of the affected joint after magnetic-field exposure). The best results were obtained with patients who participated in therapeutic exercises following magnetic field therapy, and maintained control of body weight and bone mineralization. Control patients reported a complete absence of any benefit when (unknowingly) exposed to sham treatment. Upon subsequent exposure to the active PEMF unit, these controls obtained the same results as the patients who were exposed to the active unit [164].

**Rheumatoid Arthritis**
Rheumatoid arthritis (RA) is a chronic condition in which an individual suffers from inflammation of the joints, resulting in feelings of pain, stiffness, and swelling. There is no known cause of this disorder but it has been implicated as being auto immune in
nature. In testing individuals for the presence of rheumatoid arthritis, screening can be conducted for an antibody known as the rheumatoid factor (RF). The rheumatoid factor is present in the blood of 80% of adults suffering from rheumatoid arthritis [165]; however, its presence or absence does not necessarily indicate that one has rheumatoid arthritis. Individuals who possess the rheumatoid factor are classified as serological-positive, while those lacking the antibody are categorized as serological-negative.

Ganguly et al. [165] conducted a study investigating the effectiveness of PEMF stimulation in reducing pain, tenderness, swelling, joint functional disability, and joint spasm with deformity in 35 patients suffering from rheumatoid polyarthritis (multiple joint disorders). Patients in this study were assessed according to serological grouping. Results indicated that those individuals lacking the rheumatoid factor (i.e., patients who were serological negative) showed earlier responses to the PEMF (rectangular pulse) for pain and swelling, and a much earlier improvement for pain, tenderness, and joint functional disability relative to serological-positive individuals. The same trend appeared for joint spasm with deformity; however, the overall treatment effect for this symptom was low for both groups. These findings provide empirical support for clinicians to treat individuals with and without the rheumatoid factor differently, as PEMF was not shown to be as effective a therapy for those possessing the antibody [165].

**Osteoarthritis**

Osteoarthritis is the most common rheumatic disorder, affecting older people in industrial countries [141]. It is characterized by degeneration of articular cartilage (cartilage at a joint), and the presence of hypertrophic (enlargement of organ due to increase in size of constituent cells) tissues [166]. Those suffering from the disorder, experience pain, swelling, tenderness, and stiffness in the weight-bearing joints of the lower extremities [141]. Approximately 80% of the population over 75 years of age displays radiological signs of osteoarthritis, with 40%-80% of these individuals also having clinical symptoms of the disease [150, 166].

Treatment for osteoarthritis has begun to shift away from drug therapies - which have, in large part, been found to be ineffective and toxic - and towards more unconventional modes of healing [141]. This shift has resulted despite the firm position of the American College of Rheumatology that there is currently inadequate scientific documentation to warrant the use of PEMF therapy for treatment of osteoarthritis of the hips and knees [150]. Nevertheless, PEMF stimulation has been gaining increasing
support as a treatment for osteoarthritis. It has been suggested that magnetic fields are beneficial in the treatment of osteoarthritis because they suppress inflammatory responses at the level of the cell membrane [167].

An attempt to demonstrate the clinical importance of magnetic-pulse treatment for knee osteoarthritis was conducted by Pipitone and Scott [150]. These authors found no significant improvement of magnetic-field-treated patients (unipolar pulse, 7.8 Hz in morning, 3 Hz in evening; < 50 T/s) relative to placebo-treated patients at the end of the study. However, the authors did find that magnetic field-treated patients reported significant improvements in a questionnaire assessing pain, stiffness, and physical disability at the end of the study relative to their baseline scores on these measures. In contrast, no significant changes were observed for placebo-treated patients in these measures between baseline and the end of the study. This work suggests that PEMF stimulation should be included as a part of the treatment protocol for individuals suffering from osteoarthritis; however, further experimentation using different magnetic devices, treatment populations, and experimental protocol should be considered.

Rotator-Cuff Tendinitis
Rotator-cuff tendonitis (inflammation of one or more of the muscles that holds the ball of the shoulder joint tightly against the socket), is a common cause of shoulder pain among adults. Conventional treatments, such as corticosteroid injections, are not always effective; therefore, alternative therapies have been evaluated. A randomized double-blind experiment designed to assess the effect of PEMF stimulation [73 ± 2 Hz; 2.7 mT, 7.9 T/s] on individuals suffering from rotator-cuff tendonitis was conducted. The design of this experiment consisted of three phases. During the first phase, one group of patients received PEMF treatment, while the other group received sham treatment. The second phase involved the administration of PEMF exposure for both groups of patients. In the third phase, no PEMF stimulation was given to either group. This design allowed for obvious group differences to be detected upon the introduction of the second phase, and also enabled all subjects to receive the PEMF treatment following four weeks (the beginning of second phase), as opposed to only offering such therapy to the treatment group. Upon presentation of PEMF stimulation to the control group at the beginning of the second phase, a remarkable decrease in pain ratings and an increase in active range were noted. These scores were in the direction of those of the treatment group, with no significant group differences present following the four-week mark of the study. These
findings demonstrate the ability of PEMF stimulation to reduce pain and increase activity among individuals suffering from rotator-cuff tendinitis, and implicate such therapy for individuals who suffer from the disorder, and art: unresponsive to, or noncompliant with the administration of, corticosteroid injections. Overall, Binder et al. found that more than 70% of all patients in this study improved following PEMF therapy [168].

