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Sex Differences in Bone Loss – An Evolutionary Perspective on a Clinical Problem

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A B S T R A C T

The dramatic increase in the world's population that has occurred over the past 100 years has come largely through reductions in death due to infectious disease. An epidemiologic transition to a preponderance of deaths due to degenerative conditions such as cardiovascular disease and cancer is occurring in the developing countries as well as in the industrialized ones. In the industrialized countries, demographic profiles now reflect the increased life expectancies of both sexes. However, female life expectancies exceed male by six or more years. Further change in mortality patterns will accompany success in the reduction of the number of mortalities attributable to such degenerative conditions as cardiovascular disease and cancer. In the 21st century, conditions associated with senescence will be of increasing concern. Adaptive strategies that enhanced reproductive success throughout most of human evolution may now prove detrimental to human health as average life expectancies reach unprecedented length. In this environment, differences in the survival mechanisms deployed by males as opposed to females will become increasingly important.

Key words: *osteoporosis, gender, mortality, aging*

Introduction

That males and females are different is an obvious fact. However, the extent of the biological differences between the sexes is greater than generally appreciated. In fact, many otherwise well-designed biomedical research projects have been designed as though the sexes were identical. Thus, for instance, most of what is known about the etiology of heart disease has, until quite recently, been learned from research done largely on male populations. Often, the dosage of medications prescribed for patients of either sex has been determined by the results of

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clinical trials conducted with male subjects with the only adjustments being for body weight. With major initiatives in research on women's health issues, some of the hazards of this approach are being recognized and corrective measures taken. Along with the improvements in medical care that these initiatives have generated, has been expanded understanding of the magnitude of human sex differences[1].

The evolutionary implications of human sexual dimorphism clearly deserve the attention of human biologists. The adaptive strategies of human populations under various forms of environmental stress have been the focus of numerous studies in which epigenetic adjustments made to accommodate challenges such as malnutrition have been shown to differ in males and females[2,3]. Sexual differences in mortality rates throughout the human life cycle are well known, although not fully understood.

It has only been within the past 50 years that the average life expectancy has approached the biblical three score and ten years. In modern, industrialized societies, women live longer than men. This was not always the case. Nor is it the case everywhere today. In both past and present populations where the life expectancies of women are short, there is a strong negative correlation between female life expectancy and fertility. Bearing children is a stressful, biologically expensive process. Natural selection has favored physiological mechanisms that enable women to cope with the demands of reproduction. The selective pressures associated with these demands tend to amplify the elements of sexual dimorphism that give rise to these mechanisms. These mechanisms provided the margin of survival over thousands of generations of human evolution during which survival beyond the reproductive years was uncommon. It is only very recently that the potential costs of these mechanisms later in life have become manifest, as larger numbers of women have lived long enough to experience them.

The trend of increasing life expectancy started in the western industrial countries during the 19th century and has, with a few notable exceptions, gradually spread throughout the world. The areas in which reversals of this trend have occurred are those where a combination of rapidly spreading infectious disease and civil unrest has produced extraordinary mortality rates among the reproducing and pre-reproducing segments of the population[4]. In such areas it is possible to find examples of negative population growth despite high fertility rates. However, it is likely that this situation is a temporary one and that the worldwide trend will continue for a time. The trend has, in large part, been attributable to technological advances in the prevention and treatment of infectious disease. Recent advances in the prevention and treatment of cardiovascular diseases and cancer may significantly alter the mortality pattern for future generations. However, since their life extending benefits are most often experienced in the middle and late years of the life span, their impact on the fertility rate will be more limited[5].

Several investigators have attempted to use current demographic and epidemiological trends to predict future life expectancy[6]. They have concluded that even if it is possible to eliminate all heart disease and cancer mortality, the limits of human longevity will come into play and average life expectancy will never exceed 100 years. They do not, however attempt to predict what the leading causes of mortality will be in the middle of the 21st century. While acknowledging that advances in biomedical science including promising breakthroughs in tissue engineering make any such predictions risky indeed,

the present study will attempt to highlight some aspects of the aging process, among them some that differ according to sex, that may represent intrinsic limits to the human life span[7,8]. Viewed from this perspective, conditions such as osteoporosis, never included among the leading causes of mortality, may be recognized as potentially significant contributors to morbidity and mortality in future populations.

Current demographic trends

Largely due to the increase in life expectancy, the past century has been marked by an unprecedented increase in the world's population. Although reductions in deaths attributed to infectious disease have been a major factor in this increase, a small number of diseases, such as malaria, schistosomiasis, and trypanosomiasis, continue to pose a serious threat to human survival in specific geographical areas. The influenza virus continues to produce new variants although none have attained the degree of virulence exhibited by the strain associated with the worldwide 1918 pandemic. Other diseases, such as tuberculosis and certain streptococcal infections, have shown signs of becoming resistant to conventional medications and therefore remain a serious concern. Recently, still other disease entities such as the HIV and Ebola viruses have emerged. There is, in fact, considerable evidence that claims of victory in the war against infectious disease were, at best, premature. Nevertheless, there have been significant changes in the patterns of human mortality. A sharp decline in the number of premature deaths associated with infectious disease has restructured the world's demographic profile[9].

