DISTANCE RUNNING OVER THE LONG TERM:
OBSERVATIONS ON BONE MINERAL DENSITY AND TESTOSTERONE IN MEN

by

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Abstract

In recent years, physical activity has become an important focus in the prevention of osteoporosis. Mechanical usage of bone through vigorous physical activity can increase the bone modeling and remodeling processes which evoke architectural adaptations and/or increase bone mass. Much of the research in this area has focused on women due to the higher incidence of osteoporotic fractures in this population. However, men sustain one-third of hip fractures worldwide, and are more likely than women to die within one year of the injury (Seeman, 1995). Although physical activity is advocated to increase bone mineral density (BMD) of the hip area and decrease the risk of fracture in old age, the optimal ‘osteogenic’ exercise program remains undefined.

Running is a weight bearing activity which loads the lower extremity. However, the magnitude of bone strains at the hip and spine associated with long distance running are lower than those associated with high impact sports and weight lifting (Frost 1997). Conflicting results have emerged from various studies of BMD in male runners, as both higher and lower proximal femur and lumbar spine BMDs were noted in male distance runners when compared to less active controls (Bilanen et al, 1989; MacDougall et al, 1992; Hetland et al, 1993; Bennell et al, 1997; Lane et al, 1998). Both training and absolute age, as well as training volume are important factors that have not been controlled in previous studies. In situations of chronic, high volume endurance training in men, alterations in the regulation of the anabolic sex hormone, testosterone, have been observed (Wheeler et al, 1984, Ayers et al, 1985; Arce et al, 1993). Clinically low levels of testosterone are associated with low BMD (Jackson et al, 1990).

This study was designed to examine the effects of long term distance running in men over the age of 40 (range = 40 - 55), in terms of BMD measured by DXA (g/cm²), total testosterone
(TT nmol/L), and free testosterone (FT pmol/L) levels. Two groups of men, distance runners (DR) training at a minimum weekly volume of 64 km per week for over 20 years (n=12), and age-matched, normally active, healthy controls (C) (n=12), were compared using the student’s t-test. Body weight and BMI were not significantly different between groups. As a secondary comparison, the distance runners were divided into moderate (64 to 90 km/week, n=7) and high (95 + km/week, n=5) volume training groups (MV and HV), and compared to C, using single factor ANOVA and Tukey’s HSD to compare means.

BMD of the femoral neck (FN) (0.86 +/- 0.14 vs. 0.78 +/- 0.071), trochanteric region (T) (0.81 +/- 0.13 vs. 0.73 +/- 0.053) and total proximal femur (PF) (1.04 +/- 0.15 vs. 0.94 +/- 0.056) were significantly greater (p<0.05) in DR when compared to C. Lumbar Spine (LS) BMD was not significantly different between DR and C (0.98 +/- 0.15 vs. 0.92 +/- 0.095). MV had significantly higher BMD at FN (0.91 +/- 0.16), T (0.85 +/- 0.14), and TPF (1.09 +/- 0.17) than C. All other BMD comparisons between MV, HV, and C were not significant.

HV had the lowest mean for TT (33.7 % lower than MV and 16.8 % lower than C) and FT (21.2 % lower than MV, and 26.2 % lower than C). These differences in TT and FT were not significantly different between groups. TT and training volume for DR were significantly negatively correlated (r=-0.73, p<0.005), as was FT and training volume (r=-0.79, p<0.002). BMD and TT/FT were not significantly correlated (TT vs. FN: r= 0.12 (p=0.56); TT vs. T: r=0.12 (p= 0.58); TT vs. TPF: r= 0.03 (p=0.88); TT vs. LS: r=0.13 (p= 0.55); FT vs. FN: r= 0.05 (p=0.82); FT vs. T: r=0.16 (p=0.45); FT vs. TPF: r= 0.13 (p=0.55); FT vs. LS: r= 0.19 (p=0.37)).

In summary, our results from a small, cross-sectional sample of distance runners suggest that lifetime distance running in men had a positive effect on BMD of the proximal femur, when training volumes did not exceed 90 km/week. BMD was not maintained at a higher level in
distance runners training more than 95 km/week when compared to moderately active men. There was an association between training volume and testosterone levels, although the relationship between testosterone and BMD at high levels of training needs to be more clearly defined.
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**Glossary of Terms/Abbreviations**

**ARF:** Activation, resorption, formation sequence typical of bone remodeling

**BMC:** Bone mineral content (grams); the absolute amount of mineral present in a bone or regions of a bone

**BMD:** Bone mineral density in g/cm$^2$ when measured by DXA; the relative amount of bone mineral per measured area of bone; or, BMC divided by the area of the region scanned

**BMU:** basic multicellular unit of bone remodeling

**C:** Control subject

**DR:** Distance Runner

**DXA:** Dual energy x-ray absorptiometry

**FT:** Free testosterone; the unbound, circulating portion of amount of testosterone, measured in pmol/L

**HV:** High volume runner, with a training volume of 95+ km/week

**MESm:** minimum effective strain for switching mechanically controlled bone modeling drifts on; middle of threshold is ~ 1000 microstrain

**MESr:** minimum effective strain range for mechanical control of BMU-based remodeling (~50 - 100 microstrain)

**modeling:** the biologic processes that produce functionally purposeful size and shapes to skeletal organs

**MV:** Moderate volume runner, with a training volume of 64-90 km/week

**osteopenia:** less bone than usual for most healthy people of the same age, height, weight, gender, and race.

**remodeling:** turnover of bone in small packets by BMUs

**strain:** the deformation or change in dimensions and/or shape caused by a load on any structure or structural material

**stress:** the resistance of the intermolecular bonds of matter to the deformation or strain induced by an applied load

**TT:** Total testosterone; free testosterone + bound testosterone, measured in nmol/L
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1. Introduction

In recent years, the impact of various types of exercise on the human skeleton has become a prominent topic in medical research. This is largely due to the perceived benefits of certain types of activities in preventing osteoporosis in old age. Based on the higher incidence of osteoporotic fracture in women, and the rapid acceleration of bone loss at the menopause, much of the research has focused on the dynamics of the female skeleton in relation to various regimes of weight bearing exercise. These regimes range from the intense, endurance-oriented workout schedules of elite marathoners, to walking and light resistance programs in elderly women. The knowledge amassed has allowed for some educated recommendations for the maintenance and augmentation of bone health in women. On the other hand, similar research on men is much less common, and consequently, recommendations for men are arrived at through conjecture on the studies of women.

The health burden of osteoporosis is increasing in proportion to the increase in the aging population. In 1990, there were 1.7 million hip fractures worldwide, 30 percent of which occurred in men. According to Cooper's 1990 projection, the number of hip fractures seen in elderly men in 2025 will be equal to the number seen in women today. Although men are less likely than women to sustain a hip fracture, they are 25% more likely to die within one year of the injury. Between 1987 and 2006 the incidence of hip fractures in Canadian men is projected to increase 70.2 percent, as compared to 73.7 percent in women. From 1972 to 1984 the incidence of hip fractures increased only 42
percent in men, compared to 60 percent in women. Therefore, the number of fractures is estimated to increase at a faster rate in men than in women.

Preventing osteoporosis and osteopenia begins very early in life, and recommendations for physical activity that maximizes bone health during the developmental years have evolved from animal models and research on athletes. In the general population, regular exercise might decrease the risk of hip fracture by at least half, although the exercise prescriptions remain undefined. There is strong evidence to support the theory that the greatest gains in bone mass result from high impact loading of the skeleton during growth. However, the maintenance of existing bone mass throughout adulthood also plays a critical role in preventing osteoporotic fractures. Older adults who have committed to lifetime physical activity through labor or exercise maintain bone better than their sedentary counterparts.

Theoretical models exist that seek to explain the effects of mechanical usage (physical activity) on bone. The mechanostat model, proposed by Frost (1987), likens the mechanism controlling bone modeling and remodeling to a thermostat: the mechanism turns “on” in response to a disturbance in the system (i.e., increased mechanical usage), and “off” in the absence of the disturbance. Modeling refers to the addition of bone to surfaces that are undergoing high loading, while remodeling is the replacement of fatigue-damaged bone with new bone. Bone adapts architecturally to accommodate the level of usage; more bone mass develops through modeling to reduce the stress within bone of subsequent applied strains.

The second theory, “the error strain distribution hypothesis”, proposed by Lanyon and colleagues, places emphasis on the type of strain that is applied to bone.
populations respond to strain distribution errors (i.e., unusual strains), making architectural adjustments to maintain the skeleton's structural competence. The theory holds that infrequent, unusual strains elicit greater modeling and/or remodeling, for a net positive effect on bone, than the frequent strains of usual or repetitive activity.

Functional load bearing and calcium regulating hormones are the primary controlling inputs for bone (re)modeling in adults. However, bone regulation is a complicated process that involves the interactions of a number of factors, including cytokines, growth factors, and sex hormones, which can have profound effects on bone (re)modeling.

The effects of various types of physical activity on bone are evident in both females and males. Determining the ways that the human body adapts to the strain of mechanical loading over the long term is important for research that attempts to isolate modes and magnitudes of physical activity that might be beneficial in preventing osteoporosis. The interactive effects of functional loading and influences such as estrogen and testosterone on bone are of central concern to athletes and those who prescribe exercise to maintain bone mass in adults.

1.1 Women, Physical Activity and Bone Mineral Density

The skeletal impact of various sports has been compared in female athletes involved in many types of training. For the most part, menstrual status has been a key control variable, as the combined effects of estrogen and physical activity on bone can be either positive or negative. Studies of intensely training young female swimmers revealed anovulatory menstrual cycles, short luteal phases, and lower levels of follicular stimulating
hormone, estradiol and prolactin compared to age-matched controls and fertile adult women. The prevalence of menstrual disturbances was noted to be significantly higher in ballet dancers, gymnasts, rowers and distance runners, when compared to swimmers or athletes in team sports.

Importantly, menstrual disturbances both with and without the occurrence of amenorrhea may have negative effects on bone, as noted in a study by Prior et al (1990), in which recurrent short luteal phases and anovulation were associated with spinal bone loss of approximately 2 to 4 percent per year. The disturbances noted in some athletes theoretically make it possible to research the effects of intense training on the skeleton, in combination with low estrogen in amenorrheic athletes and the presumably normal estrogen in eumenorrheic athletes. A number of researchers have set up studies to investigate this.

It is commonly accepted that estrogen is a bone building hormone, which specifically affects the numbers of new bone remodeling units and the working efficiency of existing osteoclasts and osteoblasts. It follows that several cross-sectional studies involving amenorrheic distance runners and their eumenorrheic counterparts, and/or sedentary controls, have demonstrated lower axial bone mineral density in the amenorrheic athletes, with differences ranging from 5.4% to 17.0%. Estrogen plays an important role in bone’s adaptive response to load bearing. Robinson et al (1995) demonstrated that similar incidences of amenorrhea in gymnasts and distance runners do not result in low bone mineral densities in both groups. The greater stress of mechanical loading in the gymnasts appeared to be great enough to override the negative implications of the low estrogen and progesterone associated with amenorrhea. Distance running is
an activity that involves repetitive strains of low magnitude,\textsuperscript{32} which may not be great enough to compensate for low levels of ovarian steroids.

The benefits of weight bearing exercise are better illustrated in populations that do not undertake extreme physical activity. There is strong evidence to support the idea that bone mass may be increased and/or maintained in normally menstruating women who engage in high impact sport,\textsuperscript{33,34,35,36} weight-bearing activities,\textsuperscript{37,38} or resistance training\textsuperscript{39} over the course of a lifetime.

1.2 \textit{Testosterone and Bone Mineral Density in Men}

The interactions between endurance training, hormone production, and bone mineral density are less obvious in men. Due to the absence of a clearly defined clinical condition analogous to amenorrhea, it is difficult to determine 1) male athletes who may have reproductive hormone abnormalities and 2) the point at which a lowered testosterone level becomes clinically significant. For men, bone is an important target tissue of testosterone and its metabolites. The appropriate timing of androgen secretion in adolescence seems to be related to optimal peak bone mass, and in adults, androgens are involved in the maintenance of the male skeleton.\textsuperscript{40} Through interactions with androgen receptors on bone cells, testosterone and dihydrotestosterone stimulate osteoblasts to achieve bone-sparing effects.\textsuperscript{41}

Studies of clinical conditions that cause low testosterone levels support the theory that testosterone is necessary to maintain a healthy skeleton in human males. For example, adolescent boys who experienced delayed puberty, and therefore, a delay in the normal
pubertal surge of testosterone, typically display retarded bone growth, and lower peak bone densities later in life.\textsuperscript{42-44} In addition, failure to produce testosterone occurs in Klinefelter’s Syndrome, a genetic condition resulting in testosterone deficiency and infertility.\textsuperscript{45-46} Significantly lower bone mineral densities have been observed in patients with Klinefelter’s syndrome compared to age-matched controls, and a significant inverse relationship between the extent of the bone deficit and the serum testosterone concentration was noted.\textsuperscript{47}

Gradually declining levels of serum total testosterone, free testosterone, and non-SHBG-bound testosterone are part of the normal aging process in men.\textsuperscript{48} The cross-sectional study of men at different ages demonstrated an age-related decline in bone mineral density beginning at age 40, resulting in a 34\% decrease in the femoral neck bone mineral density by the age of 70.\textsuperscript{49} The rate of bone loss in men increases with age. The bone loss rate is typically 3 to 4 \% \textit{per decade} in men beginning at age 40,\textsuperscript{106} and increases after age 60: BMD of the femoral neck was found to decrease by 0.82 percent \textit{per year} after the age of 60 in a prospective study of older men.\textsuperscript{50} This differs from the rate of bone loss observed in women, as a 5 to 10 \% reduction in bone mass is typically observed in the decade following menopause,\textsuperscript{150} with a reduction in the rate in the subsequent decades. Some researchers feel that the menstrual disturbances observed in some endurance-trained females may be considered similar to the occurrence of exercise-induced hypogonadism in male endurance athletes.\textsuperscript{51} For all of these reasons, further research of the impact of physical activity on the male skeleton is important to compare the types of long-term exercises that might improve or maintain bone mass, possibly in combination with the hormone irregularities that coincide with intense endurance training.
Bone mineral density has been measured in many studies involving male athletes. Similar to the results seen in women, physical activity has a positive effect on bone mass in several cases. Cross sectional studies have revealed higher radial bone mineral content in tennis players compared to sedentary controls, higher femoral bone mineral density in weight lifters, throwers, runners, soccer players, and swimmers as compared to inactive controls, and significantly higher spinal bone mineral density in weight lifters and water polo players when compared to nonexercising controls. Physical activity interventions involving weight bearing and weight training had positive effects on tibial bone mineral density in young males, and on femoral neck bone mineral density in older men.

A problem lies in accepting the idea that all physical activity provides skeletal benefits. To influence bone architecture, loads on bone need to be functional, as not all strains are equally effective osteogenic stimuli. Unusual strain distributions, high strains, and high strain rates are most effective. Activities that do not provide an adequate stimulus for bone modeling, that is, the strains are not great enough to turn Frost’s mechanostat “on”, may have little effect on bone mineral accrual. This would encompass endurance-oriented activities, such as running and nordic skiing. The weight-bearing strains of running are great enough, however, to elicit bone remodeling changes, which are beneficial in terms of bone maintenance. To further complicate the issue, it is unclear whether: 1) the suppression of reproductive hormones in some male endurance athletes might have a negative effect on bone; or 2) similar to the situation in post-menopausal women, low testosterone might raise the set points at which bone responds to mechanical usage.
Therefore, areas of interest are focused on the site specificity of bone mineral accrual related to sport, and types of activities that when performed in excess may be detrimental to either the maximizing or maintaining of bone mineral density.

Recent cross-sectional studies of male athletes support the idea that skeletal benefits are specific to certain types of activities. Matsumoto (1997) studied age and sex-matched collegiate judoists, swimmers, and long distance runners, and found significantly higher total bone mineral density in the judoists as compared to the other two groups. Endurance cyclists had significantly lower lumbar spine mineral bone densities than inactive controls, weight lifters and boxers. A longitudinal study by Bennell and colleagues (1997) more convincingly demonstrates the various levels of skeletal modifications that can occur depending on the type of loading inherent to specific track and field events. Power athletes (sprinters, jumpers, hurdlers, and dec/heptathletes) had significantly higher measures of spinal bone mineral density than endurance runners, and significantly higher densities at the lumbar spine, upper limb, and lower limb than less active controls. The endurance runners in this study had greater bone mineral density than the controls only at lower limb sites. Athletes and controls both demonstrated modest significant increases in femoral bone mineral density over 12 months, which might be related to the young age of the subjects: all were between 17 and 26 years of age. These findings support the idea that the bone response to mechanical loading is site specific, and therefore, sport specific, and possibly maximized in the highest impact sports (i.e., judo, sprinting, jumping, weight lifting).

The most controversial sport in terms of skeletal benefits is running. The combination of endurance training and weight bearing complicates the conclusions arrived
at in terms of recommending physical activity for bone health. High volume endurance training (i.e., greater than 100 km per week of running) may disrupt normal functioning of the hypothalamic-pituitary-gonadal axis in some athletic males, causing circulating testosterone to be maintained at a lower level and possibly reducing its anabolic effect on bone. Depending on mileage and recovery time between workouts, the creation of resorption cavities in bone remodeling in some endurance runners may exceed bone mineralization. This results in a period of potentially several weeks during which new bone is at its weakest. As net bone loss has occurred, bone strength may not be great enough at this time to keep strains below the 'microdamage threshold'. Accumulation of microdamage causes stress fractures, and may have long term implications for the maintenance of bone strength.

Studies of chronic running training seek to determine the effects of maintaining a high volume of training on bone's ability to compensate. Research focusing on the bone mineral density of male long distance runners can be differentiated on the basis of mileage, as well as both the actual and training ages of subjects. Conflicting results have emerged from these studies. Low mileage runners (under 20 miles per week) had greater tibial bone mineral density than controls, and high mileage runners (60 to 75 miles per week) exhibited equal tibial bone mineral density to controls. All subjects in this study were between 20 and 45 years of age, and had been training consistently for at least 2 years. Hetland (1993) found lower bone mineral content and Bilanen (1989) found lower bone mineral density of the lumbar spine in male long distance runners training greater than 100 and 90 km per week respectively, when they were compared to normally active
The age range in the former study was 19 to 56 years, while that of the latter fell between 22 and 35 years. Neither study controlled for years of training.

Studies of older athletes tend to control for years of training, but not as well for mileage. Higher calcaneal bone mineral density was demonstrated in lifetime male runners and nordic skiers over the age of 70 when compared to age-matched sedentary controls,\textsuperscript{72} and as much as 40 percent higher bone mineral content was noted in male runners over 50 years old when compared to controls matched on age, sex and education.\textsuperscript{73}

Recently, 3 groups of male runners aged 42 to 73, all of whom had been competitive distance runners 20 years prior, were classified as high, moderate or not trained depending on their most recent activity level. Lumbar and proximal femur bone mineral density were similar between groups, and not significantly different from normative values from the Hologic DXA reference database.\textsuperscript{74}

To demonstrate the more lasting effects, as opposed to the transient effects, of endurance running on the male skeleton, age and accumulated years of consistent, high mileage training become important factors, which have not been strictly controlled for in previous studies. The positive and negative effects of chronic endurance running seem to lie in the balance between the combination of a weight-bearing influence on bone mass control mechanisms and the hormonal implications of this type of training. This study seeks to isolate a group of men who will demonstrate the long term bone effects of endurance running when they are compared to a similar group of moderately active adults.
2. Review of Literature

This review is divided into seven areas to highlight relevant work. Included is 1) an overview of bone biology, and the theories of mechanisms controlling bone mass in response to mechanical usage, 2) a general review of osteoporosis in men and women, 3) a discussion of literature describing the measurement of bone mineral density with dual energy x-ray absorptiometry, 4) a specific look at studies investigating bone mineral density in female athletes, and 5) male athletes, 6) a discussion of the production, circulation, actions and measurement of testosterone in the human male, and 7) research focusing on the effects of exercise on testosterone levels.