Lateral Humeral Epicondylitis

The success of PEMF therapy in treating rotator-cuff tendinitis prompted rheumatologists to consider the use of such therapy for other chronic tendon lesions, such as lateral humeral epicondylitis (better known as "tennis elbow"). A randomized, double-blind assessment of the effectiveness of PEMF therapy in treating this condition (a minimum of eight weeks of treatment) in 30 patients failed to find a significant beneficial effect of PEMF stimulation (single pulse, 200 ms duration, 15 Hz) to warrant its use over placebo conditions. This conclusion may be related to the 53% spontaneous healing found among patients in the placebo group, or to the use of different pulses in treating lateral humeral epicondylitis relative to other rheumatological disorders [169].

Spinal Fusions

Spinal fusions are conducted when an individual is suffering from a painful vertebral segment. This type of surgery is invasive, and is used only after more conservative methods of treatment have been explored (e.g., bed rest, drug therapy, exercise, massage) [170]. Once spinal fusions are deemed medically necessary, the surgical team wants to ensure that recovery will be as quick as possible, and that minimal pain will be endured. One method is to achieve these goals through the use of PEMF stimulation. Marks [170] found that spinal fusions for discogenic low back pain were successful in 97.6% of the surgeries of patients in the PEMF stimulation group, as opposed to the low 52.6% success rate among patients in the unstimulated group, indicating that PEMF stimulation allows for bony bridging in lumbar spinal fusions [170].

A complication of spinal fusions arises when an individual also suffers from Pseudoarthrosis. The use of PEMF therapy to reduce Pseudoarthrosis has been shown to be effective in a rabbit fusion model [171]. Twenty adult white rabbits were randomly assigned to either a PEMF or a sham exposure for four hours daily for six weeks. Characteristics of the electromagnetic field included asymmetric rise and fall times (3 ± 1 T/s and 9 ± 4 T/s) using a 26-ms pulse burst, a 670 ± 10-ms burst interval, and a pulse
rise and fall time of 400 ms. The animals were euthanised at six weeks, at which time radiologic and histologic samples were taken. Radiographic analysis indicated that six of the 10 animals in the placebo group, and eight of the 10 animals in the PEMF group, had solid fusions. In the rabbits that demonstrated solid fusion, there was a significant increase in stiffness of the fusion mass, a significant increase in area under the load-displacement curve (representing energy absorbed by each motion segment), as well as a significant increase in the maximum load before fusion failure among the PEMF-exposed animals relative to the placebo controls [171]. The implication of these findings to human studies is of importance, as this study provided preliminary support for the idea that exposure to PEMFs can reduce Pseudoarthrosis, thereby reducing pain among human patients with lower back pain.

**Interbody Lumbar Fusions**

Interbody lumbar fusions are performed to help release stress from a damaged disk that has caused a pinched nerve root. The rates of lumbar fusion are unpredictable; however, following evidence that PEMFs have the ability to aid in bone formation, it has been shown that the presence of these fields has a significant effect on spinal fusions. Using a double-blind prospective approach, Mooney [172] assessed the success of spinal fusions in 195 patients who were undergoing initial attempts at spinal fusions. Success rates were defined as radiographic evidence of solid fusion. For those patients who complied with the methodology of using the brace for at least eight hours each day, there was a success rate of 92.2% in the active treatment group (PEMF, 0.18 mT, 1.5 Hz). This rate was significantly higher than the 67.9% success rate found among patients in the placebo group. The patients' age, sex, fusion level, number of grafts, graft type, or internal fixation did not affect these success rates. Smoking made very little difference, yet showed a decreased trend in success rates for both active and placebo group patients [172].