As already mentioned, the trend toward reduced early mortality has been in progress the longest in the industrialized nations. In these countries, socioeconomic factors associated with reduced infant mortality have operated to reduce fertility concurrently with increases in life expectancy. The result has been a decline in birth rates to a point where they are now below replacement level. Table 1[10] shows life expectancies, infant mortality rates and fertility rates of seven European countries. Note that life expectancies for women in these countries are all more than 77 years, while male life expectancies average 6.4 years less. None of these seven countries has a fertility rate approaching the 2.0 needed for replacement of the present reproductive population. With fewer people entering the reproducing segment of these populations, and with more entering the elderly segment, their demographic profiles are all,

TABLE 1
SEX RATIOS, LIFE EXPECTANCIES, INFANT MORTALITY AND FERTILITY OF SEVEN INDUSTRIALIZED COUNTRIES

Country	Population (1000's)	Population under 15%	Growth rate %/year	Sex ratio	Life expectancy		Infant mortality	Total fertility
					Male	Female		
Austria	8,161	17.7	0.86	103	72.8	79.3	7	1.47
Denmark	5,248	17.5	0.32	102	72.5	77.8	8	1.75
France	56,543	19.4	0.48	105	73.8	82.4	7	1.70
Germany	82,190	16.1	0.55	104	72.6	79.1	6	1.30
Italy	57,240	15.0	0.06	106	74.2	80.6	8	1.24
Netherlands	15,661	18.3	0.66	102	74.1	80.2	6	1.59
United Kingdom	58,201	19.3	1.00	104	73.7	79.0	7	1.78

to varying degrees, departing from the broad-based pyramidal form characteristic of young, dynamic populations.

The epidemiologic transition

Along with the reduced mortalities to infectious diseases experienced by populations undergoing the demographic transition has been an increase in the proportion of the population dying of so-called degenerative conditions such as cardiovascular disease and cancer. Table 2 compares the leading causes of death in the developed and the developing countries in 1990. Note that although ischemic heart disease is the leading cause of death in the industrialized countries, killing 2,695,000 people and accounting for 24.7% of all deaths, more people (3,565,000) die of this cause in the developing countries. The total number of deaths attributable to ischemic heart disease and cerebrovascular disease that year in the developed nations was 4,122,000, 52.5% of all mortalities. In the developing countries, 6,519,000 people died of these two causes accounting for 45.3% of all mortalities. Thus, although there is a tendency to regard cardiovascular disease as one of »the diseases of industrialized civilization« it accounts for nearly half of all deaths in the developing countries as well. Moreover, mortalities due to cardiovascular disease are increasing in the developing countries at the same time they are decreasing in the developed ones. As can be seen in the comparisons in Table 2, cancer accounts for a far higher proportion of deaths in the industrialized nations. However, the disparity in the proportion of deaths attributable to some form of cancer does not signal an epidemic of cancer in industrialized nations. Instead, both the absolute and relative increases

TABLE 2
THE 10 LEADING CAUSES OF DEATH IN 1990 – DEVELOPED AND DEVELOPING REGIONS COMPARED

Developed Regions			Developing Regions		
Cause of death	Deaths (1000's)	Cumulative %	Cause of death	Deaths (1000's)	Cumulative %
All causes	10,912		All Causes	39,554	
1. Ischemic heart disease	2,695	24.7	1. Lower respiratory infections	3,915	9.9
2. Cerebrovascular disease	1,427	37.8	2. Ischemic heart disease	3,565	18.9
3. Trachea, bronchus, and lung cancer	523	42.6	3. Cerebrovascular disease	2,954	26.4
4. Lower respiratory infections	385	46.1	4. Diarrheal disease	2,940	33.8
5. Chronic obstructive pulmonary disease	324	49.1	5. Conditions connected with childbirth	2,361	38.7
6. Colon and rectal cancers	277	51.6	6. Tuberculosis	1,922	43.4
7. Stomach cancer	241	53.8	7. Chronic obstructive pulmonary disease	1,887	46.1
8. Road traffic accidents	222	55.8	8. Measles	1,058	48.7
9. Self-inflicted injuries	193	57.6	9. Malaria	856	50.9
10. Diabetes mellitus	176	59.2	10. Road traffic accidents	777	52.8

in cancer mortality can be explained by the increase in the proportion of the population surviving into the later, cancer-prone stages of life.

Presumably, the number of deaths caused by such diseases as lower respiratory infection, diarrhea, diseases associated with childbirth, tuberculosis, measles and malaria will decline in the foreseeable future. All told these diseases now account for almost 32% of the deaths occurring in the developing world. As these diseases come under control, many people whose lives are spared will live long enough to become candidates for cancer or heart disease. Although it is possible that the epidemiological transition that has taken place in the developed countries will be replicated over time in the developing nations, a variety of factors may intervene to produce a different pattern than that seen in Europe, Japan and the United States today. A question of considerable interest is: what will be the primary causes of mortality in non-industrialized countries if and when mortalities due to infectious disease in developing countries have been reduced to the level now observed in industrialized nations? The answer to this question has been the subject of intense scrutiny by epidemiologists[11]. This is because, in addition to changes in rates of incidence and prevalence for major diseases, the demographic profile has also changed. Consequently, the standard population used as the basis for projections of future mortality rates is sufficiently different to yield substantially different results. An illustration of the effect of using different sample populations for projections of future mortalities can be seen in Table 3.