2.1 Bone Biology and Mechanisms Controlling Bone Mass

Bone Composition. At the gross level, two basic structural components make up the bones of the adult human skeleton. Cortical (or compact) bone forms the hard, dense outer layer found in the walls of bone shafts and on external bone surfaces, and makes up approximately 80% of total bone mass.\(^75\) Within cortical bone, thin plates called trabeculae surround the connective tissue, collagen. This porous type of bone, that makes up the remaining 20% of total bone mass, is known as trabecular (or cancellous) bone, and is more spongy and lighter in weight than cortical bone.\(^{76,77,75}\) The difference in porosity and blood supply is what separates cortical and trabecular bone, as the molecular and cellular compositions are identical.\(^77\) The greater porosity of trabecular bone gives rise to a higher proportion of metabolically active surface area.\(^78\) Both types of bone are
composed of protein in the form of collagen, and mineral in the form of hydroxyapatite (a form of calcium phosphate).\textsuperscript{79}

Osteocytes, living bone cells, are sustained in trabecular bone by the nourishment they receive from blood flow in the surrounding marrow spaces, and through the incorporation of specialized Haversian systems that allow the passage of blood, lymph, and nerve fibers in cortical bone.\textsuperscript{77} Osteocytes are actually osteoblasts that have become totally entrapped in the bone matrix being synthesized. Osteoblasts cover most of the surface of bone and are responsible for bone formation. They constitute a single layer of cells and are active when they are engaged in bone matrix production. The other type of bone cell is the osteoclast. These large cells reside in exclusive foci, and are specialized for bone resorption. When an osteoclast is actively resorbing bone matrix, an irregularity is produced in the bone surface that matches the size and shape of the osteoclast.\textsuperscript{112,18,75}

Osteoblasts and osteoclasts are key players in the Activation-Resorption-Formation (ARF) sequence necessary for bone remodeling. Together, the cells form Basic Multicellular Units (BMU) which cause bone turnover. BMU remodeling begins when cells close to a bone surface are stimulated. Resorption occurs by the action of osteoclasts removing a local packet of bone, and bone formation follows when osteoblasts refill the local resorption bay.\textsuperscript{113,75} The amount of bone remodeled per unit time depends on the osteoblastic and osteoclastic activity at the BMU site, and on the activation frequency (the rate at which BMUs are formed). Activation frequency can vary by 50 to 100 %, and is an important regulator of bone turnover in disease states.\textsuperscript{78}
The Mechanical Usage of Bone. The mechanostat theory, originally proposed by Frost in 1987\textsuperscript{17} and refined in 1996,\textsuperscript{80} attempts to explain the mechanisms controlling bone mass. The mechanostat monitors the mechanical usage (MU) of bone, and matches the biological response within bone to ensure that the resulting mass is sufficient for the bone usage. Its basic premise is analogous to a thermostat: the mechanism is turned "on" in response to a disturbance in the system, and goes "off" in its absence.\textsuperscript{17}

Figure 1. The mechanostat model: a proposed mechanism for controlling bone mass. [Adapted from: Frost H. Perspectives: a proposed general model of the mechanostat. The Anatomical Record 1996; 244: 139-147.]

In the model of the mechanostat, Figure 1, MU refers to mechanical usage, C\textsubscript{1} to C\textsubscript{n} represent the sequential cells, biochemical reactions, and related molecular-biologic events, L represents the local agents which might have an effect on bone (i.e., innervation,
genes, local perfusion, electrolytes, temperature, etc), S is the systemic, blood-borne agents such as hormones, vitamins and proteins, and MES is the minimum effective strain.¹⁰

**Mediator Mechanisms.** Two ‘highways’, or mediator mechanisms, are presented as the routes by which mechanical usage of bone elicits change in bone mass. The first is the modeling highway, which refers to the large scale changes (or macromodeling) of bone during growth. Modeling affects the shape, tissue content and distribution, and size of bone through ‘drifts’ that move bone surfaces in tissue space to influence diameter and cortical cross-section area.¹⁷ ⁸¹ Osteoblasts in formation drifts add new circumferential lamellar bone over broad regions of bone surface, while osteoclasts in resorption drifts remove bone over these broad regions.⁸² Bone modeling greatly decreases after skeletal maturity, as its main function is to ensure a match between the bone’s architecture and the mechanical demands of an individual’s existence (with respect to physical activity, body weight, and neuromuscular function).⁸²

The second highway, or mediator mechanism, the remodeling highway, remains active on all bone surfaces throughout life.¹⁷ Bone remodeling refers to the turning over of tissue in packets through the activities of BMUs. A human BMU replaces about 0.05 mm³ of bone over 4 months.⁸³ It is influenced by many factors, one of which is mechanical usage.⁸¹ On average, a typical BMU tends to resorb more bone than it replaces, at about 20 parts of bone resorbed for 19 parts formed.¹⁷ This results in a negative bone formation which can be lessened by increasingly vigorous mechanical usage, as compared to the activities of daily living. To a certain point, a higher level of mechanical usage of bone
tends to decrease the number of BMUs that are recruited. This equalizes bone resorption and formation, and may even result in a net bone gain in selected areas.\textsuperscript{17}

**Bone Strain and (Re)Modeling.** The levels of strain in bone affect the recruitment of BMUs. Strain refers to a deformation in bone due to the application of a load.\textsuperscript{81} In Frost's theoretical models, the Minimum Effective Strain (MES) is a term that describes the minimum magnitude of bone strain that evokes architectural adaptations in bone.\textsuperscript{84} Studies have indicated that bone remodeling proceeds rapidly under mechanical usage that causes peak bone strains in the range of 100 microstrain, indicating a 'set point' at this level of strain.\textsuperscript{85} This is the MESr (remodeling), that begins to depress BMU creations and equalize resorption and formation.\textsuperscript{83} Osteogenic loading increases existing osteoblast activity and osteoblast recruitment.\textsuperscript{19} In effect, increased remodeling tends to conserve bone, preserving existing mass and strength, and preventing osteopenia.\textsuperscript{16} A higher set point would have the same effect as decreased mechanical usage in this situation.\textsuperscript{17}

There is also a minimum effective strain specific to bone modeling (MESm) which lies somewhere between 2000 and 3000 microstrain. Strains in this range cause architectural changes at the macro level that reduce subsequent bone strain to levels below that cutoff.\textsuperscript{17,84} Peak bone strains from voluntary effort in rapidly growing children lie in the range of 2000 to 4000 microstrain, while voluntary effort in adults only elicits peaks of 800 to 1200 microstrain. Modeling therefore proceeds at a rapid rate in children as their bone strains more frequently exceed the MESm threshold. Adults must have an increased vigor of mechanical usage to switch bone modeling "on", as the strain levels in their bones are reduced through previous bone adaptation in the formative years.\textsuperscript{16}
Figure 2 demonstrates the relative contributions of bone modeling and remodeling to bone mass and strength in relation to bone strain. In the adult, the mechanical usage of bone in long distance running would tend to elicit frequent strains that fall into the Physiological Loading Zone, or possibly, just inside the Overload Zone. In this range, the MESr is exceeded and bone mass is conserved through remodeling. However, the MESm is most likely not exceeded except in short bursts of sprint training, and therefore, bone modeling does not proceed at a notable rate. The architecture of the bone in long distance runners does not need to change to accommodate these low magnitude strains, regardless of how frequently they are applied.

However, adults who perform high impact training involving jumping, or weight training, most likely elicit bone strains of much higher magnitudes, and would therefore require greater skeletal adaptations. Modeling and remodeling would then take place in adults performing high impact training, and higher bone mass and strength would be the result. A theory proposed by Lanyon (1996), known as the error strain distribution hypothesis, specifies that unusual, uneven strains applied to bone through dynamic physical activity are much more effective at eliciting an osteogenic response in bone than repetitive, lower impact activities. In his scheme of the strain distribution error, it is indicated that “the more unusual the strain distribution, the more potent its osteogenic potential.” These two ideas help explain why higher bone mass is noted in weight lifters and power athletes than long distance runners, and age/weight-matched controls.
1000 microstrain ($\mu \varepsilon$) = 0.1% change in length

$50 \mu \varepsilon = \frac{1}{480}$ fracture strain

$200 \mu \varepsilon = \frac{1}{120}$ fracture strain

$2000 \mu \varepsilon = \frac{1}{12}$ fracture strain

$4000 \mu \varepsilon = \frac{1}{6}$ fracture strain

**Figure 2.** Mechanical usage windows, as defined by Frost’s mechanostat theory. [From: Bailey D, Faulkner R, McKay H. Growth, physical activity and bone mineral acquisition. In: Exercise and Sport Sciences Reviews. Baltimore: Williams & Wilkins, 1996: 233-66. vol. 24]
Nonmechanical Factors. Frost (1987) proposed that some circulating agents might have an effect on the MES mechanisms, and in effect makes them somewhat "deaf" or overreactive. In his 1996 update of the mechanostat model, Frost lists several systemic, blood-borne agents (hemoglobin, hormones, blood pH, electrolytes, blood osmolality, gas tensions, drugs, amino acids, blood glucose, vitamins, toxins, lipids serum proteins, body temperature) and local agents (cytokines, autocrine effects, cell-cell interactions, local osmolality, local electric charge, mitogens, specific ion effects, cell membrane receptors, paracrine effects, cell-matrix interactions, local perfusion) as potentially influential on the mediator mechanisms controlling bone mass. The impact of hormones, specifically testosterone, on bone is central to this project and will therefore be the focus of the examination of circulating agents and bone modeling/remodeling.

Research has shown that hypogonadal men have lower bone mineral density. The evidence to support the idea that androgen deficiency causes low bone mass lies in the demonstration of androgen receptors on osteoblasts with receptor affinities comparable to those found in the prostate, direct metabolism of testosterone in bone tissue, and androgen effects in bone cells.

Androgens directly stimulate proliferation of osteoblasts in vitro according to many, but not all studies. Osteoclastic bone resorption is inhibited through the combined effects of androgens causing decreased levels of interleukin-6, and prostaglandin E₂, inhibition of parathyroid effect on osteoblasts, or through the inhibition of osteoclastogenesis. Figure 3 demonstrates the various effects of androgens on pathways affecting bone.
Figure 3. Androgen effects on bone pathways. [From: Vanderschueren D, Bouillon R. Androgens and bone. Calcified Tissue International 1995; 56: 341-6.]

Frost (1996) discusses the "deafening" effect of lowered estrogen levels in postmenopausal women on the MES system in the mechanostat model. Further research is needed to determine if this theory can be applied to the situation occurring in hypogonadal men. Frost proposes that the endocrine changes that occur in menopause raise the MES setpoints by a certain percentage, and the mechanostat "perceives" excess bone of the same amount. Remodeling then begins to remove the excess bone, and since the increase in bone is only a perception by a confused remodeling system, the spongiosa becomes osteopenic and cortices are thinned. Postmenopausal bone loss in women can be considered as an "estrogen-related failure of the mechanically adaptive response to conserve structurally appropriate levels of bone mass." For osteogenic loading to elicit a bone response in an estrogen-depleted system, it would have to be increased beyond premenopausal levels.
Further research is necessary to define a relationship between the age-related declines in testosterone and bone loss in men.
2.2 Osteoporosis

Osteoporosis is described as a state of decreased bone mass per unit volume of bone, or as a syndrome characterized by insufficient bone mass that leads to fractures under conditions of minimal trauma. This state occurs when the rate of bone resorption exceeds the rate of bone formation, resulting in a net bone loss\textsuperscript{104}. The World Health Organization (WHO) defines osteoporosis as bone mineral density greater than 2.5 standard deviations below the young adult reference mean\textsuperscript{105}. Osteopenia is simply defined as less bone tissue than age- and sex- comparable norms, and it may occur with or without symptoms\textsuperscript{106}. In terms of bone mineral density, the WHO definition for osteopenia is BMD between 1 and 2.5 standard deviations below the young adult reference mean\textsuperscript{105}. This disease occurs partially due to the increasing inefficiency of bone remodeling with increasing age, as small bone deficits persist at the end of the remodeling cycles and account for bone loss. Osteoporosis affects men and women in a 1:2 ratio, and fractures occur in the vertebrae and hip due to both trabecular and cortical bone loss\textsuperscript{104}.

The increasing incidence of hip fractures in men and women represent a public health concern. The number of fractures continues to increase with the increase in the growing number of elderly people in the North America. Therefore, the financial burden of treatment for these patients is also rising\textsuperscript{1}. This injury typically requires hospitalization and surgery, and may result in permanent disability. Hip fractures in men represent one-third of all hip fractures, and men have a higher mortality rate than women\textsuperscript{1}. Trabecular thinning seems to be the primary cause of hip fractures. Vertebral fractures, although debilitating, are less costly to treat and are associated with lower mortality rates than hip
fractures. They are not as common in men as in women, and the predominant cause is a loss of connectivity in bone.¹

Osteoporosis is a multifactorial disease, but a few key factors are commonly accepted as contributing to the onset of the condition. The most important of these is the one that can not be manipulated: family history, or, genetics. Variance and mutation genes that control bone mass and bone turnover likely play a role in the maintenance of bone mass, and therefore the incidence of osteoporosis. As reviewed by Snow Harter et al. (1991), estimates of the genetic component of osteoporosis range from sixty to ninety percent.¹⁰⁷ More recently, a study by Krall and Dawson-Hughes (1993) measured familial resemblance in bone mineral density at skeletal sites, and demonstrated that 46 to 62 percent of the variance was attributable to heredity.¹⁰⁸

The non-genetic components of osteoporosis include circulating androgens and estrogens, physical load, and nutrition, as well as habits that can cause secondary osteoporosis such as alcoholism, tobacco use, and chronic use of steroids, antacids and glucocorticoids.¹⁰⁹

Sex Hormones. In an evolutionary sense, gonadal hormones are important to instigate processes that influence the bone mineral accretion necessary for reproduction. Thus, it is a philosophical question as to whether bones were meant to be maintained only during the reproductive period (which is longer in men than women), or if lifestyle factors are more important in the maintenance of bone mass in old age.¹⁰⁹ Factors predisposing women and men to osteoporosis may be masked during times of maximum estrogen and testosterone production, and it is the accumulative effect of these factors that manifests as
osteoporosis after menopause in women, or when testosterone begins its age-related
decline in men.\textsuperscript{110} However, the possibility of a 38 to 54 percent contribution of
exogenous factors, such as physical activity, to BMD is reason to give attention to this
more modifiable component.\textsuperscript{109}

There is no doubt that estrogen plays an essential role in bone maintenance in
women, just as testosterone has an anabolic effect on bones in men. If bone loss has not
already begun prior to menopause, studies confirm that trabecular bone loss accelerates
when estrogen levels drop at menopause, with the greatest loss occurring from five to
eight years after menopause.\textsuperscript{2,111-113}

Testosterone and its derivatives gradually decrease in aging males, due to a
decreased number of Leydig cells, changes in hypothalamic-pituitary function, and
coexistent illness.\textsuperscript{114,115} As the age-related decrease in testosterone is more gradual than
the female menopause, the bone effects related to the decline in testosterone levels in men
are less severe than the related decrease in estrogen in women. However, Rudman et al.
(1994) found testosterone to be the strongest predictor of bone mineral density in healthy
older men.\textsuperscript{115} Also, 59 percent of male patients with hip fractures had low testosterone
levels, as compared to 18 percent of controls.\textsuperscript{116} Hypogonadism may be more common in
men with vertebral fractures.\textsuperscript{117} A disadvantage of these two retrospective studies is that
it is not clear whether low testosterone levels existed prior to fracture, or decreased after
fracture (due to the stress of the injury). As the pathophysiology of bone loss with age in
men is multifactorial, the relationship between gonadal function and bone loss represents
only one portion of the problem. This is represented in the following figure (Figure 4).
Physical Load. As discussed in the previous section (2.1, Bone Biology), adult bones require loading to conserve mineral through the optimization of the remodeling process. The mechanisms that control bone mass are stimulated by mechanical usage of bone. By the time hip fractures occur in elderly men and women, these individuals may have assumed a sedentary lifestyle. Sedentariness was an additional risk factor for fractures independent of bone mineral density in hip fracture patients. Immobilization of body parts results in disuse atrophy due to lack of strain on bone, as osteoblasts become inactive and older bone is not replaced. As demonstrated in Figure 2, in disuse, strains fall into the ‘trivial loading zone’, which causes a decrease in bone mass.

Figure 4. Multifactorial pathophysiology of bone loss in men. [Adapted and simplified from: Jackson J, Kleerekoper M. Osteoporosis in men: diagnosis, pathophysiology, and prevention. Medicine 1990; 69 (3): 137-152.]

Factors related to calcium, vitamin D, Vitamin K, genetics

osteoblast function

↓ gonadal function

osteoclastic bone resorption

CORTICAL AND TRABECULAR BONE LOSS

FRACTURE

factors related to muscle mass, exercise, mechanical loading, remodeling activity, biomechanical strength, microfracture repair, propensity to fall
Many cross-sectional studies have attempted to evaluate the effectiveness of physical activity on bone mineral density. Evidence from these types of studies in children support the idea that higher levels of dynamic, weight bearing physical activity (as in gymnastics and weight-lifting), lead to higher bone mineral densities. Similar studies show that moderate physical activity is associated with higher bone mineral densities in active women and men than in their less active counterparts, and that physical activity is an important predictor of bone mineral density in adult men. Retrospective studies assessing the impact of lifetime physical activity level on bone mineral density provide evidence for their positive association in many, but not all cases.

Prospective observational studies also support the idea that bone mineral density is increased through physical activity in young athletes. Collegiate-age track and field athletes in all events had significantly higher bone mineral densities after one year of continuous training, and bone mineral density also increased during 27 weeks of training in varsity gymnasts. A nine year study of older male and female runners (female age range at the beginning of the study was 51 to 69) revealed that the lumbar BMD remained higher in the runners than the nonrunner controls, but that the changes in lumbar spine BMD with age were similar between groups.

Finally, prospective intervention trials provide the most definitive evidence to support or refute a theory. Studies conducted to determine the effects of exercise interventions in postmenopausal women were recently reviewed by Berard et al. (1997). A significant effect of exercise on the maintenance of spinal BMD was noted in studies published after 1991; however, the studies did not show an effect on radial or femoral
An endurance-oriented activity program consisting of 18 months of walking, stair-climbing, cycling and jogging targeted at peri-menopausal women, resulted in the maintenance of the pre-study bone mineral density at the femoral neck, while a sedentary control group demonstrated a decline in bone mineral density at this site. One intervention study engaging older men (age range 57 to 62 years) in weight training activities for 14 weeks demonstrated a significant increase in femoral neck BMD. The number of intervention trials with women as subjects far exceed those involving men. It seems that exercise interventions in previously inactive women to maintain BMD, if they do show an effect. Little can be said about the effects of exercise interventions in men without further research.