**Osteoporosis**

Osteoporosis, the most common skeletal disorder, is associated with decreased bone mass. Consequences of this condition include the inability of the skeleton to resist stresses of everyday life, resulting in numerous fractures. The main goals of this thesis is to address the issue of osteoporosis and its management through the PEMF treatment. The beneficial application of PEMF stimulation in healing non-union bone fractures suggested the possibility that such treatments might be beneficial to patients with osteoporosis.
Twenty post-menopausal women participated in an investigation of the effectiveness of PEMF therapy in increasing bone density. During twelve weeks of daily 72 Hz pulsating magnetic field exposure (380 is quasi-rectangular wave, followed by 6 ms quasi-triangular wave), bone densities of exposed bone regions increased; however, during the 36 weeks following treatment, bone densities decreased significantly. These rebound results suggest the immediate effectiveness of PEMF therapy, and indicate the need for continued treatment to ensure prolonged increased bone density [161]. A decrease in initial improvement is not exclusive to PEMF treatment; any treatment (including drug therapy) given to improve symptoms associated with osteoporosis is expected to show declines following its removal.

Several laboratories have examined different osteoporotic animal models exposed to capacitively coupled electric field (CCEF). Li [143] tested a CCEF signal (60 Hz symmetrical sine wave) for osteoporotic treatment. After treatment with CCEF the animals were tested for restoration of bone mass and strength. The author found a statistically significant enhancement of wet weight, dry weight, ash weight, ultimate strength and cortical area.

Brighton et al [174] determined the dose response relationship of a low voltage, 60 KHz CCEF signal on an established osteoporosis in a rat tibial model with sciatic neuroectomy. In the first part of the study, rats were subjected to different intensities of CCEF (0.25, 0.50, 1.0, 2.5, and 5.0 V (p-p) ) for twelve days. On the 28th day after sciatic neuroectomy all showed mean losses of tibial ash weight that were significantly less than those of the controls. The rats that had a 0.5-volt P-P signal showed the least mean loss of tibial ash weight (only 6 percent). In the second part of the study, the duty cycles of a sine wave, 60 KHz, 0.5V p-p signals were varied (12.5, 50 and 100 percent on) and the wet, dry and ash weights were determined and compared with those of unstimulated Osteoporotic controls. Only 100 percent duty cycle was effective in reversing the loss of bone mass in the neurectomized tibiae.

In a neurectomy model for localized disuse oseoporosis, single PEMFs were found to prevent the loss of tibia trabecular bone mass and mineral strength by evaluations of histomorphometry and mechanical testing system methods [175]. Electrical or mechanical stimulation can be equally effective in maintaining or improving bone mass [176, 177]. Low energy time varying magnetic fields, induce specifically configured electrical currents in disuse osteoporotic rats. In another study conducted on functionally isolated ulna of an adult turkey was developed as a localized osteoporotic model after
eight weeks of disuse by proximal and distal epiphyseal osteomis [178]. Through 1 mm incision the results revealed that short daily periods of PEMF stimulation (induced electric power between 0.01 and 0.04 tesla² per second, an effective intensity window) had the ability to inhibit bone loss in the absence of function. Some other reports also confirm positive reports of capacitively coupled fields on bone density [179]. Experimental results suggest that PEMF stimulation exerted a preventive effect against bone loss of osteoporotic hind legs [180]. Studies carried out by other investigators [172, 181 and 182] had the same experimental results of bone loss inhibition by PEMF [176]. The clinical results [183] showed that bone mineral density of the treated radii increased significantly as compared to the contralateral control radii.

Chang and Chang [184] have demonstrated that reduction of trabecular bone mass, destruction of trabecular bone structure, and increase of serum PGE₂ concentration resulting from estrogen deficiency in the ovariectomized female rats were inhibited when exposed to PMEF stimulation. These workers used a stimulating waveform having the characteristics: repetitive single pulses with a pulse duration of 0.3 ms and frequency of 7.5 Hz. The intensity of magnetic field was 4–8 G. Since this PEMF stimulation had no effects on the bone formation rate, it seems reasonable to infer that the prevention effect of this PMEF stimulation on trabecular bone loss might be due to the suppression of bone resorption rate.

Some other investigators [175, 176] have found that the field with characteristics (frequency 72 Hz, pulse width 380 μs and induced electric field intensity of 1.5 mV/cm) were as effective as pulse bursts in preventing disuse osteoporosis in rats. They applied fields by whole body coils for 24 h/day. Tabrah et al [185] reported that the same PEMF used by these authors has the capability to prevent bone loss in osteoporosis prone women [186]. They found the pulse burst waves at a positive amplitude of 25 mV, burst width of 4.2 ms, pulse width of 230 μs and repetition rate of 12 Hz to be effective in preventing osteoporosis caused by bilateral ovariectomy and right sciatic neuroectomy in rats. It was found that pulse burst with pulse width of 30 ms, repetitive rate of 1.5 Hz and positive amplitude of 2.5 mV had the capability to inhibit the bone loss in disuse osteoporosis.