As can be seen in Table 3, use of a sample population wherein the age structure is strongly influenced by the inclusion of substantially more individuals in the later stages of the life cycle yields different expectations of mortality due to most causes. Notable are significant reductions in deaths due to atherosclerosis and cardiovascular diseases and increases in those attributable to chronic obstructive pulmonary disease, pneumonia and influenza, diabetes, and Alzheimer's disease. In reality, death due to cardiovascular disease has been decreasing in frequency in the United States since about 1960. This decline, along with that for death due to chronic liver disease provide evidence that the long-cited trend of replacement of infectious disease by chronic degenerative conditions as leading causes of mortality is more complicated than once thought. Also somewhat surprising is the relative stability in the number of cancer deaths. The inevitable question that arises when these statistics are examined is: what will be the leading causes of death in the middle of the 21st century? There is no clear trend to provide a ready answer to this question. A related question is: will the trend toward increasing life expectancies continue indefinitely? Some possible answers to these questions will be explored later in this discussion, but first, another aspect of the changing demographic profile in one industrial country, the United States, will be examined from another perspective, namely that of the projected remaining years of life at a given age. Clearly, this is a more realistic estimator of life expectancy than the more often cited life expectancy at birth. This is true in part because the disproportionately hazardous first year of life can be excluded from the calculation for the later years. Examination of the data in Table 4[12] will illustrate this point.

As can be seen in Table 4, beyond age 20, the male increment in predicted age at death exceeds the female increment at every age. The disparity increases with increasing age. For instance, in 1996, the projected age at death for women of all races aged 20 years in the United States

TABLE 3
ESTIMATED NUMBER OF DEATHS PER 100,000 POPULATIONS ATTRIBUTED TO VARIOUS CAUSES USING 1940 AND 2000 UNITED STATES POPULATION PROFILES FOR ESTIMATION

Cause of death	1979	1985	1990	1995	% change
All causes					
1940	577.1	548.8	520.2	503.9	–12.7
2000	1,011.1	988.1	938.7	918.5	–9.2
Heart disease					
1940	199.6	181.4	152.0	138.3	–30.7
2000	401.7	374.9	332.1	296.3	–26.2
Malignant neoplasms					
1940	130.8	134.4	135.0	129.9	–0.7
2000	204.0	211.3	216.0	211.7	+3.8
Cerebro–vascular disease					
1940	41.6	32.5	27.7	26.7	–35.8
2000	97.3	76.6	65.5	63.9	–34.3
Chronic obstructive pulmonary disease					
1940	14.6	18.8	19.7	20.8	+42.9
2000	25.5	34.5	37.2	40.5	+56.7
Pneumonia & influenza					
1940	11.2	13.5	14.0	12.9	+15.6
2000	26.1	34.5	36.8	33.8	+29.4
Diabetes mellitus					
1940	9.8	9.7	11.7	13.3	+36.1
2000	17.5	17.4	20.7	23.4	+33.8
HIV					
1940	0	0	9.8	15.6	+184.2
2000	0	0	10.2	16.4	+189.8
Alzheimer's disease					
1940	0.3	1.6	2.2	2.7	+980.0
2000	0.4	4.1	6.4	8.4	+1862.8
Atherosclerosis					
1940	5.7	4.0	2.8	2.3	–58.4
2000	17.9	12.6	8.5	6.9	–61.5
Chronic liver disease					
1940	12.1	9.7	8.6	7.6	–37.0
2000	14.8	12.3	10.7	10.0	–32.8

Data from Anderson and Rosenberg (1998)[12]

was 79.9 years. For males of the same age, the projected age at death that year was 74.2 years. However, at age 85, the projected age at death for women was 91.4 years, and that for men was 90.4 years. The narrowing of the life expectancy gap appears to accelerate from age 55 onward. Coincidentally, this is the age when the level of circulating estrogens usually declines sharply in women. The changes in body composition associated with reduced sex steroid secretion in both

TABLE 4
PREDICTED AGE AT DEATH FOR VARIOUS AGES COMPARING U.S. DATA FOR 1995 AND 1996 – ALL RACES AND ETHNIC GROUPS COMBINED

Life expectancy								
	Males				Females			
Age	1995	1996	PAD	INCR	1995	1996	PAD	INCR
0	72.5	73.0	73.0	–	78.9	79.0	79.0	–
1	72.1	72.6	73.6	0.6	78.5	78.6	79.6	0.6
5	68.3	68.7	73.7	0.1	74.6	74.7	79.7	0.1
10	63.3	63.8	73.8	0.1	69.7	69.7	79.7	0
15	58.4	58.9	73.9	0.1	64.7	64.8	79.8	0.1
20	53.8	54.2	74.2	0.3	59.9	59.9	79.9	0.1
25	49.2	49.6	74.6	0.4	55.0	55.1	80.1	0.2
30	44.6	44.9	74.9	0.3	50.2	50.2	80.2	0.1
35	40.1	40.4	75.4	0.5	45.4	45.4	80.4	0.2
40	35.6	35.9	75.9	0.5	40.7	40.7	80.7	0.3
45	31.3	31.5	76.5	0.6	36.0	36.0	81.0	0.3
50	27.0	27.1	77.1	0.6	31.4	31.5	81.5	0.5
55	22.9	23.0	78.0	0.9	27.0	27.1	82.1	0.6
60	19.1	19.2	79.2	1.2	22.9	22.9	82.9	0.8
65	15.6	15.7	80.7	1.5	18.9	18.9	83.9	1.0
70	12.4	12.5	82.5	1.8	15.3	15.3	85.3	1.4
75	9.7	9.8	84.8	2.3	11.9	11.9	86.9	1.6
80	7.2	7.3	87.3	2.5	8.9	8.9	88.9	2.0
85	5.2	5.4	90.4	3.1	6.3	6.4	91.4	2.5