The greater gains in BMD with an exercise intervention are most likely made in the growing years, as illustrated by a study by Morris et al (1997) that measured the effects of three, thirty minute exercise sessions per week over the course of ten months. The BMD of the schoolgirls participating increased by 10.3 percent at the femoral neck, and 3.6 percent at the lumbar spine. Significant gains in tibial bone mineral density were observed in male military recruits between the ages of 18 and 21 after 14 weeks of strenuous training.

**Nutrition.** Barr and McKay (1998) recently reviewed nutrition in relation to bone status. In their review, several dietary factors are indicated as important in bone matrix formation, and therefore, bone growth. These include protein, zinc, vitamin C, vitamin A, vitamin D, and vitamin. Caloric inadequacy can compromise linear growth, and is associated with
menstrual cycle disturbances in females, anorexia nervosa and concurrent hypogonadism has also been documented in men. Low bone mineral density may be a result of amenorrhea, or severe hypogonadism in men.

Calcium is a major component of bone mineral, and is necessary for bone growth and development. Many retrospective studies have indicated a positive association between BMD and lifetime calcium intake in adult women. Cross-sectional studies have associated high calcium intakes with higher BMDs or BMCs at the lumbar spine in boys, at the os calcis, total body, lumbar spine and femur in women, and at the spine and wrist in men. Many other cross sectional studies did not detect such associations. The inconsistency across studies may be related to the difficulty and varied mechanisms used in quantifying calcium intake, or to the 'threshold effect of calcium: above a certain intake, greater effects on bone are not observed.

The effects of adequate or supplemented calcium intakes are better noted in intervention studies, as reviewed by Barr and McKay (1998). Consistently, children who receive calcium supplements show greater increases in BMD or BMC than their unsupplemented controls.

Specker (1996) reviewed 16 studies that examined the interaction of physical activity and calcium intake on lumbar spine or radial BMD. Studies incorporating a mean calcium intake of greater than 1000 mg per day reported beneficial effects of physical activity on BMD, with a greater modifying effect of calcium on BMD at the lumbar spine.

As early as 1977 it was stated that individuals with osteoporosis had lower calcium intakes and absorption rates than unaffected individuals. By the age of 60, physiological
mechanisms for accommodating dietary deficiencies become less efficient in both men and women, and the effects of a low calcium intake become apparent. This loss of efficiency leads to hypersecretion of parathyroid hormone which subsequently causes an increase in plasma calcium at the expense of bone mineral. For men over the age of 50, the Recommended Nutrient Intake (RNI) for calcium is set at 800 mg, and vitamin D is 5 ug; these are the highest recommendations for these two nutrients since the teenage years. An intake of 1200 mg of calcium per day, which is recommended for women over 50, will help slow the rate of age-related bone loss, but cannot replace bone. Elderly American men have higher oral intakes of calcium than age-matched women, but intakes fall below 800 mg per day in 60% of adult men, and below 500 mg in 25%.

**Secondary Osteoporosis.** Certain lifestyle factors can increase the risk of osteoporosis, and osteoporosis can present after the chronic use of some medications, or secondary to another disease state. Risk factors include excessive alcohol intake, tobacco use, inactivity, leanness, low calcium intake, reduced strength, and chronic use of drug therapies such as corticosteroids, anticonvulsants, heparin, and thyroid replacement. Alcohol has a toxic effect on osteoblasts, illustrated by a study of healthy men who consumed 60 g of alcohol daily for 3 weeks and subsequently showed a marked decrease in serum osteocalcin (a marker for osteoblast activity). Chronic steroid use inhibits osteoblast activity and calcium absorption, subsequently increasing parathyroid hormone and osteoclast activity.
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2.3 Measurement of Bone Mineral Density with Dual Energy X-ray Absorptiometry (DXA)

Bone mineral density is primarily measured in clinical situations to detect osteoporosis or osteopenia, most often in older women. Indications for bone densitometry include the determination of suitability for hormone replacement therapy in menopausal women, irregular periods in premenopausal women, male hypogonadism, radiographic osteopenia, atraumatic fracture, chronic use of steroids, corticoids, and glucocorticoids, family history of osteoporosis, post-cancer chemotherapy, primary hyperparathyroidism, and monitoring effectiveness of therapies.\textsuperscript{152}

Radiographic absorptiometry was the initial form of measurement employed in bone mineral density measurement in the 1960’s; it was replaced by single photon absorptiometry (SPA) in the next decade. Dual photon absorptiometry (DPA) replaced SPA in the 1980’s, and popularized the measurement of spinal bone mineral density in research and clinical evaluations.\textsuperscript{153} First generation dual energy x-ray absorptiometers (DXA) became available in 1988, which were capable of providing spine and femur scans in five to eight minutes. This scan time improved to two minutes when fan-beam densitometers were introduced in 1991. Fan-beam geometry with a linear array detector can expose a larger area detector per unit time, as compared to the pencil-beam approach.\textsuperscript{154,155}

DXA of the spine and hip is the most widely used technique for bone mass measurement in North America.\textsuperscript{156} The Hologic QDR 4500 X-ray Bone Densitometer uses “X-rays of two different energies produced by an X-ray tube to estimate bone mineral content and bone mineral density.”\textsuperscript{157} The use of two X-ray energies eliminates the need
for water bath immersion that was required in single x-ray absorptiometry (SXA) to equalize soft tissue attenuation. The DXA system scans the skeletal site in a rectilinear fashion, recording separate low- and high-energy transmitted photon intensity values on a pixel-by-pixel basis. DXA measures trabecular plus compact bone mineral (without differentiating between the two types of bone), and the data are expressed as bone mineral content (BMC), for the amount of bone in grams in a designated region, and areal bone mineral density (BMD, g/cm²) for the amount of bone mineral per square centimeter of bone area.

The Hologic QDR 4500 uses a low level of X-rays. The effective dose equivalent sums up the total radiation exposure for a patient measured by DXA: it is approximately 3.8 uSv (micro-Sievert) for the lumbar spine, and 1.3 uSv for the hip. This is less radiation risk than an individual is typically exposed to on a two to three hour commercial airline flight, or during one full day outdoors.
2.4 Female Athletes and Bone Mineral Density

Much of the research related to the impact of athletics on the skeleton has focused on amenorrheic and eumenorrheic female athletes in endurance-oriented and esthetic sports, as well as older active females. These investigations have been spurred on by an urgency to discover effective means to reduce the incidence of osteoporosis in the elderly female population. Physical activity has been proposed as beneficial, although the correct volumes and modes to prescribe remain controversial.

Cross-sectional studies of female athletes in various sports have provided evidence to support the mechanostat theory of bone development: increased mechanical usage of bone through vigorous activity stimulates bone modeling and remodeling.\(^{17}\) BMD at many sites including the lumbar spine, femoral neck, distal radius, distal femur, patella, proximal tibia and calcaneus was found to be between 9 and 26% higher in young female weight lifters than in endurance athletes and controls.\(^{37}\) Female athletes in high impact sports such as figure skating and gymnastics demonstrated higher total body, trunk, leg and pelvis BMD (skaters),\(^{34}\) and lumbar spine and femoral neck BMD (gymnasts),\(^{36}\) than controls. Regularly menstruating young female runners have shown greater lower extremity BMD than non runners.\(^{37,38}\)

Estimates of the incidence of menstrual disturbances in athletes range from 1 to 44%, as reviewed by Loucks et al. (1985).\(^{160}\) It cannot be said that menstrual dysfunction is a serious problem in all athlete populations. Female athletes who combine inadequate energy intakes with intense training seem to be at the highest risk for menstrual cycle dysfunction; gymnasts, endurance athletes, and ballet dancers seem to be affected most often.\(^{161}\) Female runners with amenorrhea or oligomenorrhea have demonstrated
consistently lower axial BMD than eumenorrheic runners.\textsuperscript{26, 27, 28, 29, 30, 162, 163, 164} Athletes with menstrual cycle disturbances have also been shown to have spinal BMD that is lower than the BMD of eumenorrheic sedentary controls.\textsuperscript{27, 30, 165}

The bone mineral of the lumbar spine may be more susceptible to change under the influence of menstrual abnormalities. In their 1991 review, Snow-Harter and Marcus discuss the possibility that the lumbar vertebrae's high proportion of trabecular bone, which has a greater surface area and a higher turnover rate than cortical bone,\textsuperscript{79} is responsible for the decreased bone mineral in this region.\textsuperscript{108} For comparison, the average total body cortical bone content is approximately 80\%, while the trabecular content is 20\%.\textsuperscript{76} Areas of high trabecular bone content are the distal radius (20\%),\textsuperscript{166} vertebra (33 to 42\%),\textsuperscript{167} femoral neck (33\%),\textsuperscript{168} and calcaneus (90\%).\textsuperscript{169}

Amenorrhea seems to have less of an impact on the largely cortical bone of the lower extremity. The negative influence of lower hormone levels is most likely offset by the osteogenic effect of weight bearing in amenorrheic runners.\textsuperscript{161} Higher impact sports such as gymnastics seem to increase BMD, even when the incidence of menstrual disorders is similar to runners.\textsuperscript{31}

Studies of older female athletes help to shed some light on the lasting effects of physical activity on BMD, and the effect of physical activity on bone in conjunction with menopause. Research investigating long term physical activity in relation to BMD is of particular relevance to the current study.

Of the studies reviewed, 3 were cross-sectional studies of currently active women, middle-aged and older.\textsuperscript{36, 170, 171} Michel and colleagues (1989) examined the lumbar spine BMD of currently training women runners.\textsuperscript{170} Of the 28 women measured, 26 were post-
menopausal. They found a positive association between running and BMD, up to training volumes of 270 minutes per week. Unfortunately, the training age of these women runners was not stated, although it was indicated that the women who had the lowest BMDs were training an average of 300 minutes per week, and began running after the age of 40. This study implies that a late start to training combined with high volumes is negatively associated with BMD.

A similar cross sectional study of postmenopausal women runners (mean age 62 years) compared to sedentary controls found significantly higher BMDs of the spine and radius in the runners, when body weight was controlled for. Again, training history was assessed only to the extent of meeting the study criteria of a minimum of two years of running. Interestingly, the mean serum estrone level of the athletes was lower than that of the controls, illustrating how the weight-bearing effect of running might offset the negative influence of low hormone levels.

One cross-sectional study by Dook et al. (1997) selected women who had begun participation in their sport before the age of 13, and had been actively training in the last 20 years. All women had had one menstrual period within the previous 12 months. Total body, femoral neck, and upper arm BMD of women runners aged 42 to 50 years was compared to the BMD of athletes in higher impact (netball and basketball) and non weight bearing sports (swimming), and sedentary controls. The high impact and running groups had greater total body and regional leg BMD than controls; the high impact group was also greater than the swimming group on these two measures, and had the highest overall values for both BMD measures. The upper arm BMD of all athlete groups was greater than the upper arm BMD of the controls. This study indicates that high impact
sports are superior to running and swimming in the osteogenic stimulus they provide. From the cross-sectional studies, it seems that running and participation in higher impact sports over the age of 40 in women is positively associated with BMD, and that a longer training history and a training volume up to 300 minutes per week might be the most beneficial.

Retrospective, cross-sectional studies of former highly trained female athletes demonstrate the lasting effects of early activity on BMD, even in the absence of continuous training. The lumbar spine and femoral neck BMD of ex-elite tennis players and distance runners was higher than both active and inactive age-matched controls. Retrospective, cross-sectional studies of former highly trained female athletes demonstrate the lasting effects of early activity on BMD, even in the absence of continuous training. The lumbar spine and femoral neck BMD of ex-elite tennis players and distance runners was higher than both active and inactive age-matched controls. The femoral neck BMD of retired ballet dancers with a mean age of 51 years was strongly (positively) related to hours of training between 10 and 13 years of age, but not to current activity level. The importance of starting age is illustrated by a study that compared the BMC of the playing and nonplaying arms elite adult female squash and tennis players, and the dominant and nondominant arm BMC of age-, weight- and height-matched controls. The average difference in BMC between the dominant and nondominant arms was 4 percent in the controls. A 13 percent difference between the BMC of the playing and nonplaying arms was observed in the tennis and squash players, with greater side-to-side differences noted in those athletes who began training before menarche.

A nine year longitudinal study involving women runners training between the ages of 50 and 72 showed that the runners had higher BMD at years 0, 3, 6, and 9 than the age-matched nonrunners. All women had started running after the age of 40, and trained an average of 35 km per week. The decreases in BMD over the years were similar between
the two groups. At year 9, the BMD of the runners was similar to the year 0 BMD of the nonrunners; this suggests that the spinal BMD of a 60-year-old female runner might be similar to that of a 51-year-old nonrunner. Although the higher BMD of the runners might be attributable to training, a lifetime activity assessment was not made in this study. The runners might have been more active than the nonrunners during childhood or adolescence, and the impact on BMD might have been greatest during that time.

From these studies it is apparent that activity level influences BMD in women. For female athletes, the age at the start of training most likely influences the amount of bone formed, while the years of continuous training probably influence maintenance of existing bone mass.
### 2.5) Bone Mineral Density in Male Athletes

**Table 1.** Cross Sectional Studies of Bone Mineral Density Involving Male Endurance Athletes.

[BMD=Bone Mineral Density; T= Testosterone; >= greater than; <= less than; ~ = approximate.]

<table>
<thead>
<tr>
<th>Researchers/Year</th>
<th>Subjects</th>
<th>Hormones Tested</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Longitudinal Cross Sectional Studies</strong></td>
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<tr>
<td>Bennell, Malcolm, Khan, Thomas, Reid, Brukner, et al. 1997.</td>
<td>27 power track athletes -31 endurance track athletes - 27 nonathlete controls (age range= 17 to 26 yrs)</td>
<td>none</td>
<td>1. BMD of power athletes (lower limb, lumbar spine, upper limb)&gt; endurance athletes and controls 2. BMD of endur. athletes (lower limb)&gt; controls 3. Both athlete groups showed significant increases in total body BMC and femur BMD after 12 months</td>
</tr>
<tr>
<td>Lane, Oehlert, Bloch, Fries, 1998.</td>
<td>-28 distance runners, between the ages of 50 and 72 at the beginning of the study -average training volume was 43 km/week at beginning of study, decreasing to an average of 27.5 km per week at the end of 9 years -average training age at start of study was 21 years</td>
<td>none</td>
<td>1. Lumbar spine BMD of distance runners &gt; controls at each measurement time (0, 3 yrs, 6 yrs, 9 yrs) 2. Changes in lumbar spine BMD were similar for runners and nonrunners over 9 years</td>
</tr>
</tbody>
</table>
Table 1 (continued)

<table>
<thead>
<tr>
<th>Researchers</th>
<th>Subjects</th>
<th>Hormones Tested</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retrospective Cross-Sectional Studies (Runners)</strong></td>
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<tr>
<td>Pollock, Mengelkoch, Graves, Lowenthal, et al., 1997.173</td>
<td>-male runners, highly competitive &gt;20 years prior; 60-69 yr: n=10; 70-78 yr: n=6; 79-89 yr: n=4; 90+ yr: n=3.</td>
<td>none</td>
<td>1. total BMD significantly lower in 90+ age group, all other BMD measures (lumbar spine, trochanter) not sig. diff. based on age 2. regional arm BMD significantly greater in athletes performing weight training compared to those who did not</td>
</tr>
<tr>
<td>Goodpaster, Costill, Trappe, Hughes, 1996.79</td>
<td>male runners, aged 42-73, competitive 20-25 yrs prior; classified as highly trained (HT, n=17), moderately trained (MT, n=29), untrained (UT, n=10) based on most recent training</td>
<td>none</td>
<td>1. no significant differences between lumbar or proximal femur BMD between HT, MT, or UT 2. no sig. diff between runners and matched values from reference database</td>
</tr>
<tr>
<td><strong>Cross-Sectional Studies: Runners</strong></td>
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<tr>
<td>Hetland, Haarbo, Christiansen; 1993.71</td>
<td>-120 physically active men, running 0 to 160 km/week, age range 19-56 yrs.</td>
<td>-serum total testosterone -serum progesterone -serum estradiol -free estradiol -luteinizing hormone, follicle stimulating hormone, SHBG -free testosterone index calculated</td>
<td>1. all runners had normal concentrations of gonadotropins and sex hormones 2. bone mineral content of the lumbar spine, total body, distal forearm, and trochanter were sig. less in elite runners (training over 100 km/week) than in non-running controls. 3. femoral neck content was not sig. diff. between elite runners and controls</td>
</tr>
<tr>
<td>Researchers</td>
<td>Subjects</td>
<td>Hormones Tested</td>
<td>Results</td>
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</tr>
<tr>
<td>MacDougall, Webber, Martin, Ormerod, Chesley; 1992.⁷⁰</td>
<td>-male runners grouped by weekly mileage: 5-10 mi/wk (n=5), 15-20 mi/wk (n=11), 25-30 mi/wk (n=12), 40-55 mi/wk (n=9), 60-75 mi/wk (n=16); and sedentary controls (n=22)</td>
<td>serum total testosterone</td>
<td>1. lower leg BMD of 15-20 mile group&gt; controls and 5-10 mile group 2. general trend of decreasing lower leg BMD with increasing mileage of 20 mi/wk 3. T similar in all groups</td>
</tr>
<tr>
<td>Bilanen, Blanchard, Russek-Cohen; 1989.⁷²</td>
<td>-13 long distance runners (training ~ 90+ km/week) -11 nonrunners</td>
<td>none</td>
<td>1. runners’ vertebral BMD sig. lower than controls 2. tibial and radial BMD did not differ between groups</td>
</tr>
</tbody>
</table>

**Cross-Sectional Studies: Athletes in Various Sports**

<table>
<thead>
<tr>
<th>Researchers</th>
<th>Subjects</th>
<th>Hormones Tested</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsumoto, Nakagawa, Nishida, Hirota, 1997.⁶¹</td>
<td>-24 long distance runners -14 judoists -21 swimmers (collegiate athletes)</td>
<td>none</td>
<td>total BMD and urinary deoxypyridinoline highest in judoists</td>
</tr>
<tr>
<td>Nilsson, Westlin; 1971.⁵⁵</td>
<td>-64 athletes of various sports -39 healthy non-athletic, age-matched controls</td>
<td>none</td>
<td>1. femoral BMD of athletic group was sig. higher than femoral BMD of control group; 2. general trend: femoral BMD of weight lifters&gt; throwers&gt; runners&gt; soccer players&gt; swimmers= controls</td>
</tr>
<tr>
<td>Hanmdy, Anderson, Whalen, Harvill; 1994.⁷⁴</td>
<td>male athletes between the ages of 19 and 42 -11 weight-lifters -12 runners -8 cross-trained -9 recreational</td>
<td>none</td>
<td>1. upper limb BMD of weight-lifters&gt; runners 2. runners had the lowest upper limb BMD</td>
</tr>
</tbody>
</table>
Table 1 summarizes findings from cross sectional investigations of BMD involving male endurance athletes. Frequently, long distance runners have been included in these studies, and compared to non-athletic controls and/or athletes of different sports such as weight lifting and high impact, low repetition activities (i.e., judo). There are some important considerations to make when comparing these studies: subject height and

<table>
<thead>
<tr>
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<th>Results</th>
</tr>
</thead>
</table>
| Sabo, Bernd, Pfeil, Reiter, 1996 | - internationally ranked male athletes (~age range 20-28)  
-28 weight lifters (n=28)  
-6 endurance cyclists  
-6 boxers  
-21 moderately active male controls | none            | 1. lumbar BMD of weight lifters > controls (24% higher)  
2. lumbar BMD of boxers > controls  
3. lumbar BMD of endurance cyclists was 10% lower than controls |
| Smith, Rutherford; 1993       | -male athletes (~age range: 18-34)  
-21 rowers  
-8 triathletes  
-13 sedentary controls | serum total testosterone | 1. spine and total body BMD of rowers > triathletes, controls  
2. BMD of triathletes = controls  
3. T of triathletes < controls; T of rowers and controls not sig. diff. |
| Tsai, Kao, Wang; 1996         | -adolescent athletes: -8 baseball players  
-5 swimmers  
-7 judoists  
-8 mid/long distance runners  
-8 non-athletic controls | none            | 1. combined athletes lumbar BMD>controls  
2. lumbar BMD of judoists> baseball players, swimmers, track athletes, controls  
3. lumbar BMD of baseball players> controls  
4. femoral neck BMD of baseball players > swimmers, judoists, track athletes and controls. |
weight, site of BMD measurement, training age and absolute age of research subjects, age at the beginning of training, subjects’ specific sports activities and supplemental training (i.e. weight training).