A repetition rate of 1.5 Hz and each burst containing 120 repetitions of an assymetrical pulse was effective in preventing bone loss by regulating cortical bone remodeling. Simske et al [182] found that the twin pulses with the pulse width of 25 μs, separated with 875 μs, and pulses in the pairs that were separated by 75 μs were capable of strengthening the biomechanical properties of tibiae of disuse osteoporosis (caused by
tail suspension in mice). However Takayama et al [187], had found the same result in PEMF exposure (square wave with frequency of 15 Hz, peak magnetic field strength of 15 G).

Chang and Chang [188], reported that there was a 29% decrease in PGE$_2$ level from OVX animals to PEMF+ OVX animals. These authors using a bilateral ovariectomized rat model system, demonstrated that the ability of specific PEMF with pulse duration of 0.3 ms, frequency of 7.5 Hz, magnetic field strength of 4-8 G and induced electric field of intensity of 1-2 mV/cm, prevented trabecular bone loss of proximal tibiae resulted from estrogen deficiency, and PGE$_2$ might relate to this preventive effect. Using Helmhetz coils and self developed pulsed electromagnetic fields (PEMF) stimulations to generate uniform time varying electromagnetic fields, the effects of extremely low frequency electromagnetic fields on osteopenia were investigated in bilateral ovariectomized rats. These experiments demonstrated that extremely low intensity, low frequency, single pulse electromagnetic fields significantly suppressed the trabecular bone loss and restored the trabecular bone structure in bilateral ovariectomized rats [189]. These investigators examined bone mineral density changes of the radii of osteoporotic women during 12 weeks of daily PEMF exposure. Increased bone density in the PEMF treated limb was also reported during treatment, with a return to the contralateral control values after the treatment was terminated.

Another way of looking at the management of osteoporosis by electromagnetic fields is to consider the role of osteoclasts. For instance, experiments in which cultured bone marrow cells were exposed to 60 Hz electric fields at 9.6 $\mu$V/cm for 8 days. The formation of osteoclast like cells in marrow culture were suppressed [185].

Pulsed electromagnetic field exposure has been applied to a variety of orthopedic pathologies, mostly with positive, successful indications. For example, Traina et al. [146] reported that PEMF therapy was a successful modality of treatment of congenital-pseudoarthrosis, pseudoarthrosis, delayed union, fracture at risk, recent fracture, bone grafts, vertebral arthrosis, and avascular necrosis. Limb lengthening, however, was not successfully achieved through the use of PEMF stimulation.
Rats as an animal model for postmenopausal osteoporosis induction.

We have used rat as an animal model for osteoporosis and this review will concentrate on the rat. The OVX rat exhibits most of the characteristics of human postmenopausal osteoporosis. With the fast generation time, rodents are often a starting point for preliminary screenings, efficacy and toxicity of a new pharmacological agents or therapeutic modality, followed by verification in other species, before undertaking clinical trials in human patients [190]. Advantages of rodents are numerous. They are inexpensive, easy to house, and the general public is accustomed to the role of rodents for use in research. With intense interest in transgenic animals, availability of strains of mouse mutants with altered the bone marrow function, availability of recombinant murine cytokines, mice will always be the logical starting point for manipulation of the genome [191]. A Senescence- Accelerated Mouse (SAM) mouse has been developed as a model for age-related spontaneous osteopenia [192]. There is extensive literature studying the OVX rat including the histomorphometric changes, biochemical markers, methodology for bone densitometry and evaluation of bone fragility [193-198]. Genetically specific strains can be acquired, thus removing some variability in studies. Their shorter life span enables studies on the effects of aging on the bone. Because the rodent has been used so extensively in research of all types, much is known about bone turnover and the effect of diet in this process. Cortical thinning and increased fragility are well documented in aging rat and mouse bone, but it is unclear if this results in increased fractures. Weight gain in OVX rats can result in an increase in bone mass with increase in mechanical loading, resulting in protection of OVX animals against age-related loss of bone strength [199]. Therefore bone changes are seen as osteopenia rather than osteoporosis. Rodents do not experience a natural menopause but OVX has become a time-honored method used to produce an artificial menopause [193]. In young rats a limited naturally occurring BMU-based remodeling takes place and they do not have Haversian system. So they may not be used in osteoporotic model. Mature rodents have Haversian systems and OVX results in a significant bone loss. They have lamellar bone (although most is “fine-fibered”), trabecular remodeling, and some secondary osteonal remodeling [195-197]. Thus we have taken mature rats of 3 months of age for ovariectomy.