PAD = Predicted age at death; INCR = Added life expectancy from preceding age group

sexes involve the loss of bone and skeletal muscle. The result of this loss is an increase in the ratio of fat to total body mass. The relationship of this decline in lean body mass to mortality risk is a matter of special interest in populations where life expectancies have increased the most.

The results of a number of studies provide evidence that unintended weight loss, particularly loss of muscle mass, is an indicator of increased risk of mortality in older individuals. There are many reasons for this being the case. Some of the proposed explanations implicate compromised immune competence[13]. A comprehensive review of these explanations is beyond the scope of the present discussion, but the changes documented in a number of populations provide a useful vantage point from which to review certain aspects of the aging process and their role in determining the limits of the human life span. As the demographic and epidemiological transitions outlined in this discussion progress, intrinsic factors involved in the aging process itself will gain importance with respect to their role in limiting the length of the life span. It is in this area of research that the most promising evidence for genetic determinants of human longevity will most likely be found. Before focusing on the topic of changes in body composition associated with the aging process, however, one of the peculiarities of the patterns seen in

the increase in predicted age at death should be noted.

As was pointed out in the discussion of the increments in predicted age at death, the advantage enjoyed by women with respect to life expectancy is the greatest at birth and, using 1996 statistics for all races, shrinks from six years to only one year at age 85. Equally interesting is comparison of the increase in life expectancies experienced by Americans of African origin with that experienced by individuals of European origin shown in Table 5.

TABLE 5
PREDICTED REMAINING YEARS OF LIFE AT BIRTH AND AT AGE 85 FOR AMERICANS OF EUROPEAN AND OF AFRICAN DESCENT

	European-American			
Age	Men		Women	
	1995	1996	1995	1996
0	73.4	73.8	79.6	79.6
85	5.2	5.3	6.3	6.3
	African-American			
	Men		Women	
	1995	1996	1995	1996
0	66.2	66.1	73.9	74.2
85	5.1	5.3	6.2	6.3

The comparisons in Table 5 reveal some striking aspects of the demographic transition presently in process in the United States. First, the sex difference in life expectancy at birth in the African American population (8.1 years) is more pronounced than among the population at large (6.0 years), and in the population of European ancestry (5.8 years). However, at age 85, the disparity has shrunk to only one year just as it has among those of European descent. Most notable is the fact that the predicted age at death for male Americans of European descent is identical to that predicted for males of African descent. The same holds true for females.

Included among the explanations offered for this observation are those positing a genetically determined tendency to longer life span among individuals of African descent. Variations of this explanation posit the action of strong selection in the early stages of life when high infant and child mortality rates prevail. The survivors of this process are those individuals fortunate enough to possess an effective immune response and other attributes conducive to survival in a rigorously stressful environment. The phenomenon of »selective survival« under such circumstances, repeated over many generations would favor retention of genes beneficial under the prevailing conditions. Eventually, the genome of the population could be expected to reflect these adaptations. Future trends in these statistical measures along with continued convergence of the socioeconomic status of racial groups in the United States promise to provide useful clues in the search for genetic determinants of longevity.

Emerging patterns of mortality

As infectious and major chronic degenerative diseases account for fewer of the deaths in industrialized populations, what will take their place? Even if life expectancies continue to increase, there are limits to the life spans of all known metazoan organisms. It should be stressed that, despite convincing evidence that individual cells age and lose their ability to divide because of telomeric shortening[14], it is highly unlikely that there is any single underlying mechanism that determines the rate of senescence and the age at death. Rather, the occurrence of many small failures occurring over time and exerting a cumulative effect on the physiological systems that maintain the organism is the more likely pattern leading to senescence and death. Thus, close scrutiny of failures in these systems is necessary to achieve greater understanding of

the limits of human longevity. If, for instance, we use the generally accepted upper limit of the human life span of 120 years, it is possible to construct mathematical models that parameterize the accumulation of such failures to produce the observed curve of declining fitness. This curve closely approximates the one for observed survivorship rates cited earlier[15]. What kind of physical changes are associated with declining fitness? Ideally, it should be possible to conduct serial measurements of them in order to assess the extent to which rate as well as the type and extent of change signal decline in fitness.