Few longitudinal studies of BMD in male athletes have been made. Total body and femoral BMD increased in experienced middle and long distance runners over a 12-month training period.\textsuperscript{33} The subjects were between 17 and 26 years of age. In the previously mentioned 9 year study of runners aged 50 to 72 years, the lumbar spine BMD of male athletes decreased continuously over the measurement time, even though training was maintained.\textsuperscript{130} In both studies, the runners had higher BMD than nonathlete controls. These studies indicate a positive effect of running on BMD in younger male athletes, while this effect may only be maintained in older runners.

Two retrospective studies of the BMD in older male distance runners investigated the impact of elite level training engaged in 20 years prior. One classified the subjects according to current training status, and found that there were no significant differences in the lumbar or proximal femur BMD between currently highly trained, moderately trained, or untrained athletes, or between any of the running groups and the Hologic (DXA) reference database.\textsuperscript{75} The men fell in an age range of 42 to 73 years. The other study divided the former competitive runners (age range 60 to 95) into 4 age groups, and found that there were no differences in BMD of the lumbar spine or greater trochanter among any of the age groups, but the total body BMD was significantly lower in the 90+ age group.\textsuperscript{173} The men in this study did have different current training status, ranging from highly trained to untrained, but BMD was not differentiated on this basis. The results of these two studies seem to indicate that former elite running training has a constant effect
on BMD, that is not influenced by current training status, or possibly, by age in older men
(until very old age is reached, ie, over 90 years).

Cross-sectional studies of young long distance runners and BMD in relation to
current training volume report similar results. MacDougall (1992), Hetland (1993), and
Bilanen (1989) found significantly lower BMD of the lumbar spine, total body, distal
forearm, trochanter, and tibia in their high mileage male distance runners when they
were compared to sedentary or much less active men. Two of the studies isolated the
lower BMD to men training at volumes greater than 90 km per week and the other
indicated a correlation between decreasing BMD and increasing training volume over 32
kilometres per week. Two groups of investigators also measured testosterone levels of
the runners concurrently with BMD. In both cases, serum total testosterone was normal
and did not vary significantly between runners and controls. These three studies
shared common selection criteria for subjects: the athletes were young men, and had been
training for a minimum of 2 years. These studies indicate that lower BMDs in male
runners than nonrunners are specific to groups doing high volumes of training, and
specifically, volumes in excess of 90 km per week.

Several cross-sectional studies have compared male athletes from a variety of
sports to investigate the impact of specific types of loading on BMD. Researchers have
commonly compared: 1) weight-lifters (athletes who train for strength and continually
load bones at high resistance); 2) athletes involved in high impact team sports that
incorporate running (ie, soccer); 3) swimmers and cyclists (athletes training in non weight-
bearing sports); and 4) endurance athletes such as runners, cyclists, and triathletes.
Nilsson and Westlin (1971) were among the first to compare BMC in a cross section of male athletes. The study compared athletes’ bone mineral content of the femoral shaft using dual photon absorptiometry (DPA), and showed that BMC was higher in the athletes than age-matched controls. When the athletes were grouped by sport, the BMC decreased with decreasing loads, so that the swimmers did not differ significantly from the controls. The descending order from highest BMC to lowest was: weight-lifters, throwers, runners, soccer players, swimmers. Although this study is important in that it sparked further research in the area, it is at fault in that it compared BMC between athletes that had very different weights and heights, and then attributed the differences to sport training. The larger bones of the throwers who averaged 191 cm in height and 106.7 kg in weight would logically have a higher BMC than the smaller bones of runners who averaged 179 cm in height and 66.2 kg in weight. In more recent studies, BMD as measured by DXA allows for comparisons between athletes of different sizes, as the amount of bone mineral per measured area of bone is calculated.

Studies comparing endurance athletes to those involved in less repetitive, higher impact sports report lower BMDs in the runners at a variety of measurement sites. Smith and Rutherford (1993) reported lower lumbar spine and total body BMD in triathletes than rowers; the BMD of the triathletes did not differ from that of a control group. This particular study also indicated lower total testosterone levels in the triathletes than controls. Similarly, Sabo and colleagues (1996) measured endurance cyclists who had lumbar BMD 35% lower than weight lifters, and 10% lower than inactive controls.

The specificity of loading site as well as the impact level of a particular sport is important to BMD. Upper limb BMD was found to be lowest in a group of high mileage
runners when compared to weight-lifters, cross-trainers, and recreational athletes. However, all other measures (lumbar spine, femoral neck, greater trochanter, Ward's triangle) were similar between groups. A number of recent studies have found athletes training for high impact sports to have superior BMD to long distance runners. Specifically, judoists have demonstrated higher total body BMD and lumbar spine BMD than distance runners, and power track athletes (hurdlers, sprinters, jumpers) had higher measures on lower limb, lumbar spine and upper limb BMD than endurance track athletes.

From the studies discussed, it is apparent that the skeletal response to physical activity is specific to both loading site and the mode of exercise. It is thought that bone modeling and remodeling respond to the largest strains, and smaller ones have less of an effect, regardless of the frequency at which they are applied. Peak accelerations of the body's mass occur in sports such as judo, soccer, and sprinting, and elicit larger bone remodeling responses. Furthermore, in the case of weight lifters, throwers, and other power athletes, the correlation between muscle and bone strength is evident: larger muscles place larger forces on bone. In these cases, bone needs to have a greater mass to reduce internal stress (refer to Bone Biology: Minimum Effective Strain). Thus, bone adapts as a function of the loads placed on it through the combined strain of physical activity and muscle pull, to reduce the risk of fracture under subsequent similar loads.

To fairly compare studies of male distance runners, some key variables need to be controlled from study to study. Subject selection with regards to age is important as the age related onset of bone loss begins between the ages of 30 and 50. Thus, a study that includes men between the ages of 18 and 45 and attributes BMD differences to training,
may in fact be demonstrating an age-related loss of bone. Other variables are training volume, which should be consistent between subjects and over the years of training, and the age of starting training. Accumulated training is an important issue that requires control within these studies, as very different skeletal and hormonal regulatory mechanisms may be occurring in runners who have been training intensely at high mileages for 2 or 3 years, than in those who have maintained a relative intensity for more than 20 years. Furthermore, the impact of training done outside of running workouts, for example, cross training and weight training, should be taken into account in studies of BMD in these athletes.
2.6 Testosterone: Production, Circulation, Actions and Measurement

The hypothalamus, pituitary and gonads are physiologically integrated in the human male as the hypothalamic-pituitary-gonadal axis, and function as a united control in the manufacturing and release of sex hormones. Gonadotropin releasing hormone (GnRH) is secreted by the hypothalamus, and regulates the secretion of luteinizing hormone (LH) from the pituitary. Testosterone is secreted in a pulsatile fashion by the Leydig cells of the testes following stimulation by luteinizing hormone.\(^{177}\) (Figure 5)

**Figure 5.** Control of Testicular Function and Testosterone Production. [From: Sherwood L. Human Physiology. New York: West Publishing Company, 1993, p. 708.]
Testosterone is a steroid hormone synthesized from cholesterol through a series of reactions catalyzed by five enzymes: 20,22-desmolase, 3B-hydroxysteroid dehydrogenase, 17-hydroxylase, 17,20-desmolase, and 17-hydroxysteroid dehydrogenase. The testicular androgenesis pathway is depicted in Figure 6. Most of the testosterone in the blood binds to sex hormone binding globulin (SHBG), a protein which can fluctuate in concentration. About 40% of testosterone circulates in a weakly bound state to the two other testosterone transport proteins, albumin and cortisol binding globulin (CBG). The remaining testosterone, about 1 to 3% of the total, circulates freely, and elicits biological effects. The concentration of free testosterone should increase if the total testosterone level increases, and should decrease with an increase in SHBG.

Once released from the testes, testosterone either acts directly on target tissues, or acts as a prohormone in the formation of two different metabolites that are mediators of androgen action in peripheral tissues. The enzyme 5 alpha-reductase irreversibly converts testosterone to dihydrotestosterone (DHT), and the aromatase enzyme complex catalyzes the conversion of testosterone to the potent estrogen, 17B-estradiol (E$_2$). (Figure 6).
DHT and E2 may act directly on the tissues of origin, or enter circulation and act peripherally. The physiological consequences of circulating testosterone are represented by the sum of the total effects exerted by the estrogen and androgen metabolites of the parent molecule, and the direct action of testosterone itself. The normal concentration range for total testosterone in healthy men is 10.4 to 38.2 nmol/L, with the lower limit falling between 10.4 and 12.1 nmol/L. The free testosterone range is between 50 and 130 pmol/L.

In the healthy human male, testosterone is a hormone that fluctuates in fairly constant patterns on a daily basis, is thought to display circadian rhythm patterns, and has very predictable peaks and patterns of increase and decline over a life span. The variation in testosterone over the course of the normal human male lifespan are depicted in Figure

---

**Figure 6.** Testicular androgenesis of testosterone and its metabolites.

7, and Figure 8 represents the typical 24 hour pattern of testosterone fluctuation in the human male.


Total testosterone (TT) measurements have traditionally been used to help screen for hirsutism in women, or primary gonadal failure or secondary hypogonadism in men. In light of the fact that free testosterone (FT) represents the most biologically
potent portion of total testosterone, the measurement of FT directly or indexed by the T/SHBG ratio would correlate better than TT with the occurrence of clinical conditions. Both free and total testosterone can be assessed by radioimmunoassay.

The Coat-A-Count™ free testosterone procedure is a direct (or single tube) assay, which employs a tracer that does not bind to steroid hormone transport proteins (albumin and CBG), and an antiserum with an affinity for testosterone that is just less than SHBG's affinity for the hormone. This isolates the unbound (free) portion of testosterone for analysis. The kit is sensitive for free testosterone values ranging from 1.9 to 173 pmol/L (normal physiological range is 50 to 130 pmol/L), and can detect as little as 0.52 pmol/L free testosterone. Precision has been calculated at 3.83% CV for within-run tests, and 4.2% CV for run-to-run tests.

Total testosterone can be assessed with the Chiron Diagnostics ACS: 180™ testosterone assay. This is a competitive immunoassay, using direct, chemiluminescent technology, and employing a releasing agent to release bound testosterone from SHBG, albumin and CBG. Sensitivity for the ACS: 180 Testosterone assay falls between testosterone concentrations of 0.35 nmol/L and 52.0 nmol/L, with a reported precision of 6.5% CV within the normal physiological range for total testosterone (8.4-28.7 nmol/L).
### 2.7 Exercise and Testosterone Levels in Men

**Table 2.** Cross Sectional and Prospective Studies of Reproductive Hormone Levels in Male Endurance Athletes.

[DR= distance runner; SC= sedentary control; TV= training volume; TT= total testosterone; SHBG= serum hormone binding globulin; FT= free testosterone; LH= luteinizing hormone; FSH= follicle stimulating hormone; PRL= prolactin; C= cortisol; E= estradiol; GnRH= Gonadotropin Releasing Hormone; subjects are male unless otherwise stated.]

<table>
<thead>
<tr>
<th>Researchers/Year</th>
<th>Subjects</th>
<th>Hormones Tested</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td><strong>Prospective Studies</strong></td>
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</tr>
<tr>
<td>Remes, Kuoppasalmi, Adlercreutz; 1979.184</td>
<td>-n= 39 military recruits, during first 6 months of training  -age range 19 to 28 years</td>
<td>plasma TT, androstenedione, LH, SHBG capacity  -single samples drawn at beginning of 1st month and end of 6th month</td>
<td>• sig. increases in TT, androstenedione, and LH by end of 6th month  • ratio of TT: SHBG capacity increased</td>
</tr>
<tr>
<td>Guglielmini, Paolini, Conconi; 1984.185</td>
<td>-n= 7 competitive walkers, tested before and after a 20 km race;  -n= 9 middle distance runners, tested before and after 1 hour of training;  -n= 16 marathon runners, tested before and after a marathon race;  -n= 30 ultramarathoners, tested before and after 107 km ultramarathon  -age = 17 – 39 years</td>
<td>serum TT  -single samples collected before and after sessions</td>
<td>• non significant increase in TT in walkers, significant increases in middle-distance runners and marathoners  • significant decrease in TT in ultramarathoners</td>
</tr>
<tr>
<td>Fellman, Coudert, Jarrige, et al.; 1985.186</td>
<td>-n= 6 healthy males initiating a 40 week cycle ergometer training program  -mean age = 35.8 +/- 4.4 years</td>
<td>plasma TT, C, androstenedione  -single samples drawn before and immediately after training session at day 0 and at the 10th, 20th, 30th, and 40th weeks of program</td>
<td>• resting values of hormones did not change  • post-exercise values of TT, C, and androstenedione were increased</td>
</tr>
<tr>
<td>Urhausen, Kullmer, Kinderman; 1987.187</td>
<td>-n= 9 elite rowers (6 men + 3 women)  -mean age 20.0 +/- 0.8 years</td>
<td>serum TT, C, SHBG  -single samples collected weekly during 7 consecutive weeks of competition period</td>
<td>• T, T/SHBG, and T/C continuously decreased during 7 weeks of competition</td>
</tr>
<tr>
<td>Researchers/Year</td>
<td>Subjects</td>
<td>Hormones Tested</td>
<td>Results</td>
</tr>
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<tr>
<td>Urhausen, Kinderman; 1987.</td>
<td>n= 8 moderately trained triathletes -mean age = 25.4 +/- 2.8 years</td>
<td>serum TT, C, SHBG -samples collected prior to triathlon, and once/day on following 4 days</td>
<td>• T decreased nonsignificantly during days post-competition • T:SHBG (as expression of FT) sig. reduced on 2nd, 3rd, and 4th days post-comp • C increased during competition, and decreased during days following</td>
</tr>
<tr>
<td>Hackney, Sharp, Runyan, et al.; 1989.</td>
<td>-n= 8 athletic men on eight wk intensive training program, involving continuous and interval cycling -age of subjects not stated</td>
<td>TT, PRL -single resting samples collected at 2 wk intervals</td>
<td>• 4 to 6 wk TT levels sig. reduced, PRL sig. elevated • sig. negative correlation (-0.934) between TT and PRL</td>
</tr>
<tr>
<td>Hakkinen, Keskinen, Alen, et al.; 1989.</td>
<td>-n= 9 elite endurance swimmers; mean age = 20.0 +/- 2.7 years -n= 8 elite weight lifters; mean age = 24.3 +/- 1/5 years</td>
<td>serum TT, FT, C -single samples collected every 4 months</td>
<td>• no statistically sig. changes in hormones of either group over the year; hormone levels not sig. different between groups</td>
</tr>
<tr>
<td>Griffith, Dressendorfer, Fullbright, et al.; 1990.</td>
<td>-n= 6 endurance athletes engaging in 2 weeks of prolonged running and cycling -age range = 22 -44 years</td>
<td>plasma TT -single samples collected before and after 2 weeks of increased training</td>
<td>• TT decreased by 17% from beginning to end of program</td>
</tr>
<tr>
<td>Seidman, Dolev, Deuster, et al.; 1990.</td>
<td>-n= 35 untrained subjects, engaging in an 18 week strenuous training program -age range = 18 to 20 years</td>
<td>serum TT and C -single samples collected at 3 week intervals</td>
<td>• TT increased at week 6 and decreased at week 12; TT did not differ from pre-training at week 18 • C increased at week 18 • T/C ratio decreased at 12 and 18 weeks of training</td>
</tr>
</tbody>
</table>
### Table 2. (continued: Prospective Studies)

<table>
<thead>
<tr>
<th>Researchers</th>
<th>Subjects</th>
<th>Hormones Tested</th>
<th>Results</th>
</tr>
</thead>
</table>
| Tsai, Johansson, Pousette, et al.; 1991.\(^{192}\) | -n= 9 male and n= 7 female elite endurance athletes  
- age range 22 to 29 years | serum C, TT, FT, non-SHBG bound T, dehydroepiandrosterone, 4-androstene-3, 17-dione, SHBG  
- single samples collected during off-season, early competitive season, and at the end of the competitive season | - no sig. differences observed in androgen concentrations or androgen:cortisol ratios within 2 groups |
| Jensen, Oftebro, Breigan, et al.; 1991.\(^{193}\) | -n= 7 well trained men, experienced in strength and endurance training  
- age range 23 to 29 | serum TT  
- single samples collected before and after strength and endurance training sessions, and on the day following exercise sessions | - TT increased 27% after weight training and 37% after endurance training, and levels returned to normal within 2 hours of training |
| Roberts, McClure, Weiner, et al.; 1993.\(^{194}\) | -n= 5 endurance trained men (participating in running, swimming, cycling)  
- mean age 24.8 +/- 1.3 years  
- engaged in 2 week period of overtraining | plasma TT, C  
- single samples collected before overtraining, immediately and 3 months after overtraining | - TT decreased 36% from the pre-overtraining measure to immediately post-overtraining; C increased 30% during this time |


<table>
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<tr>
<td>Ponjoc, De Rooy, Vader; 1994</td>
<td>-n= 18 marathon runners</td>
<td>serum TT, C, dehydroepiandrosteronesulfate (DHEAS), SHBG, 3alpha-AdiolG</td>
<td>• sig. increase in C, T, free T index, DHEAS, and 3alpha-AdiolG observed from pre to post race</td>
</tr>
<tr>
<td></td>
<td>-age range 20 to 40 years</td>
<td>-single samples collected 18 prior to marathon, and immediately post-race</td>
<td></td>
</tr>
<tr>
<td>Jensen, Wiswedel, McLoughlin, et al.; 1995</td>
<td>-n= 24 marathon runners</td>
<td>plasma TT, LH, FSH, PRL, E, progesterone -single samples collected every 2 months for 1 year</td>
<td>• sig. rise in PRL levels during period of increased training, accompanied by a fall in progesterone levels</td>
</tr>
<tr>
<td></td>
<td>-age range 25 to 54</td>
<td></td>
<td>• no other hormones exhibited sig. changes</td>
</tr>
</tbody>
</table>