Changes in body composition provide one such indicator of declining fitness[3,16]. Simple anthropometric measurements including stature, weight, circumferential dimensions and skinfold thickness reveal a great deal about the aging process. With the addition of more intrusive (and expensive), but more precise measures such as bioelectric impedance, bone densitometry, dual energy x-ray, magnetic resonance, and computer assisted tomography, it is possible to assemble a comprehensive record of the course of this important aspect of the aging process. It is well known that sustained and unintentional weight loss is associated with a poor prognosis in aging patients[17]. When subjected to closer scrutiny, such weight loss usually involves loss of lean body mass. Although it is not always possible to monitor elderly patients using expensive diagnostic instrumentation, anthropometric measurements that can be used to estimate lean body mass are usually feasible[18–22].

At a time when the costs of health care for the aging population are a matter of national concern[23], such relatively simple, low cost diagnostic procedures that can be conducted by properly trained non-physicians have much to recommend them. In most cases, only cursory attention is given to the height and weight measurements done in the physician's office. Little attention is paid to such aspects of standardization as removal of shoes or other items of clothing. Circumferential measurements and/or skinfolds are seldom taken. Consequently, the physician usually relies upon the imprecise, nonstandardized information placed in the patient's file to supplement the impressions gained during the physical examination. Moreover, the examination itself is usually brief and may not occur more than once a year. Even the most skilled and conscientious physician may remain unaware of significant changes under these circumstances. Regular monitoring of indicators of change in body composition by accredited anthropometrists could provide the physician with a valuable diagnostic tool at relatively low cost. If simple anthropometric procedures reveal change exceeding normative standards, more intrusive measures would be warranted. Such monitoring would facilitate early intervention, such as nutritional counseling, to deal with conditions that might otherwise eventually require more expensive treatment.

Bone loss and aging

In a longitudinal study of bone density change conducted at the University of Arizona we have found high correlations between anthropometrically derived indices such as the body mass index (BMI) and measures of lean body mass and total body fat. Other investigators[18–22,24] have developed a set of age and sex-specific prediction formulas to estimate body composition from bioelectric impedance values and body mass index. These investigators have been able to demonstrate that while these predictive equations are quite reliable when applied to individuals of a specific ethnic group, there are ethnic differences in the relationship between percent body fat and body mass index[21,24].

In the Arizona population, serial measurements confirm that body mass index increases through middle life and then decreases. Both body mass index and body surface area are highly correlated with bone density in the later stages of life.

Losses in bone density are observed in both sexes as aging progresses. Although it is widely believed that osteoporosis is more prevalent in women, the problem is one shared by both sexes by age 80[25,26]. In the Arizona longitudinal study, the bone density of every subject, male or female, over age 90 had declined to a level well within the generally accepted definition of osteoporosis. While osteoporosis is not one of the conditions included among the leading causes of mortality, it is frequently implicated in the rapid decline in functional capacity preceding death. The consequences of spinal and hip fractures are especially debilitating. Non-traumatic hip fractures in women are associated with a mortality exceeding 20% within the following year.

The consequences of spinal fractures, although less easily linked to mortality, have long been recognized as morbidity factors. Depending upon the location of the fracture and the number of vertebrae involved, spinal fractures alter the curvatures that facilitate normal weight transfer and thus often have pervasive effects on locomotion and balance. Vertebral crush fractures can reduce the length of the spine appreciably, effectively reducing the space available for the viscera. The effect on digestion and respiration can impact the general state of health in numerous ways, each of which can ultimately result in mortality. If and when cardiovascular disease and cancer are no longer major causes of mortality, conditions like osteoporosis, that progressively and cumulatively reduce the individual's functional capacity, will become ever more important concerns for the health care delivery system.

In many respects, conditions that cause gradual decline in functional capacity have the characteristics one would expect in the aging process itself[27]. If the human life span has limits, and if those limits have an evolutionary history, it can be expected that such causes of mortality will be far less susceptible to dramatic breakthroughs in intervention strategies. The evolutionary value of individual death is quite clear if one accepts the premise that all species must be able to evolve in order to survive and that resource limitations will always place an upper limit on the size of the population that is supportable.

When increased age is associated with declining reproductive potential, as is clearly the case for our species, the evolutionary advantage accruing to the species through timely death of the elderly is explicit. However, senescence is less easily explained on evolutionary grounds. It may be argued that conditions such as osteoporosis may be associated with senescence because of antagonistic pleiotropies wherein traits that enhance reproductive success early in life have deleterious effects in later life. The physiology of bone and its close association with maintenance of calcium homeostasis may provide an example of such pleiotropy. If so, the association would necessarily involve endocrine factors, which would most certainly include vitamin D and its metabolites.

Vitamin D: A steroid hormone

The importance of vitamin D in the maintenance of calcium is well known. The occurrence of rickets in children receiving insufficient sunshine exposure in northern European countries was traced to their incapacity to synthesize enough of the vitamin through the long and cloudy winters at high latitudes. Dietary intake of vitamin D can compensate for its low endogenous synthesis, as can be seen

in the low incidence of rickets in northern Europe today. However, the problem of insufficient production of active vitamin D still exists, although in a different segment of the population. Lack of outdoor activity and, in recent times, concern about the risk of skin cancer, lead to very little sun exposure for some older people, particularly those in nursing homes. Vitamin D supplementation to prevent bone loss is now frequently recommended under such circumstances[28,29]. However, there is evidence that vitamin D supplementation should be undertaken with discretion. For instance, Moon et al.[30] point out that routine use of vitamin D as a food supplement coincides with epidemic onsets of atherosclerosis and osteoporosis, and that excess vitamin D induces both conditions in laboratory animals and in humans.

The pathway of vitamin D synthesis, starting in the skin with ultraviolet conversion of ergosterol to cholecalciferol and its conversion to active vitamin D_3 by hydroxylations in the liver and kidney has also been known for a considerable length of time. The best-understood aspect of vitamin D's role is its stimulation of calcium uptake in the gut. This is affected by direct action of the hormone with nuclear DNA of cells of the intestinal epithelium. The synthesis of messenger RNA and the synthesis of a calcium transport protein, calbindin, are the result. Calbindin binds to and transports ionic calcium from the mucosal surface of the intestinal epithelial cell to the serosal side and releases it to diffuse across the plasma membrane and into the blood.

Vitamin D also has a more rapid effect on calcium absorption that has been termed *transcaltachia.* This rapid form of transport functions through the opening up of channels in the membrane of intestinal epithelial cells, is allowing calcium to flow into the cell down a concentration gradient. The rapidity of transcaltachia compared to the DNA (genomic) pathway derives from the fact that there is no delay while the processes of transcription and translation are carried out when transcaltachia occurs. Transcaltachia does not occur when serum calcium levels are high. Consequently, the efficiency of calcium absorption increases as serum calcium level decreases[31–34]. Experiments reported by Norman and his colleagues yield convincing evidence that there are two separate receptors for vitamin D on the membrane of the intestinal epithelial cell, one that mediates the genomic and the other the non-genomic response[35–41]. These investigators have also shown that calcitriol stimulates the opening of calcium channels in the plasma membranes of certain target cells with the result being synthesis of osteocalcin by osteoblasts and of kidney calcium binding protein, by kidney cells.

Stimulation of membrane phospholipid turnover with increased formation of inositol 1,4,5-triphosphanate by calcitriol in *in vitro* experiments in the same laboratory[42], is evidence that one of vitamin D's effects is the transduction of information via G-proteins and second messengers. The discovery of vitamin D receptors on a wide range of cells, including some cancer cells, is evidence that this vitamin/hormone has many functions yet to be discovered. DeLuca[43] cites several other known functions of vitamin D including suppression of parathyroid hormone release, (also reported in a recent clinical trial in England)[44] recruitment of cells for osteoclast formation, development of the skin, and regulation of aspects of female reproduction. It also has the ability to regulate growth and differentiation of epidermal keratinocytes and active lymphocytes[45], evidence of interrelationships between the skeletal and immune systems.

Supplementing the diet with vitamin D is now recognized as an important safe-

guard against bone loss in the elderly. However, the benefits are limited when vitamin D is taken in its simple ergosterol form. This is the usual form of vitamin D included in multiple vitamin preparations, and it does have the effect of lowering parathyroid hormone (PTH) levels, thus mitigating the secondary hyperparathyroidism frequently associated with osteoporosis. However, this effect is most closely related to the presence of calcidiol (25(OH) D_2), not calcitriol (1,25 $(OH)_2$ D_3). In a recent study[46], a high percentage of hospitalized patients were found to have low blood calcidiol levels. In fact, the same study showed similarly low levels in a surprisingly high proportion (42%) of younger patients. It has been estimated that 10–20% of older people in the United States experience vitamin D deficiency at least seasonally[47–49]. European populations also exhibit low calcidiol levels, possibly because most dairy products consumed there are not vitamin-D fortified and multivitamin use is less common[50–52]. There is strong evidence that vitamin D deficiency associated with secondary hyperparathyroidism is the major factor responsible for hip fracture in the elderly, especially those who are institutionalized or housebound[53–57]. A supplement of 700–800 IU of ordinary vitamin D precursor has a relatively modest effect on the bone mineral content of such long bones as the femur, but may reduce the incidence of hip fracture[47,58,59]. There is evidence that some populations, including Asians, may require higher doses of vitamin D supplement to keep PTH concentrations at normal levels[60–62].

Despite its beneficial effects on circulating PTH levels, ordinary vitamin D supplementation only increases intestinal absorption of calcium when taken in very high doses[63]. In contrast, administration of calcitriol increases absorption at low doses, and has its greatest effect on patients with the poorest intestinal calcium absorption[64]. Therefore, to reduce the risk of osteoporosis in postmenopausal women and in older individuals who do not respond to supplementation with precursors, it may be necessary to provide active vitamin-D analogs, such as calcitriol-hormone or alphacalcidiol[65,66]. Osteoporosis patients of both sexes frequently have poor intestinal absorption of calcium, a condition that may indicate intestinal resistance to vitamin D[67]. Therefore, such conditions as inflammatory bowel disease may play a role in the etiology of osteoporosis because of their impact on vitamin D activity in the gut[68]. It does not appear that active vitamin D analogs increase bone resorption, but are necessary for the induction of cell differentiation and the stimulation of osteoblasts[69,70]. Combining the administration of active vitamin D analogs with medications, such as estrogen or bisphosphanates promises to enhance the effectiveness of both[71]. It remains to be determined just how much the vitamin D receptor genotype influences these effects[72,73].