**Cross Sectional Studies**

<p>| Wheeler, Wall, Belcastro, et al., 1984 | -n=31 DR, TV= minimum of 64 km/wk;            | serum TT, non-SHBG bound T, FT, LH, FSH, PRL, C -single blood sample          | • TT, non-SHBG bound T, and PRL significantly lower in DR |
|                                       | -n=18 SC                                      |                                                                          | • All hormone levels within normal phys. range                              |
|                                       | -age range= 18-56 years                      |                                                                          | • TT sig. lower in DR; 14 DR subjects had TT outside normal phys. range    |
| Ayers, Komesu, Romani, et al., 1985   | -n=20 DR, TV= min 48 km/wk for min. 18 months; | serum TT, E, LH, FT, dehydroepiandrosterone sulfate (DHEA-S) -single blood sample | • FT, DHEA-S, E not sig. different between groups (trends demonstrated lower FT and E in DR) |
|                                       | -n= 10 SC                                     |                                                                          | • LH pulse frequency lower in DR                                           |
|                                       | -age range = 26-42                           |                                                                          | • LH amplitude, and response to increasing dosages of GnRH was lower in DR |
| MacConnie, Barkan, Lampman, et al.;   | -n= 6 DR, TV= 125 to 200 km/wk;              | serum LH, FSH, T, PRL, C -samples for LH and FSH drawn every 20 min for 8 hours -samples for T drawn every 2 hours for 8 hours |                                                                         |
| 1986.198                              | -n= 13 non-competitive, recreational athletes |                                                                          |                                                                         |
|                                       | -mean age = 25 years                          |                                                                          |                                                                         |</p>
<table>
<thead>
<tr>
<th>Researchers</th>
<th>Subjects</th>
<th>Hormones Tested</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hackney, Sinning,</td>
<td>-n= 11 endurance athletes (majority runners); mean age= 28.1 +/- 1.2 years -n= 11 SC; 24.7 +/- 1.0</td>
<td>serum TT, FT, E, LH, PRL, C</td>
<td>• TT, FT sig. lower in endur. athletes</td>
</tr>
<tr>
<td>Bruot; 1988.66</td>
<td></td>
<td>-blood samples collected every 60 min for 4 hours</td>
<td>• LH sig. higher in endur. athletes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• E, PRL, C did not differ between groups</td>
</tr>
<tr>
<td>Hackney, Sinning,</td>
<td>-n= 5 DR, mean TV= 17.7 km/day; mean age = 30.8 +/- 1.1 years -n= 5 SC; mean age = 25.8 +/- 2.1 years</td>
<td>serum T, FT, E, LH, PRL, C</td>
<td>• TT, PRL sig. lower in DR; LH sig. higher in DR</td>
</tr>
<tr>
<td>Bruot; 1990.57</td>
<td></td>
<td>-blood samples collected every 20 min for 4 hours</td>
<td>• dopamine challenge produced a greater integrated PRL response in the DR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-also performed dopamine and GnRH challenge to pituitary-testes</td>
<td>• DR had blunted LH response to GnRH challenge as compared to SC</td>
</tr>
<tr>
<td>Bagatell, Bremner;</td>
<td>-n= 12 marathon runners; -n= 12 age matched, lean controls -age range= 21-37 years</td>
<td>serum TT, FT, SHBG, C, FSH, LH</td>
<td>• immunologically active LH higher in marathoners; all other hormones were similar between groups</td>
</tr>
<tr>
<td>1990.199</td>
<td></td>
<td>-six single blood samples drawn at 2 week intervals</td>
<td></td>
</tr>
<tr>
<td>MacDougall, Webber,</td>
<td>-n= 53 DR, TV ranged from 8 km/wk to 120 km/wk, and divided TV -n= 22 SC -age range = 20 to 45 years</td>
<td>serum TT</td>
<td>• serum TT did not differ between groups</td>
</tr>
<tr>
<td>Martin, et al.; 1992.70</td>
<td></td>
<td>-two single blood samples drawn on separate days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arce, De Souza,</td>
<td>-n= 10 DR, TV= min. 96 km/wk for 1 year -n= 8 weight-lifters (WL) n=10 SC -age range = 18 to 35 years</td>
<td>plasma TT, serum FT, LH, FSH, PRL, E, urinary LH -3 samples drawn at 20 minute intervals for 60 minutes</td>
<td>• sig. lower TT and FT in DR and WL than SC</td>
</tr>
<tr>
<td>Pescatello, et al.;</td>
<td></td>
<td></td>
<td>• all other hormones not sig. different. between groups</td>
</tr>
<tr>
<td>1993.200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith, Rutherford;</td>
<td>-n=12 rowers -n= 8 triathletes -n= 13 SC -age range = 18 - 24</td>
<td>serum TT</td>
<td>• serum TT sig. lower in triathletes than SC</td>
</tr>
<tr>
<td>1993.175</td>
<td></td>
<td>-single samples collected</td>
<td>• no sig. difference between SC and rowers</td>
</tr>
</tbody>
</table>
The prospective and cross-sectional studies researching the effects of exercise on male testosterone levels are summarized in Table 2. Exercise sessions of short duration (less than 2 hours) have been associated with almost immediately measurable hormonal responses in male athletes. Notably, testosterone levels have been shown to rise from pre to post exercise, and this seems to be independent of exercise mode. The prospective studies summarized in Table 2 indicate that this rise is a response typical of both elite athletes and formerly untrained men (Guglielmini et al., 1984; Fellman et al., 1985; Jensen et al., 1991, Ponjee et al., 1994; Table 2.) Exercise sessions lasting longer than 2 hours have been associated with decreased levels of testosterone as compared to pre-competition levels in triathletes and ultramarathoners. Furthermore, sessions and competitions of longer duration may be associated with a lasting anabolic deficit, represented by elevated cortisol levels (which increases catabolism), and depressed free testosterone index (which decreases anabolism), in the days following the events. Unfortunately, prospective studies have overwhelmingly used quite small sample sizes, most likely due to the questionable ethics and discomfort involved in overtraining and repetitive blood sampling. Generalization of results is therefore limited.

The majority of research investigating the impact of chronic endurance training, and periods of intense overtraining, on basal testosterone levels indicate lower testosterone levels when male athletes are compared to sedentary controls or to their pre-overtraining values. However, some studies have found no differences between the testosterone levels of distance runners and sedentary controls. Studies of chronic endurance training are summarized in the Cross-Sectional section of
Table 2, while studies of overtraining by Griffith et al., 1990; Roberts et al., 1993, Hackney et al., 1989, and Urhausen, Kullman et al., 1987, are presented in the Prospective section of Table 2. Interestingly, a study by Remes et al. (1979) demonstrated an increase in total testosterone over 6 months of intense training in young military recruits. The type of exercise associated with military training is not strictly endurance-oriented, which may account for the different result compared to studies of increased training in endurance athletes.

Subject selection criteria for studies of chronic endurance training in males has typically included a minimum weekly training volume of 60 km/week, with some subjects training as much as 200 km/week, an age range of approximately 20 to 45 years, and participation in a consistent training program for at least 2 years. To more accurately assess the impact of endurance training on reproductive hormone physiology, subject groups need to be narrowly defined in relation to training age and absolute age. Very different mechanisms of reproductive hormone control may exist in a 25 year old runner who has been training for 5 years, and a 45 year old runner who has been training for 25 years. Also, starting age of training may play a role in the level of hormone regulation that is achieved in these athletes over time.

Comparison of research results would be more meaningful if similar hormones were tested in each study. Comparing levels of total testosterone between athletes and non-athletes may not be as clinically relevant as a comparison of levels of free testosterone (the most biologically active portion of the total hormone), and therefore, the amount of SHBG binding. Consistency in blood sampling technique would also allow for more accurate study comparison, as the research seems divided between those that employed
serial sampling techniques versus those that used isolated samples. However, in this regard, Hackney (1996) discusses the similarity of results regardless of isolated or serial sampling technique. Research has overwhelmingly demonstrated a lower level of serum testosterone in endurance runners (typically defined as athletes with a minimum training volume of 64 km/week), equalling 60-85% of age-matched, untrained men. 201
3. Subjects and Methods

3.1 Research Questions and Hypotheses

This investigation will look at the relationships between long term endurance running and BMD, long term endurance running and free/total testosterone, and BMD and free/total testosterone. Central research questions are:

1. Is there a difference between BMD at the lumbar spine and proximal femur of long term male endurance runners and their moderately active counterparts?
2. Is there a relationship between BMD and free and/or total testosterone in the exercising male?
3. Is there a difference in the free and total testosterone levels between long term male endurance runners and their moderately active counterparts?

Hypotheses:

Primary Hypotheses:

1. BMD of the lumbar spine and proximal femur will be significantly lower in a group of male, long term distance runners when compared to a group of moderately active controls.
2. Free and total testosterone levels will be lower in the group of long term distance runners, as compared to the moderately active control group.
3. BMD and free testosterone will be positively correlated when the subjects are pooled.

Secondary Hypotheses: The existence of a set of secondary hypotheses became apparent subsequent to data collection. The group of distance runners was divided into 2
subgroups: High volume (HV, n=5) runners, who ran more than 95 km per week, and moderate volume runners (MV, n=7), who ran between 64 and 90 per week.

1. BMD of the lumbar spine and proximal femur will be significantly higher in the MV runners than the HV runners and moderately active controls. BMD of the lumbar spine and proximal femur will be significantly lower in the HV runners compared with the moderately active controls.

2. Total and free testosterone will be similar between the HV and MV runners, and significantly lower in the HV and MV runners than the moderately active controls.

3.2 Subjects

Distance Runners

Twelve competitive Caucasian male distance runners were recruited for this study. BC Athletics provided a mailing list of male masters runners over the age of 40 who were registered with the cross country/road running/track and field association, and had therefore competed in a race within the year. Fifty-seven potential subjects were sent letters describing the study and invited to respond if they were interested and met the following criteria:

1. Current age between 40 and 55 years

2. Presently training at a minimum weekly running volume of 64 km/week

3. Planning to compete in a running competition of at least 10 km within the year

4. Training consistently at a minimum weekly running volume of 64 km/week for at least 20 years
5. Non-smoker

Eighteen men responded; twelve of them met the selection criteria, were satisfactorily screened, and measured on the variables in question.

Controls

Twelve healthy Caucasian male adults were recruited to participate in this study as moderately active control subjects; these subjects were not meant to represent a sedentary control group. The subjects were recruited subsequent to the recruitment of the distance runners in order to select men of similar body weight. Sixteen volunteers came forward after reading about the study in an advertisement in a local paper, or by hearing about it through word of mouth. Potential subjects responded if they were interested and met the following criteria:

1. Current age between 40 and 55 years
2. Non-smoker
3. Moderately active, participating in non-endurance type activities 2 to 4 times per week
4. Current weight between 61 and 87 kg

Subject Screening

Exclusion criteria for members of both groups included the presence of those conditions or therapies which affect hormone levels and/or bone metabolism: anorexia or bulimia, tobacco use, alcoholism, osteoporosis, rheumatism, Addison's Disease, Cushing’s Disease, osteoarthritis, hyperparathyroidism, hyperthyroidism, malabsorption, hypercalciuria, hypercalcemia, hypoparathyroidism, hypothyroidism, immobilization for
greater than one month, use of anabolic steroids, calcitonin, diuretics, heparin, oral cortisone, thyroid preparations, chronic use of 1) anti-inflammatories, 2) corticosteroids, and 3) antacids. (See Screening Questionnaire, Appendix A).

All subjects were provided with details of the testing procedures, and an expectation of the time required (approximately 1 1/2 hours) for their participation. Subjects had an opportunity to ask questions, and completed a written informed consent before testing commenced, in compliance with The University of British Columbia Clinical Screening Committee for Research and Other Studies Involving Human Subjects (see Informed Consent, Appendix B). Every subject that enrolled in the study followed it through to completion.

3.3 Study Design

This was an observational cross-sectional study, designed to compare chronically endurance trained male distance runners, to moderately active, healthy, male controls, of similar age and weight. With 12 subjects per group, the power = .99 to determine significant differences between groups, and was calculated based on the effect size observed in previous studies of BMD in distance runners and nonrunners. The key outcome variables measured were: BMD of the lumbar spine and proximal femur, serum total testosterone and free testosterone. As well, descriptive data pertaining to age, height, weight, Body Mass Index, sum of skinfolds, training habits, injuries, and nutrition was collected.
IV. Instruments and Procedures

A. Questionnaires

Upon recruitment, the Screening Questionnaire (Appendix A) was administered to potential subjects. Questions pertaining to training history and habits for the runners, and participation in physical activities for the controls, were also contained within this questionnaire. Informed consent was obtained from those who met the screening criteria. Subjects were verbally instructed on the correct way to keep a three day food record, as well as given written instructions.

The 3 day food record was analyzed using Foodsmart™, a computerized dietary analysis system. Foods are entered item by item, and meal, daily, or 3 day averages can be calculated for all nutrients. Twenty subjects received complete 3 day analyses, and total daily energy (kcal) and calcium (mg) were described. The test-retest precision averaged 6.65% for total daily energy intake, and 15.2% for daily calcium intake. Four subjects did not complete and return the diary (DR3, C7, C11 and C12), and therefore, nutrition data is not available for these subjects.

B. Anthropometric Measures

Height (m), weight (kg), and 7 skinfolds (mm) including tricep, bicep, subscapular, suprailliac, abdominal, thigh, and medial calf, were measured on all subjects. The Canadian Physical Activity, Fitness and Lifestyle Appraisal (CPFLA) Guidelines for taking skinfold measurements were followed. Two measures were taken at each site, and a mean was
recorded. If the difference between the two skinfolds was greater than 0.4 mm, a third measure was taken, and the two closest values were averaged. The seven skinfolds were summed (SOS) to compare the two groups on a fatness measure. Body mass index (BMI) was calculated by the formula: weight/(height)².

C. Bone Densitometry

BMD of the proximal femur (femoral neck, trochanter, total) and the lumbar spine (L1-L4) was determined using dual energy X-ray absorptiometry (DXA; Hologic QDR 4500, Hologic Incorporated, Waltham, Mass.).

All bone mineral density scans were performed by the same registered technician, at approximately the same time of day, at Fairmont Bone Density, 750 West Broadway in Vancouver. The proximal femur scans were performed on each subject’s non-dominant side. The QDR 4500 is equipped with quality control (QC) software programs, and a QC phantom was scanned daily to monitor system operation and ensure the reliability of bone mineral density measurements. The measurement precision of this instrument is estimated between 0.76% and 0.97% for the lumbar spine, and between 1.38% and 1.8% for the femoral neck. The scans were conducted over a 4 month period as subjects were recruited.

D. Hormone Analysis

Subjects reported to the Allan McGavin Sports Medicine Centre between 7:00 am and 9:00 am after 12 hours of fasting, and 36 hours without strenuous exercise. Blood samples were taken by one physician. A single 10 mL blood sample was collected
from each subject and clotted at room temperature. Samples were then centrifuged at
3200 rpm and 4° C. Serum was separated from the rest of the sample, and stored at -70°
C until the batch could be analyzed together by a single qualified technician at Clinical
Chemistry, Vancouver Hospital. Hormone analyses were performed on serum, and used
competitive binding radioimmunoassays. Serum total testosterone (TT) was analyzed
using the Chiron Diagnostics ACS: 180 Testosterone Assay; free testosterone (FT) in
serum was assessed using the Coat-A-Count Free Testosterone radioimmunoassay.

E. Statistical Analysis

1. Primary Hypotheses

The student’s t-test was used to analyze differences between Distance Runner
(DR) and Control (C) group means, with a significance level of p<0.05. Group means for
the following variables were compared:

- Age
- Weight
- Height
- Sum of 7 Skinfolds
- Femoral Neck BMD
- Trochanteric BMD
- Total Proximal Femur BMD
- Lumbar (L1-L4) BMD
- Total Testosterone
- Free Testosterone
- Calcium Intake
- Energy Intake

Pearson Product Moment Correlations were performed to investigate the relationship
between:

- BMI and BMD
- Age and BMD
• Weight and BMD
• Free/Total Testosterone and BMD
• # of Training Years and BMD
• Training Volume and Free/Total Testosterone
• Training Volume and BMD

2. Secondary Hypotheses

The means for the moderate volume running group (MV), high volume running group (HV), and control group (C) were compared using single factor ANOVA; results were considered significant at p<0.05. Tukey’s HSD Post Hoc Analysis was used to determine which groups were different for the following variables:

• Age
• Weight
• Height
• Sum of 7 Skinfolds
• Femoral Neck BMD
• Trochanteric BMD
• Total Proximal Femur BMD
• Lumbar (L1-L4) BMD
• Total Testosterone
• Free Testosterone
• Calcium Intake
• Energy Intake
4. Results

A complete set of individual subject results is included (Appendix C).

4.1 Subject Characteristics

Table 3. Physical Characteristics of Pooled Distance Runners (DR), Moderate Volume Runners (MV), High Volume Runners (HV), and Controls (C).

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>Body Mass Index (BMI)</th>
<th>Sum of 7 skinfold (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR</td>
<td>48.7 (4.7)</td>
<td>72.1 (7.0)</td>
<td>1.82 (0.06)</td>
<td>21.8 (2.59)*</td>
<td>67.0 (23.3)*</td>
</tr>
<tr>
<td></td>
<td>[41-55]</td>
<td>[64.5-89.4]</td>
<td>[1.74-1.92]</td>
<td>[18.7-27.2]</td>
<td>[32.8-106.3]</td>
</tr>
<tr>
<td>MV</td>
<td>48.0 (4.3)</td>
<td>72.1 (8.7)</td>
<td>1.81 (0.05)</td>
<td>22.11 (2.82)</td>
<td>68.8 (27.9)*</td>
</tr>
<tr>
<td></td>
<td>[42-55]</td>
<td>[68.6-80.0]</td>
<td>[1.74-1.88]</td>
<td>[19.43-27.17]</td>
<td>[32.8-106.3]</td>
</tr>
<tr>
<td>HV</td>
<td>49.1 (5.2)</td>
<td>72.0 (4.6)</td>
<td>1.84 (0.07)</td>
<td>21.30 (2.47)</td>
<td>64.4 (17.7)*</td>
</tr>
<tr>
<td></td>
<td>[41-52]</td>
<td>[64.5-89.4]</td>
<td>[1.77-1.92]</td>
<td>[18.68-24.56]</td>
<td>[40.3-85.9]</td>
</tr>
<tr>
<td>C</td>
<td>47.4 (5.3)</td>
<td>76.7 (6.2)</td>
<td>1.80 (0.06)</td>
<td>23.58 (1.73)*</td>
<td>107.0 (25.0)**</td>
</tr>
<tr>
<td></td>
<td>[40-55]</td>
<td>[68.9-86.2]</td>
<td>[1.71-1.90]</td>
<td>[21.09-26.14]</td>
<td>[48.5-140.2]</td>
</tr>
</tbody>
</table>

#significantly different between groups at p<0.05 (student’s t-test for independent samples, one tail)
* significantly different between groups at p<0.001 (student’s t-test for independent samples, one tail).
C significantly different from control group at p<0.05 (ANOVA, Tukey’s HSD)
MV/HV significantly different from HV and MV groups at p<0.05 (ANOVA, Tukey’s HSD)

Physical. The subjects’ physical characteristics are summarized in Table 3. Age, weight and height did not differ between the pooled distance runners (DR) and the controls (C), or between the moderate volume runners (MV), high volume runners (HV) and C. The mean BMI for the DR group was significantly lower than the BMI for the C group (p<0.05). The sum of 7 skinfolds for the C group was significantly higher than that of the DR group (p<0.001). The MV and HV groups also had significantly lower mean sum of 7 skinfolds than the C group (p<0.05).

Training. The mean years of consistent training for the DR group was 27.92 (SD=7.10) [range= 20-41]. Training volume was a minimum of 64 km per week, with a maximum of
112 km weekly (mean= 77.34 km, SD= 17.50). The minimum competitive distance length for this group was the 3000m steeplechase, which one subject competed in. All other subjects had competed in 10 km events, 9 had competed in marathons, 2 in ultramarathons of 100 km, and one in the Hawaii Ironman. All twelve DR subjects participated in some form of cross training during the year, which involved cycling, swimming and/or weight training. 4 of the 5 HV runners incorporated weight training into their programs, and 3 of the 7 MV runners weight trained as part of their program. For the distance runners, weight training was less than two hours of total training time per week in every reported case.