The binding of vitamin D to the plasma membrane of target cells occurs at a specific receptor that belongs to a family of nuclear receptors for estrogens, glucocorticoids, retinoic acid and thyroxine. An interesting question is: which of vitamin D's many functions arose first and may therefore be considered the primary function of vitamin D and its several active analogs?

Calcium

Adequate calcium intake must be assured to maintain physiological homeostasis. However, the amount of calcium that can be considered adequate is by no means certain. There is much variation in dietary calcium intakes of different populations. Even within a single country like China, reported daily calcium intakes vary from a low of 230 mg to a high of 724 mg[7,74,75]. Such wide variation raises

the possibility of early adaptations to low intakes. Few if any populations achieve the 1000 mg per day now recommended for young women in the United States. The advisability of regular calcium supplementation remains a topic of considerable controversy. Calcium ingested in dairy products, particularly before age 25, is associated with higher bone densities in women[76]. The efficacy of calcium supplementation during pregnancy and lactation has long concerned obstetricians. The physiological adjustments made at these crucial times in female reproductive life give evidence of the importance of calcium homeostasis for both mother and child.

Half a liter of milk and 25 grams of cheese per day will satisfy calcium requirements for most people[77]. Other foods, including broccoli, cabbage, beans, and several dark green leafy vegetables including collard and mustard greens are good sources of calcium for those who must avoid dairy products. Fish, such as salmon or sardines consumed with bones also provide dietary calcium without high fat intake. Elderly female lacto-ovovegetarians have been found to maintain bone density as well as omnivores at a calcium intake 25% below the omnivore level[78]. Not all calcium supplements are considered safe. Lead contamination in bone meal and dolomite supplements and even in some oyster shell supplements, although not at toxic levels, may have an unknown cumulative effect. There is considerable evidence that calcium intake early in life is positively correlated with peak bone mass[79,80].

Much of the controversy over recommended calcium intake is focused on the benefits of calcium supplements later in life[81]. Several large studies have shown no positive effect of calcium intake on the rate of bone mineral decline with aging[78,82–85]. Another study[86] found that calcium supplementation may play an important role in potentiating the beneficial effects of estrogen on bone mineral turnover.

Without other forms of supplementation or medication, moderate calcium supplementation, *i.e.* 500–1000 mg/day, may reduce bone resorption by no more than about 10% in postmenopausal women[87]. However, when coupled with vitamin D supplementation, high-dose (1,500 –2,000 mg/day) calcium supplementation can produce a 30–60% decrease in bone turnover[88]. Moreover, because calcium tends to decrease the amount of circulating 1,25 vitamin D, it has the potential to increase the risk of certain types of cancer. One study[89] found evidence that high dosage calcium supplementation in men was associated with increased risk of prostate cancer. As a general rule, it seems advisable that calcium supplements be accompanied by vitamin D to avoid such undesirable side effects. It has been shown that high-dosage calcium supplementation reduces zinc absorption and may therefore require increased zinc intake[90]. There is substantial disagreement concerning the effect of calcium supplementation on the absorption of non-heme iron. Some investigators, using the level of serum ferritin as the indicator of iron absorption, report no difference between subjects receiving high calcium intakes and those with low intakes[91,92]. Other investigators, using direct measurement of iron absorption, report that high calcium intakes reduce iron absorption significantly, and that adolescents, and pregnant and lactating women should restrict calcium intake at meals in which iron intake is also important[93].

High protein diets increase the level of calcium excretion[94–97]. The reason for this is thought to be the increased acidity of the urine associated with a high protein diet. A more acidic urine leads to increased excretion of calcium[98–100]. Excessive urinary calcium loss upsets calcium ho-

meostasis, leading to bone resorption[101–105]. This happens because high acidity requires buffering and calcium is an important buffer[98,106]. Increased acid secretion by the kidney is largely the result of oxidation of the sulfur-containing amino acids methionine and cysteine, abundant in animal proteins[107–109]. The association between dietary protein intake and urinary calcium loss has been shown to be linear[110]. Thus, lifelong intakes of acid-ash foods as in many Western diets may be an important risk factor for osteoporosis[104,111,112]. Avoidance of this demand for calcium buffering may be instrumental in the superior bone densities maintained by vegetarians[113–117]. Cross-cultural comparisons have found a strong association between diets high in animal protein and incidence of hip fracture[75,111,118].

While the pattern of bone loss in females conforms to expectations based on endocrinological changes occurring with age, male bone loss is less clearly defined. It is quite likely that estrogen plays a significant role in male bone metabolism independent of testosterone. One indicator of the importance of estrogen is the fact that male bone mineral density is more highly correlated with serum estrogen than with testosterone[119]. There is considerable evidence that male bones fracture at a higher bone density than those of women, and that the prevalence of vertebral fractures is actually higher in men[120]. Cody et al.[121] report a different pattern of bone loss associated with fractures of the femoral neck occurring in men from that seen in women. In men, bone density was found to decrease throughout the proximal femur. In women a combination of localized changes including loss of trabecular bone at the fracture site as well as decreased cortical bone at the point of impact was most common. Women lose more height proportionally than men as they age, and the beneficial effects of regular physical exercise in attenuating loss of stature are more pronounced in men than in women[122]. However, women with non-insulin dependent diabetes mellitus appear to maintain greater more bone density than non-diabetic women. No such difference between diabetic and non-diabetic men has been reported[123]. Davies et al.[124] report an interesting negative association between calcium intakes and body mass index in women, a relationship that has not to date been reported for males.