Examination of the training volumes recorded by subjects in the DR group identified 2 sub-groups, those subjects who currently ran between 64 and 90 km per week (n= 7, Moderate Volume =MV), and those that ran greater than 95 km weekly (n=5, High Volume=HV). There were no runners training between 90 and 95 km per week. The DR group was therefore divided (MV + HV = DR), and analyzed on the basis of a set of secondary hypotheses. Training volumes for the MV and HV groups were 68.6 (SD= 6.3) and 100.8 (SD= 7.2) respectively. The MV group ranged from 64 to 80 km per week, and the HV range was 96 to 112 km per week. The runners in the MV group reported exercising an average of 9.1 hours per week, while the HV group reported an average of 10.6 hours. All twelve DR subjects participated in some form of cross training during the year, which involved cycling, swimming and/or weight training. 4 of the 5 HV runners incorporated weight training into their programs, and 3 of the 7 MV runners weight trained as part of their program. For the distance runners, weight training was less than two hours of total training time per week in every reported case.
The control subjects participated in a number of exercise activities, none of which were endurance oriented. The minimum number of exercise sessions per week was 2, and the maximum was 4. Eight subjects took part in weight training on a weekly basis, which ranged from 2 to 4 hours of their total weekly exercise time. Five walked regularly for exercise. In addition, the subjects indicated that they hiked, cycled, played golf and tennis, and jogged. The average total exercise time was 4.8 hours per week.

II. *Bone Mineral Density (BMD)*

Table 4. Mean Bone Mineral Density of the femoral neck, trochanteric region, total proximal femur and lumbar spine for pooled Distance Runners (DR), Moderate Volume Runners (MV), High Volume Runners (HV) and Controls (C).

[presented as mean (SD)]

<table>
<thead>
<tr>
<th>Region</th>
<th>Group</th>
<th>BMD (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral Neck</td>
<td>DR (n= 12)</td>
<td>0.86 (0.14)*</td>
</tr>
<tr>
<td></td>
<td>MV (n= 7)</td>
<td>0.91 (0.16)#</td>
</tr>
<tr>
<td></td>
<td>HV (n= 5)</td>
<td>0.81 (0.074)</td>
</tr>
<tr>
<td></td>
<td>C (n= 12)</td>
<td>0.78 (0.071)*#</td>
</tr>
<tr>
<td>Trochanter Region</td>
<td>DR</td>
<td>0.81 (0.13)*</td>
</tr>
<tr>
<td></td>
<td>MV</td>
<td>0.85 (0.14)#</td>
</tr>
<tr>
<td></td>
<td>HV</td>
<td>0.76 (0.093)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.73 (0.053)*#</td>
</tr>
<tr>
<td>Total Proximal Femur</td>
<td>DR</td>
<td>1.04 (0.15)*</td>
</tr>
<tr>
<td></td>
<td>MV</td>
<td>1.09 (0.17)#</td>
</tr>
<tr>
<td></td>
<td>HV</td>
<td>0.98 (0.11)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.94 (0.056)*#</td>
</tr>
<tr>
<td>Lumbar Spine (L1-L4)</td>
<td>DR</td>
<td>0.98 (0.15)</td>
</tr>
<tr>
<td></td>
<td>MV</td>
<td>1.04 (0.16)</td>
</tr>
<tr>
<td></td>
<td>HV</td>
<td>0.90 (0.070)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.92 (0.095)</td>
</tr>
</tbody>
</table>

* Significantly different BMD between groups, p<0.05 (student's t-test for independent samples, one-tail).
#Significantly different BMD between groups, p<0.05 (ANOVA, Tukey's HSD).
Figure 9. Bone Mineral Density (BMD) of Pooled Distance Runners (DR, n=12) and Controls (C, n=12) at 4 Measurement Sites: Femoral Neck (FN), Trochanteric Region (TROCH), Total Proximal Femur (TOTAL PF), Lumbar Spine (SPINE). [* represents a significant difference (p<0.05) between groups at that site]
Figure 10. Bone Mineral Density (BMD) of Moderate Volume Runners (MV, n=7), High Volume Runners (HV, n=5), and Controls (C, n=12) at 4 Measurement Sites: Femoral Neck (FN), Trochanteric Region (TROCH), Total Proximal Femur (TOTAL PF), and Lumbar Spine (SPINE). [* represents a significant difference (p<0.05) between groups at that site]
Figure 11. Scatterplot showing femoral neck bone mineral density (BMD) data points for Moderate Volume Runners (MV), High Volume Runners (HV), and Controls (C).

Figure 12. Scatterplot showing trochanteric region bone mineral density (BMD) data points for Moderate Volume Runners (MV), High Volume Runners (HV), and Controls (C).
Figure 13. Scatterplot showing total proximal femur bone mineral density (BMD) data points for Moderate Volume Runners (MV), High Volume Runners (HV), and Controls (C).

Figure 14. Scatterplot showing lumbar spine bone mineral density (BMD) data points for Moderate Volume Runners (MV), High Volume Runners (HV), and Controls (C).
Comparison of DR and C groups (Primary Hypothesis). BMD of the femoral neck, trochanteric region, total proximal femur, and lumbar spine for the DR and C groups are presented in Table 4, and Figure 9. There were significant differences between the two groups for the femoral neck, trochanteric region, and total proximal femur (p<0.05). The group means for DR were 10.01%, 10.38%, and 9.28%, higher than C for the femoral neck, trochanteric region, and total proximal femur, respectively. BMD of the lumbar spine was not significantly different between the DR and C groups, (p= 0.11), although the group mean of DR was 6.74% higher than the C mean.

The standard deviations for all four BMD measurements were higher in the DR group (see Table 4), as can be noted in the scatterplots in Figures 11, 12, 13, 14. BMD of DR shows highs and lows that form a pattern markedly different than the more uniform C group.

Comparison of MV, HV, and C Groups (Secondary Hypothesis). BMD for the four measurement regions for the MV, HV, and C groups is presented in Table 4 and Figure 10. A significant difference (p<0.05) was noted between the MV and C groups for BMD of the trochanteric region, total proximal femur, and lumbar spine. There were no other significant differences between groups. The MV means for BMD of the femoral neck, trochanteric region, total proximal femur, and lumbar spine were 11.0 %, 10.6 %, 10.1 %, and 13.5% higher than the those of the HV group. The MV means for BMD of the femoral neck, trochanteric region, total proximal femur, and lumbar spine were 14.3 %, 14.1 %, 13.8 %, and 11.5% higher than those of the C group. The BMD means followed
a trend among groups for all measures at the proximal femur. The MV group consistently demonstrated the highest mean values, followed by the HV and C groups, respectively.

**Correlation Analyses.** Correlations between each of Body Mass Index (BMI), age, weight, training volume, and number of training years (for DR) against the four BMD measurements were not significant (Pearson Product Moment Correlation Coefficient, 2-tail significance):

BMI vs. femoral neck BMD: $r = -0.21$ (p=0.31)
BMI vs. trochanteric BMD: $r = 0.31$ (p=0.14)
BMI vs. total proximal femur: $r = 0.30$ (p=0.16)
BMI vs. lumbar spine BMD: $r = 0.34$ (p=0.11)
Age vs. femoral neck BMD: $r = 0.26$ (p=0.22)
Age vs. trochanteric BMD: $r = 0.32$ (p=0.13)
Age vs. total proximal femur BMD: $r = 0.28$ (p=0.18)
Age vs. lumbar spine BMD: $r = 0.09$ (p=0.67)
Weight vs. femoral neck BMD: $r = -0.19$ (p=0.37)
Weight vs. trochanteric BMD: $r = 0.15$ (p=0.47)
Weight vs. total proximal femur BMD: $r = 0.10$ (p=0.65)
Weight vs. lumbar spine BMD: $r = 0.22$ (p=0.30)
Training volume vs. femoral neck BMD: $r = -0.43$ (p=0.16)
Training volume vs. trochanteric BMD: $r = -0.44$ (p=0.15)
Training volume vs. total proximal femur BMD: $r = -0.48$ (p=0.12)
Training volume vs. lumbar spine BMD: $r = -0.49$ (p=0.11)
Training years vs. femoral neck BMD: $r = 0.07$ (p=0.83)
Training years vs. trochanteric BMD: $r = -0.13$ (p=0.25)
Training years vs. total proximal femur BMD: $r = -0.08$ (p=0.8)
Training years vs. lumbar spine BMD: $r = -0.36$ (p=0.25)
4.3 Hormone Analyses

Table 5. Means of total testosterone and free testosterone for pooled Distance Runners (DR), Moderate Volume Runners (MV), High Volume Runners (HV) and Controls (C).

[Presented as mean (SD)]

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Testosterone (nmol/L)</th>
<th>Free Testosterone (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR (n=12)</td>
<td>19.61 (5.01)</td>
<td>62.92 (10.81)</td>
</tr>
<tr>
<td>MV (n=7)</td>
<td>22.81 (3.57)</td>
<td>69.00 (8.30)</td>
</tr>
<tr>
<td>HV (n=5)</td>
<td>15.12 (2.60)</td>
<td>54.40 (7.93)</td>
</tr>
<tr>
<td>C (n=5)</td>
<td>18.18 (7.11)</td>
<td>73.67 (27.33)</td>
</tr>
</tbody>
</table>

No significant differences noted between groups for either total testosterone or free testosterone.

The differences between means for total testosterone (TT) and free testosterone (FT), as shown in Table 5, were not statistically significant between groups, when DR and C were compared (primary hypothesis), and when MV, HV, and C were compared (secondary hypothesis). The standard deviations were large for the TT and FT means for all 3 groups, which was most likely a factor contributing to the lack of statistical significance. The mean TT for HV was 33.7% lower than MV, and 16.83% lower than C. The mean FT for HV was 21.2% lower than MV, and 26.2% lower than C.

Figures 15 and 16 present the data points for TT and FT in all subjects. All subjects were within the normal range for TT (10.4 to 38.2 nmol/L). Two controls (C1 [36 pmol/L] and C5 [41 pmol/L]) fell well below the normal range for FT (50 to 130 pmol/L). Two other subjects, DR10 [48 pmol/L] and C11 [49 pmol/L], fell just outside the borderline of the low-normal end.
Figure 15. Scatterplot showing data points for total testosterone for Moderate Volume Runners (MV), High Volume Runners (HV), and Controls (C).

Figure 16. Scatterplot showing data points for free testosterone for Moderate Volume Runners (MV), High Volume Runners (HV), and Controls (C).
**Correlation Analyses.** TT and FT were not significantly correlated to BMD at the four regions (Pearson Product Moment Correlation Coefficient, 2-tail significance):

- TT vs. femoral neck BMD: \( r = 0.12 \) (\( p = 0.56 \))
- TT vs. trochanteric BMD: \( r = 0.12 \) (\( p = 0.58 \))
- TT vs. total proximal femur BMD: \( r = 0.03 \) (\( p = 0.88 \))
- TT vs. lumbar spine BMD: \( r = 0.13 \) (\( p = 0.55 \))
- FT vs. femoral neck BMD: \( r = 0.05 \) (\( p = 0.82 \))
- FT vs. trochanteric BMD: \( r = 0.16 \) (\( p = 0.45 \))
- FT vs. total proximal femur BMD: \( r = 0.13 \) (\( p = 0.55 \))
- FT vs. lumbar spine BMD: \( r = 0.19 \) (\( p = 0.37 \))

Training volume for the DR group and TT were significantly negatively correlated (\( P < 0.01, r = -0.73 \)). Training volume for the DR group and FT were significantly negatively correlated (\( P < 0.01, r = -0.79 \)).

**Correlation Matrices for TT/TV (= total T (DR) vs. mileage) and FT/TV (= free T (DR) vs. mileage):**

<table>
<thead>
<tr>
<th></th>
<th>TOTALTDR</th>
<th>MILEAGE</th>
<th>MILEAGE</th>
<th>FREETDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTALTDR</td>
<td>1.0000</td>
<td>-0.7273</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(12)</td>
<td>(12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.</td>
<td>.007</td>
<td></td>
<td>.002</td>
</tr>
<tr>
<td>MILEAGE</td>
<td></td>
<td>1.0000</td>
<td>-0.7900</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(12)</td>
<td>(12)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.007</td>
<td>.</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>FREETDR</td>
<td></td>
<td></td>
<td>1.0000</td>
<td>-0.7900</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(12)</td>
<td>(12)</td>
</tr>
<tr>
<td>P</td>
<td>.002</td>
<td>.</td>
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<td></td>
</tr>
</tbody>
</table>

4.4. *Calcium and Energy Intake*

Calcium intake for the DR group [1071.71 mg (SD=303.95)] was not significantly different from the C group [873.67 (SD=648.96)]. The within groups variance on this measure was quite high (note SD). The energy intakes were significantly different at \( p < 0.05 \): DR= 2518.78 kcal, SD=621.297; and C= 2119.69, SD= 391.73. Again, there was a
great deal of subject variability within groups on this measure. The means for calcium and energy were calculated from 3 day averages.

The MV and HV had similar mean calcium intakes: 1047.98 mg (SD= 330.30) and 1091.48 (SD= 310.59), respectively. These values were not significantly different from each other or from C. Their mean energy intakes were also similar: 2407.00 (SD=591.76) for MV, and 2652.92 kcal (SD=697.19) for HV. The mean energy intakes were not significantly different between MV, HV, or C.
5. Discussion

Research investigating the effect of running on bone mineral density has typically focused on women. From investigators’ findings, three important points can be made, which will later be related to the findings in men. First, bone mineral density in eumenorrheic female runners has been found to be higher than in sedentary control subjects, although this finding is largely site specific to weight-bearing bones. Second, the actual volume of running training can influence bone mineral density, especially when it is high enough to interrupt normal menstrual function and the bone formation processes. For women, this optimal amount of training may lie between training volumes of 20 km (~90 minutes) and 50 to 60 km (~300 minutes) per week. Third, menstrual dysfunction, in the form of oligomenorrhea or amenorrhea, negatively influences BMD of the lumbar spine. There is a lesser effect of menstrual disturbance on the bone mineral of the weight-bearing bones of the hip and leg, most likely due to the benefit of weight-bearing activity in female runners.

In this study, long term endurance running training had noticeable effects on the male skeleton. The comparison of these runners to a group of moderately active, healthy men demonstrated the benefits (and negative implications) specific to long term running training. Skeletal dynamics are multifactorial, therefore, the resulting bone mineral densities are not solely explained by running training, but by a combination of the endurance athlete lifestyle and genetic predisposition. However, the contribution of exogenous factors to a decreased risk of osteoporotic fracture in later life should not be ignored. As physical activity is one of the most easily modifiable factors known to have a
positive effect on BMD, defining appropriate recommendations for physical activity is important. The role that distance running plays in regards to bone health in later life is most likely related to the maintenance of bone mineral density.

5.1. Bone Mineral Density (BMD) of the Proximal Femur

Results Compared to Previous Findings. This study is unique in its finding that BMD of the proximal femur is greater in the distance runners than the controls. Other studies that have targeted groups of male distance runners largely looked at younger subjects, reported conflicting results, and infrequently tested proximal femur BMD. MacDougall et al. (1992) examined tibial BMD in runners between 20 and 45 years of age, training up to 120 km per week. BMD was greatest in those runners not exceeding a training volume of 32 km per week. Another study reported no difference between the tibial BMD of runners training more than 90 km per week and non-runners. Young male endurance track athletes, aged 17 to 26 years, had superior lower limb BMD than sedentary controls; training volume was not specified in this study. In a study of elite runners (average age 32 years) training over 100 km per week, lower BMC was noted at the trochanteric region, with no difference in femoral neck bone mineral, compared to non-runners.

In two studies of older runners training for more than twenty years, there was no difference in proximal femur BMD between athlete and control groups. Suominen
and Rahkila (1991) demonstrated superior calcaneal BMD in 70 to 81 year old endurance athletes as compared to a population sample. 

The two major variables that are inconsistent in these studies are subject age and training volume. For example, in Hetland’s (1993) study, the age range was between 19 and 56 years of age. As indicated in Snow-Harter’s (1991) review, the onset of age-related decline in BMD is a contentious issue. Reports indicated that BMD decreases starting at the second, and possibly as late as the fifth, decade of life. Approximately half of peak bone mass is accumulated during the adolescent growth spurt, and research indicates that peak bone mineral density may actually occur in late adolescence, not in the mid-twenties, as previously speculated. This might affect the results of studies that group distance runners that are in four different decades of life into one study of BMD. That no differences were observed between the femoral neck bone mineral density of distance runners and non-runners in the Hetland et al. study, may have been influenced, or confounded, by the normal age-related decline in BMD. The current study measured men of similar age, so that the BMD and hormonal effects of long term running could be demonstrated.

It is important to examine differences in running volume between studies, as the basic premise for this type of research is that endurance running training has an effect on skeletal status: more or less running should have different effects. MacDougall et al. (1992) demonstrated a trend toward decreased tibial BMD with increased training volume, over 32 km per week. Our distance running group was divided into two sub-groups based on reported training volume, which allowed us to observe BMD differences among groups attributable to training volume. The HV running group consistently showed lower
mean BMDs than the MV running group at the total proximal femur, and its femoral neck and trochanteric regions. The MV group had significantly higher femoral neck, trochanteric and total proximal femur BMD than the C group. The HV group was not significantly different than the C group on these measures. This demonstrated a threshold effect for training volume in relation to BMD. Based on our findings in a limited sample, volumes exceeding 95 km per week did not continue to have the positive effect on BMD observed in the runners training between 64 and 90 km per week. This is in agreement with Hetland et al. (1993), who found a negative correlation between both total body and trochanteric BMC and running volume from 0 to 160 km per week. 71

Possible Explanations and Mechanisms. Animal work by Lanyon (1984) where bone was loaded in vivo with various numbers of consecutive loading cycles per day over six weeks illustrated the idea that a minimum amount of weight-bearing exercise may maximize BMD. A 40% increase in BMC was noted in animals on a 36 cycle regime, while regimes of 360 or 1800 cycles per day did not elicit further increases in BMC. 86 Therefore, a threshold of running volume might limit the extent to which bone mass can be increased through bone modeling, and the influence of increased bone remodeling might account for the lower BMDs observed in the high volume runners. These ideas will be discussed in terms of the mechanostat theory of bone mass regulation.

The difference in BMD of the proximal femur between HV, MV, and C groups in our study might be explained by theories proposed by Frost. 17, 81 The mechanostat model (see Figure 1) indicates that increased mechanical usage of the skeleton through physical
activity results in bone modeling and remodeling. The net gain of bone that results from modeling under high loads or strain occurs primarily during growth.

Five of the seven MV runners indicated that they had commenced vigorous training prior to the age of 18, while only one of the HV runners began serious training before 18. Thus, the MV runners might have had a higher BMD when they reached adulthood. Kannus et al. (1995) demonstrated that ‘starting age’ of training is more closely related to peak bone mineral content than current exercise in adults. As O’Connor and Lanyon (1982) state, “the adult shape, structure and form of each bone is influenced by the mechanical circumstances to which it is subjected.” The strength of the loaded bone is increased through mechanical usage—stimulated modeling during growth, to enable the bone to withstand future loading situations. Unfortunately, the impact of childhood activity was not addressed in this study. The runners detailed their training habits from the time they commenced serious training, which was during the teenage years or as young adults in all cases. The controls were assessed on activities they typically engaged in as adults.

Contrary to bone modeling, bone remodeling occurs to replace fatigue-damaged bone with new bone. In adults, strains elicited in distance running usually fall in the physiological loading zone (Figure 2), and the subsequent remodeling has a maintenance, rather than an augmenting effect, on bone. Running exceeds the minimum effective strain for remodeling (MESr), and therefore may instigate conservation of bone in moderate volume runners. This could effectively reduce the impact of age-related related bone loss and account for the higher BMDs observed in the moderate volume
runners than the less active controls, especially when combined with a possible higher peak bone mass in the runners who began training before adulthood.

The HV runners in our study had lower (although not significant) proximal femur BMD than MV runners, and were not significantly different from the controls on this measure. The frequency and duration of strain applications in runners training upwards of 100 km per week might exceed that which allows for beneficial bone remodeling. Even normal remodeling causes temporary cavities in bone, known as the ‘remodeling space’, which equals the amount of bone temporarily removed in the BMU-based process. Under these normal conditions there is a lag between bone excavation and bone formation; the refilling process typically takes 3 to 4 months. The more frequent, continuous application of strains occurring in high mileage training would elicit more microdamage, which in turn stimulates greater remodeling. The remodeling space is therefore greater, which causes a greater porosity of bone. An increase in the number of resorption cavities can lead to loss of bone. Without a reduction in training volume, bone formation might never ‘catch up’ to bone excavation, and could result in lower BMD in high mileage runners. Once formation has proceeded, bone mass will stabilize at a new lower level.

In the Hetland study, the elite runners training over 100 km per week had markers of bone turnover that were 20 to 30% higher than those observed in men who ran, biked and swam 2 to 4 times per week. As previously reported, the trochanteric and total body BMC (corrected for BMI and height) was significantly lower in these elite runners when compared to the less active men. Exercise may directly modify the homeostatic control of calcium and bone metabolism through alterations in plasma concentrations of
parathyroid hormone (PTH). Both PTH and osteocalcin are raised immediately following exercise in young, and older men. This agrees with the higher BMD noted in our MV runners, as intermittent injections of PTH have anabolic properties, and osteocalcin is a marker of bone formation. However, chronically increased levels of PTH negatively influence bone mass, which could account for the lower BMDs observed in our HV runners, due to the extended length of their exercise sessions.

Dividing the DR group into the smaller MV and HV groups reduced the sample sizes, and therefore limits the generalizability of our results. However, important differences between the proximal femur BMD of the MV and HV runners were observed in our study. Adding a third group of runners training at volumes under 50 km per week, as well as the recruitment of more subjects for the other two training groups would have strengthened the findings.

**Calcium Intakes and Hip Fractures.** It has been shown that men who consumed more than 900 mg of calcium daily had a lower risk of hip fracture than men who had low lifetime calcium intakes. Thus, it seems important to comment on the influence of dietary calcium on BMD in the present study. When plasma calcium levels are low, parathyroid hormone stimulates bone resorption and calcium is released into the blood; high plasma calcium results in calcitonin-stimulated bone formation. The recommended intake of calcium is 800 mg per day for men over the age of 50, and slightly less for men under 50. The mean calcium intakes for the two groups in this study were both over this recommended daily intake, however, the standard deviations were high in both groups. 41% of subjects within the control group had calcium intakes below 800 mg per
day, while only 16% of the distance runners had low calcium intakes. A better assessment of calcium in this particular study would involve the estimation of lifetime calcium intakes. However, an intervention study in men would be the only way to determine an interactive effect between physical activity and calcium on BMD.

5.2. **Lumbar Spine Bone Mineral Density**

**Results Compared to Previous Findings.** Lumbar spine BMD was not significantly different between the pooled distance runners and controls. Goodpaster et al. (1996) and Pollock et al. (1997) reported similar findings for their groups of lifetime distance runners. Our result is different from findings by Michel et al. (1989), which indicated a strong positive correlation between amount of exercise and lumbar spine BMC in male subjects over the age of 50. However, as BMC is influenced by the size of the bone being measured, it is somewhat inappropriate to compare it to BMD. The longitudinal study by Lane et al. (1998), which measured spinal BMD four times over nine years in older runners and nonrunners, reported higher BMD in the runners at each measurement time, with similar decreases in both groups over time. The average training volume of the runners in this study was 43 km in 1984, and decreased to 28 km in 1993. Our runners were training at considerably higher volumes (minimum of 64 km per week).

In younger runners training at volumes greater than 90 km per week, both lumbar spine BMD, and BMC (corrected for BMI and height) was lower than the means of less active men. Similarly, our HV runners, running over 95 km per week, had a 13.5%
lower mean lumbar spine BMD than the group training between 64 and 90 km per week, and were slightly lower than the controls on this measure (HV was 0.90 +/- 0.070, and C was 0.92 +/- 0.095). Although there were only 5 subjects in our HV group, our results coupled with the results of earlier studies\textsuperscript{71,72} provide some evidence for the existence of a volume-threshold effect related to bone mass. The lumbar spine is composed of a high percentage of trabecular bone (up to 42 \%),\textsuperscript{167} which is more metabolically active than cortical bone.\textsuperscript{79} Reduced bone mass in the trabecular bone of the spine may be the result of the high bone turnover, as indicated by the high indices of bone resorption and formation in Hetland’s study,\textsuperscript{71} associated with distance running.

**Possible Explanations and Mechanisms.** That there was no difference in spinal BMD between the general running and control groups is not surprising based on the fact that distance running involves very little deformation, or muscle pull, on the bones of the spine. Furthermore, the spine is not a weight-bearing site in running. Therefore, the strains made on the spine in running training are well below the modeling threshold (Modeling MES in Figure 2), thus there is no increased bone formation at this skeletal site.\textsuperscript{32} This would explain why distance runners demonstrate lower spinal BMD than power athletes,\textsuperscript{33} rowers,\textsuperscript{175} and judoists,\textsuperscript{176} and why the spinal BMD of endurance cyclists was substantially lower than that of weight lifters.\textsuperscript{62} The narrow range of bone loading directions involved in distance running and cycling results in increases in bone strength that are very site specific to the actual loading.\textsuperscript{69} The type of physical activity our runners engaged in for more than 20 years elicits strain of the weight-bearing hip and very little strain on the spine. The result is augmented, or maintained BMD of the hip area, and less significant
differences in the lumbar spine BMD, when compared to men who have not been doing substantial amounts of physical activity.

Furthermore, the strains on the spine associated with distance running are not great, and are likely similar to those encountered in the controls’ moderate activities. This places the runners and controls in a similar situation with regards to bone remodeling. If the strains are so low, as in disuse, that they fall in the trivial loading zone, bone mass will decline (Figure 2). As all subjects in this study were healthy, active individuals, the strains to the spine most likely fall in the physiological loading zone, and runners and controls would therefore have normal remodeling, and similar bone mass of the spine. Older distance runners do not benefit from the bone maintenance effect of remodeling stimulated by mechanical usage of bone, as there is no site specific increased mechanical usage associated with running. With age, a similar decrease in lumbar BMD should be observed in runners and less active men, as noted by Lane et al.¹³⁰

In addition to the Frost’s minimum effective strain theory, the error strain distribution hypothesis proposed by Lanyon helps to explain the similar BMDs observed in the runners and controls. It suggests that bone responds to unfamiliar patterns of loading, in which dynamic, ‘unexpected’ strains are applied.¹⁹ An osteogenic response resulting in increased modeling, remodeling and adaptations, is more likely to occur under unusual strains of uneven distribution, than under the repetitive, low amplitude strains inherent to running or daily activities.¹⁹ In distance runners, low magnitude strains are applied infrequently, and the spine BMD is not significantly different from a group of less active controls.
On the other hand, the lower spine BMDs (although not significant) observed in the running group with the higher training volume (over 95 km per week), may be linked to the influence of lower free and total testosterone levels in this group. Although there were no significant differences noted between the testosterone levels of the HV, MV, and C groups, the HV group had the lowest values on both FT and TT.

Of our four BMD measurement sites, the lumbar spine is composed of the highest percentage of trabecular bone. Due to a greater surface area and higher turnover in trabecular bone than in cortical bone, and with a lack of weight-bearing strain in the spine, a lower testosterone level may more readily affect these areas. Androgens (free testosterone and dihydrotestosterone) stimulate human osteoblastic cell proliferation, thus directly increasing the number and/or activation of bone forming cells.

As part of Frost's mechanostat model, it is implied that lower levels of estrogen increase the minimum mechanical strain (MES) required to maintain or increase bone mass; a higher 'set point' necessitates higher levels of the hormone to elicit changes in bone mass. This is perhaps illustrated in a study by Robinson and colleagues (1995), in which amenorrheic gymnasts were compared to amenorrheic distance runners. Proximal femur and spine BMD of the gymnasts was higher than the runners and it was proposed that the mechanical strains involved in training were of sufficient magnitude to compensate for the gymnasts' low estrogen levels. Furthermore, animal studies have shown that estrogen amplifies the osteogenic response to bone loading sessions. Further research is necessary to determine if testosterone might enhance the osteogenic response to loading in males.
Although Frost did not go so far as to theorize about the impact of decreased testosterone levels on the bone ‘set points’ in men, the maintenance of total and free testosterone at a lower level might increase the set point at which bone responds to mechanical strain. The high volume training group had a mean free testosterone level of 54.4 pmol/L, which is very close to the lower limit of the normal physiological range, typically set at 50 pmol/L (the normal range is 50 to 130 pmol/L). This group had lower spine BMD than the other distance runners. The association between FT and BMD is speculative based on the small sample in this study, but has been discussed in previous athlete studies. Hetland (1993) reported a negative correlation between free testosterone index and training volume in male runners, and a negative correlation between spine BMC and training volume. In their study of 70 to 81 year old endurance athletes, Suominen and Rahkila (1991) reported a positive correlation between calcaneal (90% trabecular bone) BMD and free androgen index. Finally, a study by Smith and Rutherford (1993) reported significantly lower testosterone levels, total body BMD, and spine BMD in triathletes compared to rowers and controls. It is possible that the effects of a minimal amount of loading on the spine, as in distance running, and low free testosterone might be interactive in the skeletal outcome, but this is an area that requires further investigation.

5.3. Total Testosterone (TT)

Results Compared to Previous Findings. The differences between the testosterone (TT and FT) levels of the pooled distance runners and the control groups were not
significant. This result is not typical of investigations in this area. There was a large within group variability which may have reduced the likelihood of reaching a statistically significant finding.

The differences in testosterone among groups became more obvious when the distance running group was divided into MV and HV training groups. Although there were no notable differences between controls and distance runners as an absolute group, the more extreme distance runners exhibited lower means on both total testosterone (TT) and free testosterone (FT) than the more moderate distance runners and controls. The HV mean for TT was 33.7 % and 16.8 % lower than the means for MV and C, respectively. Similarly, the mean FT for HV was 21.2 % and 26.2 % lower than the mean for MV and C. Our limited sample provides some evidence that training at a weekly volume of greater than 95 km might interfere with the normal production and maintenance of circulating testosterone.

The higher TT levels observed in the MV runners might be related to the typical androgenic response to exercise. Normally, testosterone increases during exercise sessions of various modes and lengths.\textsuperscript{185,186,193} There have not been any longitudinal studies that examined the exercise effect on resting levels of testosterone over a number of years. It would be interesting to ascertain if higher basal testosterone levels are maintained in athletes who have adopted an active lifestyle that incorporates short and medium volume workouts, when compared to the age-related changes in basal testosterone in sedentary men. Thus, the moderate volume runners might be maintaining a higher basal testosterone levels due to more than twenty years of running, while the controls may be beginning to demonstrate the normal age-related decline in testosterone.
The ‘Volume Threshold’ hypothesis proposed by De Souza and Miller (1997)\textsuperscript{63} helps to explain the total testosterone findings among the 2 DR groups, which are consistent with other findings on high volume distance runners.\textsuperscript{64, 66, 67, 197, 200} They propose that high-volume training be defined as a minimum of 100 km per week for at least 8 hours per week, characterized by a consistent range of subclinical modifications in the gonadal hormone and semen profiles.\textsuperscript{63} Our HV runners had a mean training volume of 101 km per week, and a mean training time of 10.6 hours per week. In our study, there were strong negative correlations between training volume and TT, and training volume and FT among the distance runners.

**Possible Explanations and Mechanisms.** In a general sense, the stress of training at high volumes involves a number of factors that might influence reproductive hormone levels. Low body weight, low body fat, inadequate caloric intake, lack of micro/macronutrients, excessive energy expenditure, overtraining, eating disorders, elevated physical and/or psychological stress, increases in intrascrotal temperature, and testicular microtrauma during exercise, are prominent factors in the lives of many distance runners, and integral to the maintenance of testosterone levels.\textsuperscript{210} Body weight, sum of 7 skinfolds, and energy intake were not significantly different between the MV and HV runners. Although we screened for eating disorders in subject selection, other factors such as psychological and physical training stress are very individual and fluctuate depending on performance and the season.

Both peripheral and central mechanisms have been proposed to account for the commonly observed low TT levels in high mileage male distance runners. Figure 5
diagrams the H-P-G axis, and the feedback loops associated with testosterone production. Central mechanisms include those related to the hypothalamic production of GnRH, and LH production by pituitary. Peripheral mechanisms refer to actions at the level of the testes, and circulation of testosterone to other tissues.

Central mechanisms may partially explain the lower testosterone levels in the high volume runners. Crucial factors involve the pulsatile secretion of luteinizing hormone (LH), and the pituitary sensitivity to gonadotropin releasing hormone (GnRH). If low LH levels coexist with low plasma testosterone, the fault lies in the pituitary gland or hypothalamus. Investigators have found that the mean LH levels observed in runners tend to be comparable to those of sedentary controls. However, mean LH does not differentiate between LH pulse frequency and amplitude, which play key roles in the stimulation of the Leydig cells to produce and secrete testosterone. McColl et al. (1989) and MacConnie et al. (1986) found a reduction in LH pulse frequency and amplitude during their 6 to 8 hour samplings of high volume distance runners. To further support the central alteration hypothesis, the inhibition of LH pulsatile secretion is most likely accompanied by a reduced pituitary sensitivity to hypothalamic GnRH.

On the peripheral level, MacConnie et al. (1989) investigated the integrity of the hypothalamic-pituitary-gonadal axis in marathon runners to see if intratesticular failure of the Leydig cells to synthesize testosterone was responsible for the lower levels observed in the male runners. Their major finding was that the marathon runners had a deficiency of hypothalamic gonadotropin-releasing hormone (GnRH), resulting in an alteration in the stimulation of the testes, and subsequently a lower production of testosterone. This
GnRH deficiency may be caused by suppression induced by the fluctuating levels of gonadal steroids from daily exercise sessions.\textsuperscript{198,185}

Additional peripheral mechanisms that explain lower testosterone levels in the high volume runners have been proposed by Hackney (1989), and Wheeler et al. (1984). Hackney suggested that decreased blood flow to the testis during prolonged endurance training may impair testosterone production and secretion.\textsuperscript{212} Lower levels of TT may also be a function of an increased uptake of testosterone by skeletal muscle to counteract the protein catabolism associated with intense endurance training.\textsuperscript{212,64}

It is likely that energy balance plays a role in the suppression of testosterone in high volume runners, as indicated by a prospective study of initially sedentary males. Caloric intake and reduced total and free testosterone were significantly correlated when running volume was increased.\textsuperscript{214} In our study, the runners exhibited significantly higher energy intakes than the control group, but the caloric intakes of the high volume runners were not significantly different from the MV runners, and may not have been high enough to avoid a negative energy balance. Barr and Costill (1993) noted an increased energy intake in male distance swimmers with increased training volumes. The increased caloric intake did not balance with the training, however, as a reduction in the swimmers' body fat was observed over the course of the season.\textsuperscript{215} A compromised energy intake may cause an athlete's body to enter a state of energy mobilization and/or conservation. Metabolic signals may be magnified during periods of long term, high volume training (over 20 years, as in the case of our high volume distance group), and combined with a negative energy balance, might cause modifications in hormone profiles.\textsuperscript{63} Cumming et al. (1994) discuss the idea that inadequate energy states can lead to the body's sacrifice of reproductive
function in order to conserve energy for essential physiological tasks.\textsuperscript{216} This would then be represented by compromised reproductive hormone levels.

5.4. \textit{Free Testosterone (FT)}

Higher total testosterone levels should, theoretically, coexist with higher free testosterone levels.\textsuperscript{180} This was not the case in our study, as the highest mean free testosterone belonged to the control group, and the highest total testosterone belonged to the moderate volume training group. The differences between the three groups on this variable was not significant. However, the pooled distance runners had a 14.59\% lower mean free testosterone level than the controls. A lower level of free testosterone would be expected with a rise in serum hormone binding globulin (SHBG).\textsuperscript{180} SHBG is considered the primary binding protein for testosterone as its testosterone binding affinity is 1000 times greater than that of the other major carrier protein, albumin.\textsuperscript{217} SHBG may increase with training and physically stressful competitions. Triathletes had significantly decreased ratios of TT:SHBG for the four days following competition.\textsuperscript{188} Zmuda et al. (1996) found that moderate exercise in older men (aged 66 to 76 years) produced increases in total testosterone levels, which were accompanied by increases in SHBG.\textsuperscript{218}

A study by Fahrner and Hackney (1998) found that moderate, prolonged endurance exercise induced increases in free testosterone levels that were not accompanied by changes in SHBG binding affinity. They concluded that the free testosterone increase is caused by an increased production by the testes, mediated by sympathetic stimulation.\textsuperscript{219} From this study, it is impossible to assess the impact of chronic
endurance training, as they did not compare non-runners to runners at baseline. Bonifazi
and Lupo (1996) discussed the possibility of a regulatory mechanism, such as androgen
metabolism control through SHBG concentration adjustment, that maintains adequate
concentrations of FT when TT concentrations decrease. Possibly, FT is simply
maintained at an adequate level, and it is actually SHBG that fluctuates with TT. Our
small sample size and large variability in results limits the generalizability of our results.
Future research should focus on longitudinal studies with large sample sizes to more
clearly define the existence of a relationship between endurance training volume and free
testosterone levels in men.
5.5. Clinically Relevance and Implications

Exercise Programs To Improve or Maintain BMD

Our results lend support to the idea that weight bearing exercise, such as running, applied over the course of a lifetime can increase BMD. Specifically, our results emphasize the importance of moderation when the activity is endurance-oriented. Running is a repetitive activity that involves a “narrow range of bone loading directions, and will result in smaller increases in bone mass than activities which stress bones briefly but intensely in a wide variety of directions.”

In this study, the greatest benefit of lifetime running in terms of skeletal status was the high BMD of the hip region. It is noteworthy that the highest BMD values belonged to those runners training at volumes under 90 km per week. Although a healthy skeleton is the product of a great number of integrated factors, running in moderation seems to be beneficial, at least to the BMD of the hip region. Excessive endurance training, involving volumes upwards of 100 km per week, seems to cause imbalances in the body’s ability to execute normal bone remodeling.

BMD of both the spine and the proximal femur could be better enhanced through a combination of exercise modes. Loads of high magnitude and rate, that are dynamic in nature and involve varied patterns and directions of stress, should be incorporated. This is indicated in Lanyon’s error strain distribution hypothesis, as previously discussed: unusual strains of uneven distribution elicit the greatest bone modeling/remodeling responses. Thus frequent exercise sessions incorporating as many novel strain distributions are recommended. One type of exercise can not fulfill all of these requirements. Thus, a combination of running, which involves high rate, dynamic loading,
and resistance training, which involves high strain magnitude and varied patterns of stress through multi-directional loading, might be ideal.

**Implications for Osteoporosis**

The implications of maintaining healthy bones in aging men are important in our society, as millions of dollars are spent yearly in the management of osteoporotic hip fractures in men. Hip fractures are associated with a higher mortality in men than women: men are more likely to die within one year of sustaining the injury. Also, hip fractures in men account for one third of all hip fractures treated. Fracture resistance is related to both the material and structural qualities of bone, including density. Low BMD is likely to contribute to the pathogenesis of osteoporosis in men with hip fractures. Thus, the augmentation (and/or maintenance) of hip bone mineral density through the sustainment of an active lifestyle involving moderate amounts of weight-bearing exercise in the form of running, can decrease the risk of bone breakage in the event of a fall.

However, fracture risk is multifactorial, and bone mineral density makes up only one component of an individual risk profile. Hip axis length and thickness of the skin (or fat layer) over the trochanter can influence hip breakage. As well, the sheer propensity to fall is important in the incidence of hip fracture—thus living environment and balance are crucial factors.

**Endurance Training in Young Boys and Adolescents**

Some recommendations can be made based on the findings from this research for endurance training in young males. During the adolescent time of growth and
development, energy requirements are high just to sustain the normal maturation process. Since reproductive function is integrated with energy balance, a negative energy balance at the time of puberty might delay its normal onset. In cases of delayed puberty, it is normal to first investigate the possibility of malnutrition (or, inadequate energy intakes) as a primary cause. High volume endurance training (and this could be volumes which are much lower than what is considered “high” for adult males), that demands a high energy output, could therefore have negative implications for pubertal onset. A sacrifice of the normal testosterone surge that occurs at puberty, similar to that which occurs in constitutionally delayed puberty (CPD) in boys or primary amenorrhea (with low estrogen) in female athletes, can then influence bone mineral density.

According to Bertelloni et al. (1995), an “appropriate time of pubertal onset and velocity of the progression from one level of sexual maturation to another...may be important in determining the achievement of an optimal peak bone mass.” Thus, a delay in the normal pubertal testosterone surge in vigorously training young males might be detrimental to bone health in later life. Coaches and parents working with young runners should keep this in mind when prescribing training loads. Energy levels should be monitored to avoid overtraining and ensure adequate nutrition. Maintenance of a training log that records workouts as well as the positive or negative feelings associated with them (i.e., muscle soreness, fatigue, recovery, interest, quality of sleep, illness) are helpful in this regard. Over the long term, the onset of secondary sex characteristics could be monitored to give an indicator of development.

An ideal program for the adolescent should combine many activities to maximize interest as well as the benefit to bone mineral density. Running might be combined with
short sessions of weight lifting to increase strength and promote bone remodeling in many areas of the body. The greatest positive impact with respect to bone mineral density might come from supplementing activity programs with high impact jumping and bounding activities, such as those found in gymnastics.

5.6. **Limitations and Bias**

This particular study was limited in its power to show differences between populations as the samples were small. The small sample size limits the generalizability of our results to the larger population; a larger subject group selected through random sampling would allow for the most accurate representation of the male athlete population. Larger sample sizes would provide the opportunity to show meaningful differences in BMD, TT, and FT.

The magnitude of the standard deviations in the means for TT and FT were quite large, and might indicate some error in these measures. A serial blood sampling technique over 4 to 6 hours, or means of samples taken over several days might help diminish the natural variability and error. A more frequent blood sampling protocol was not feasible at the time of this study. This would involve a large increases in the cost of the study and subject time requirement for participation, as well as a serious decrease in subject comfort. Our study did demonstrate similar findings to those presented in the literature, although it is difficult to discern whether this is by chance, or if it is attributable to actual differences in resting hormone profiles.

The bias inherent to this study lies in subject selection. As participation was on a strictly volunteer basis, a certain amount of self selection occurred. However, each
subject was suitably screened for conditions that might affect bone or hormone measures. A factor that drew many subjects was the information they would receive about their individual bone health. Therefore, some subjects might have had an idea that the type of training they engaged in was either of great benefit (running in general), or detrimental to their health (i.e., continuous overtraining), and thus had a special interest.

Another limitation is self-reporting weekly training volumes for distance runners and controls. Particularly in the DR group, reporting may have involved a certain amount of ‘rounding’ for the runners to get a good estimate. Unfortunately, this might have involved rounding up, if the subjects realized that they were not meeting the minimum mileage requirement for the study, and still wanted to be included. A more accurate estimation would be arrived at by examining daily training logs and adding up the mileage recorded for each day over the course of a number of weeks. Or, ‘blinding’ potential subjects to the minimum required training volume is an alternate method of recruitment.

Subjects in the control group engaged in a range of activities that seem to reflect the physical activity patterns of males in this age group. A similar study could benefit from recruiting a more diverse group of men, i.e., those participating in high impact sports and non weight-bearing sports, as well as those who are sedentary.

5.7. **Future Directions**

To differentiate between the training effects of moderate and high volumes of running, the subject groups could be larger and include runners with accurately defined
training volumes. This might lower the SD within the groups, especially on the testosterone measures.

Altered hormone production through menstrual cycle disorder is commonly accepted as the mechanism by which BMD declines in high mileage female distance runners. Studies designed to identify probable mechanisms for the lower BMD's observed in high volume male distance runners are needed. Hormone analyses which includes serial sampling of cortisol, estrogen, parathyroid hormone, calcitonin, and various markers of bone turnover are required to answer these questions. Testosterone should be assessed by serial sampling, which might decrease the within group variability. As either the binding capacity or the absolute amount of SHBG might be affecting the concentration of FT in the runners (and controls), this should be included in the hormone analysis.

Another important study that needs to be done is a prospective evaluation of the effects of increasing and decreasing training volume over time on basal testosterone levels. This might help explain the long term regulation of this hormone, and better define the effects (if any) it might have on BMD.

An assessment of the childhood and adolescent physical activity levels (including type of activity: high impact vs. endurance training, or weight bearing vs. non weight bearing, etc), in relation to the BMD of older male athletes would help define the relative contributions of early involvement and continued involvement throughout adulthood.

It would be possible to use the data of our study as a baseline measure for this group of runners. BMD measures taken a few years later would determine changes in 1) those runners continuing at similar training volumes, 2) those runners modifying training, and 3) those runners discontinuing running training altogether. The age effects on BMD
in combination with the effects of running would be interesting to monitor as the men get older. Also, as testosterone decreases with age, the correlation with BMD in a longitudinal study would be of interest.
Primary Hypotheses:

1. The BMD at the femoral neck, trochanteric region and total proximal femur was significantly higher in the long distance runners than in the controls. The original hypothesis that the proximal femur BMD would be lower in the distance runners is rejected.

2. BMD at the lumbar spine was not significantly different between a group of male distance runners and a group of moderately active controls. The original hypothesis that spine BMD would be lower in the distance runners is rejected.

3. Total testosterone levels did not differ significantly between distance runners and controls, although the mean value was lower in the distance runners. The original hypothesis is rejected.

4. Free testosterone levels did not differ significantly between runners and controls. The original hypothesis is rejected.

5. BMD and total/free testosterone were not significantly correlated with any of the BMD regions. The original hypothesis is rejected.

6. Additional Conclusion: Training volume and total testosterone are negatively correlated, as are training volume and free testosterone in the distance runners.

Secondary Hypotheses:

1. Moderate volume runners had the highest BMD at the femoral neck, trochanteric region, and proximal femur, when compared to high volume runners and controls. The
high volume runners fell in between the two other groups with respect to proximal femur BMD. The secondary hypothesis is supported.

2. BMD at the lumbar spine was not significantly different between moderate volume runners, high volume runners and controls, although the MV runners had the highest mean, and the HV runners had the lowest mean for this measure. This supports the secondary hypothesis.

3. Total and free testosterone were not significantly different between the MV, HV, and C groups. The HV runners had the lowest means for these two measures, which lends support to the secondary hypothesis.

Conclusions in Context

1. Long term weight-bearing exercise in the form of running may have a positive influence on BMD of the proximal femur in men, due to the increased bone remodeling that results from increased bone strain in physical activity.

2. The benefits seem to be maximized when training volume is not excessive. A moderate and beneficial training volume most likely lies between 60 and 90 km per week. Volumes in excess of 95 km per week do not seem to elicit the same benefits in terms of skeletal status, as runners engaged in these high volumes do not differ from controls on proximal femur or lumbar spine BMD.

3. Distance running does not provide a good stimulus for increased bone formation at the lumbar spine, due to the lack of muscle pull and bone strain specific to that area. Also, high volumes of training that interrupt normal reproductive function may have a negative effect. Lower levels of testosterone may negatively affect the density of the
trabecular bone of the lumbar vertebrae. This situation might be avoided or improved with the incorporation of high velocity impact activities into the runners’ exercise regimes, while decreasing running volumes.

4. High training volumes are physically stressing. Evidence of this can be seen in the significant negative correlations between training volume and total testosterone, and training volume and free testosterone.

5. Weight-bearing exercise in the form of running at a moderate volume over the course of a lifetime increases proximal femur BMD. This translates into a decreased risk of hip fracture. The addition of strength training and gymnastics-type activities (i.e., jumping, high impact movements) to a running-based exercise program may further increase BMD.
References


Frost H. Perspectives: a proposed general model of the "mechanostat" (suggestions from a new skeletal-biologic paradigm). The Anatomical Record 1996; 244: 139-47.


104 Fukayama S, Tashjian A. Direct modulation by androgens of the response of human bone cells (SaOS-2) to human parathyroid hormone (OTH) and PTRrp. Endocrinology 1989; 11: 1789-94.


APPENDIX A: Screening Questionnaire

Testosterone and Bone Density in Male Runners
J. Taunton — Division of Sports Medicine, Faculty of Medicine, UBC
H. McKay, A. Martin, K. MacKelvie — School of Human Kinetics, UBC

SCREENING QUESTIONNAIRE

1. Identification
1.1 Surname ___________________________ Given Name(s) ___________________________
1.2 Telephone # (home) ___________________________ (Other) ___________________________
1.3 Date of Birth: Day ______ Month ______ Year _________
1.4 Weight _________ Height _________
   In the last 6 months have you gained or lost weight? Yes____ No____ (Go to 2.1)
   If YES, how much weight? Gained ______lbs. Lost ______lbs.

2. Training
2.1 Please list exercise activities you participate in on a regular basis, and the number of years of
   participation:
   ACTIVITY ___________________________ # OF YEARS ___________________________
   ___________________________ ___________________________
   ___________________________ ___________________________
   ___________________________ ___________________________
   ___________________________ ___________________________

2.2 FOR DISTANCE RUNNERS ONLY (other subjects go to 2.3):
   What is your current weekly mileage? _______ miles or _______ kilometres
   Has this mileage varied much over the last 20 years? __Yes ___No
   IF YES, please explain (indicate long breaks in training, times of very low or very high mileage,
   etc):
   ___________________________
   ___________________________
   ___________________________

Please indicate level of competition over the course of your career, and the event(s):
   ___ Local event: ___________________________
   ___ Provincial event: ___________________________
   ___ National event: ___________________________
   ___ International event: ___________________________

2.3 How many hours per week do you spend exercising? ______ hours
   Please break down the total hours into the following categories based on 1) EXERTION:
   maximal (>85% of maximum work capacity) _______ hours
   strong (75-85%) _______ hours
   moderate (60-75%) _______ hours
   light (40-60%) _______ hours
and 2) TYPE OF TRAINING  
running _______ hours  
weight training ________ hours  
cross-training/alternate activities ________ hours  
team sports/ stop-start activities (ie, tennis) ________ hours

4. Diet

4.1 Have you ever been on a calorie restricted diet?  
Yes______ No______ (Go to question 4.2)  
If YES, approximately how many times have you dieted? ________ times

4.2 Have you ever been anorexic or bulimic? Yes______ No______

5. Smoking/Drinking

5.1 Have you ever smoked? Yes______ No______ (Go to question 5.2)  
If YES, how much did you/do you smoke (ie, cigarrettes/day) and for how long?  
QUANTITY_________________ DURATION_________________ years

5.2 How often do you drink some kind of alcoholic beverage?  
__more than 1 time/day ___once daily ___3 or 4 times/week ___1 or 2 times/week  
___1 or 2 times/month ___less than once a month ___never

6. Medical History and Status

6.1 Have you seen a doctor in the last 6 months?  
Yes______ No______ (Go to question 6.2)  
If YES, what was the reason for your visit(s)?__________________________________________________________

6.2 Has there been any change in your general health during the last 6 months?  
Yes______ No______ (Go to question 6.3)  
If YES, please specify:______________________________________________________________________________

6.3 Have you ever been treated for any of the following conditions? (Check all that apply)
_Asthma
_Osteoporosis
_Other Respiratory Condition
_Rheumatism
_Addison’s Disease
_Cushing’s Disease
_Osteoarthritis
_Hyperparathyroidism
_Anaemia
_Hyperthyroidism
_Malabsorption
_Hypercalciuria
_Hypercalcaemia
_Hyypoparathyroidism
_Hypothyroidism

6.4 Have you ever sustained a stress fracture? ___yes ___no
IF YES, indicate when and the location of injury

<table>
<thead>
<tr>
<th>YEAR</th>
<th>LOCATION</th>
</tr>
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<tbody>
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</tr>
</tbody>
</table>

6.4 Have you had any bone fractures, other than stress fractures? Yes____ No____
If YES, how many fractures have you had? ___________
List type of fracture and approximate date of occurrence.
<table>
<thead>
<tr>
<th>TYPE</th>
<th>DATE</th>
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</thead>
<tbody>
<tr>
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</tbody>
</table>
6.5 Have you ever been hospitalized, confined to bed, or had a limb immobilized (ie, leg in a cast) for a period of 21 days or longer? Yes______ No_____  

If YES, list condition, approximate date and duration.  

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>DATE</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

7. Medication  
7.1 Are you currently taking any medications? Yes______ No_____ (Go to question 7.2)  

If YES, what medication(s) are you taking, and what are they for?  

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>REASON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

7.2 Have you ever taken any of the following medications? Please specify age at which use began, and for how long the medication(s) were used.  

<table>
<thead>
<tr>
<th>(check) MEDICATION</th>
<th>AGE AT START</th>
<th>DURATION OF USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>calcium preparations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antacids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anabolic steroids</td>
<td></td>
<td></td>
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<tr>
<td>fluoride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>calcitonin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cortisone (oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>corticosteroids (other)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-inflammatories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thyroid preparations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.3 Other comments re: Medical Conditions: ________________________________
1. Measures of height, weight and skinfolds will be taken. You will be asked to complete a questionnaire that will provide physical activity, and health information. You will also be given instructions on how to complete a dietary recall questionnaire that will provide information regarding your calcium and nutritional intake.

2. Your bone status will be evaluated by a bone densitometer to measure bone density of the hip and lumbar spine (lower back). This procedure is painless and routinely used in the practice of modern medicine and there is a minimal radiation exposure. The total exposure will be less than 5 millirem which is less than the background radiation one would receive making a return flight from Vancouver to Toronto on a commercial airline. For comparative purposes, the average annual background radiation in British Columbia due to natural sources is approximately 150 millirem per year and the current permissible level for the general population is 500 millirem per year. The typical exposure from a routine dental x-ray is over 50 millirem. These values can be used to compare the relative risk of the less than 10 millirem exposure from the bone density procedure. This procedure takes about 20 minutes.

3. You will be asked to provide a fasting blood sample at Allan McGavin Sports Medicine Centre, by appointment between 7:00 am and 9:00 am, following a 24 hour period of minimal activity.

Exclusions:
Subjects presently injured or ill and unable to engage in normal training routines are not eligible for participation. Also, conditions that call for exclusion include: diabetes, hyperparathyroidism, hypoparathyroidism, hyperthyroidism, hypothyroidism, Addison’s Disease, Cushing’s Disease, gastrointestinal disorders, chronic liver disorders, glucocorticoid or corticosteroid treatment, use of anabolic steroids, hypercalciuria, hypocalcemia, kidney disease, anaemia, osteoarthritis, rheumatism, anorexia nervosa, bulimia, alcohol abuse, smoking, conditions requiring hormone treatment.

Rights and Welfare of the Individual:

It is understood that you are free to decline to enter the study, as well as withdraw from any or all parts of the study at any time without penalty. Your identity will remain confidential and only those directly involved in the study (namely the investigators, project assistants, and Medical Imaging staff) will have access to your records and results. All individual results will remain confidential.

Please be assured that you may ask questions at any time. We will be glad to discuss your results with you when they become available and we welcome your comments and suggestions. Should you have any concerns about this study or wish further information please contact any of the researchers listed at the top of page 1. Should you have any concerns about your treatment as a research participant, please contact the Director of Research Services at the University of British Columbia, Dr. Richard Spratley (822-8598). You will receive a copy of this information and the consent form for your own records.
Participant’s Statement:

I, ________________________________,

understand the purpose and procedures of this study as described and I voluntarily agree to participate. I understand that at any time during the study, I will be free to withdraw without jeopardizing any medical management, employment or educational opportunities. I understand the contents of the consent form, the proposed procedures and possible risks.

I have had the opportunity to ask questions and have received satisfactory answers to all inquiries regarding this study.

________________________________________  __________________________________________
Signature of Participant                      Date

________________________________________  __________________________________________
Signature of Witness                          Date

________________________________________  __________________________________________
Signature of Investigator                     Date
**APPENDIX C: Individual Subject Results**

<table>
<thead>
<tr>
<th>Legend</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEIGHT</td>
<td>height; measured in metres</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>weight; measured in kg</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index = weight/ht²</td>
</tr>
<tr>
<td>SUM 7</td>
<td>sum of 7 skinfolds (triceps, biceps, subscapular, iliac crest, abdominal, thigh, calf); measured in mm</td>
</tr>
<tr>
<td>SPINE</td>
<td>bone mineral density of the lumbar spine (L2-L4); measured in g/cm²</td>
</tr>
<tr>
<td>TOTAL PF</td>
<td>bone mineral density of the total hip; measured in g/cm²</td>
</tr>
<tr>
<td>FN</td>
<td>bone mineral density of the femoral neck; measured in g/cm²</td>
</tr>
<tr>
<td>TROCH</td>
<td>bone mineral density of the greater trochanter; measured in g/cm²</td>
</tr>
<tr>
<td>TT</td>
<td>total testosterone; measured in nmol/L</td>
</tr>
<tr>
<td>FT</td>
<td>free testosterone; measured in pmol/L</td>
</tr>
<tr>
<td>TV (km)</td>
<td>average weekly training volume; estimated in km (distance runners)</td>
</tr>
<tr>
<td>yr's run</td>
<td>total number of years of training (distance runners)</td>
</tr>
<tr>
<td>TV (hrs)</td>
<td>estimated hours of physical activity per week</td>
</tr>
<tr>
<td>wt's (hrs)</td>
<td>estimated hours of weight training per week</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>average daily calcium intake; measured in mg</td>
</tr>
<tr>
<td>E</td>
<td>average daily energy intake; measured in kcal</td>
</tr>
<tr>
<td>n/a</td>
<td>not applicable; no measure taken for the subject on that variable</td>
</tr>
<tr>
<td>CODE</td>
<td>AGE (yrs)</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
</tr>
<tr>
<td>DR1 /HV</td>
<td>41</td>
</tr>
<tr>
<td>DR2</td>
<td>50</td>
</tr>
<tr>
<td>DR3</td>
<td>42</td>
</tr>
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