Male bone loss

In a recently reported Spanish study of healthy elderly men, multiple regression analysis of the relationships of bone density to hormonal and anthropometric variables indicates that body weight, sex hormone binding globulin (SHBG), and intact PTH levels are independent predictors of bone mass. However, most of the bone mineral density was explained by body weight alone. After adjusting for age and BMI, SHBG and insulin-like growth factor 1 found to be negatively correlated with bone density[125]. There seems to be little doubt that age-related changes in androgen levels have an impact on bone metabolism in males as well as in females.

However, the nature of the relationships between estrogenic hormones and testosterone is far from clear. This uncertainty is reflected in the conflicting results reported by investigators concerned with the causes of bone loss in aging men. For instance, contrary to Khosla, Melton and Riggs' previously cited report[119] that estrogen levels are more highly correlated with bone density than testosterone levels in men, other investigators[126] report that testosterone levels are the most reliable predictors of bone loss. Rapado et al.[127] found no significant correlation between male sex hormone and decrease in hip bone mineral density (BMD), and Bo-

onen et al.[128] found that both serum testosterone and hydroxyvitamin D, and dihydroxyvitamin D were all decreased in hip fracture patients. Combined administration of vitamins D_3 and K_2 has been found effective in increasing the bone mineral density of the lumbar spine in women with osteoporosis[129].

Testosterone replacement therapy has been shown to increase bone formation in men diagnosed with idiopathic hypogonadotrophic hypogonadism, although bone resorption also increases in these patients[130,131]. However, Medras, Jankowska, and Rogucka[132] report that even when long-term testosterone replacement therapy succeeds in normalizing serum androgen levels, elimination of osteopenia does not always occur. The com- plex interactions between sex hormones, body composition and behavioral[133,134] make it extremely difficult to trace direct cause/effect associations between changes in androgen production and bone mineral metabolism.

Vitamin D receptors

The role of the vitamin D receptor genotype in predisposition to osteoporosis remains under investigation. Vitamin D, its metabolites and homologues are well known to have many physiological effects. With respect to the maintenance of bone density, one of the most important and best-understood functions of vitamin D is its regulation of calcium absorption in the small intestine. The most active form of vitamin D in this regulatory function is 1,25 $(OH)_2$ vitamin D_3 (calcitriol). The receptors for this hormone have several known variants, one of which arises from a substitution of a guanine for an adenine at the 3731st position from the 5' end[135]. The G- allele exhibits reduced transcriptional activity in promoter region and reduced calcium absorption. Postmenopausal women homozygous for the G-allele was found to have a 12% lower BMD in the lumbar spine than homozygotes for the A-allele. Interactions between alleles at the vitamin D nuclear receptor (VDR) locus and alleles at the estrogen receptor (ER) locus, which is also polymorphic, are now thought to underlie some of the subtle variation in bone densities found when either VDR or ER genotypes are independently examined[136].

The best understood function of vitamin D is by way of a nuclear receptor (VDR) within the target cell. In this respect, vitamin functions through the same mechanism as other members of the steroid-thyroid hormone superfamily. The VDR, in turn, binds to the direct repeat response elements (DR-3) in the promoter region of target genes to stimulate or suppress transcription of mRNA. After ribosomal translation, the result is synthesis of proteins that perform a wide array of functions. Of particular interest is the recent discovery of vitamin D's role in the immune response, where its function may be that of a suppressor. Evidence for this role has been found in experiments with mice in which autoimmune conditions have been treated successfully with vitamin D and its analogs[138].

The vitamin D receptor is one of a family of receptors of various hydrophobic ligands. These ligands include, besides vitamin D, other steroids, retinoic acid, and thyroid hormone. All of the nuclear receptors are composed of several domains necessary for transcription to occur. There is the aforementioned domain for DNA binding (the C domain), plus a domain for hormone binding, (the D domain), and a domain for dimerization (the E domain). These domains could have evolved through gene duplication from a common ancestor. They also could have come from different independent sources.

On the basis of phylogenetic trees developed from two different domains of 30 nuclear receptor genes, Laudet et al.[139]

conclude that both duplication and swapping between domains of different origin occurred. It appears that the first nuclear receptor was one able to bind to DNA as a homodimer. This receptor appeared very early, probably around the time of origin of all metazoan phyla. Later, a period of diversification commencing with the origin of the vertebrates produced the variety of nuclear receptors present in contemporary species[140]. The close homology between the vertebrate retinoid receptor and that of Drosophila is strong evidence of the existence of these receptors before the divergence of vertebrates and invertebrates.

Sex differences in fracture incidence

In both sexes, the frequency of fracture occurrence is negatively correlated with BMD, BMI, muscle strength, and level of physical activity[141–143]. However, the structural basis for bone density loss in men may differ from that in women[144]. Male periosteal expansion exceeds female during growth and development. An important component of certain racial differences in bone density results from similar differences in the early acquisition of bone density. Blacks, both male and female, experience greater periosteal expansion early in life, and therefore have greater bone density than age- and sex-matched whites. One result of greater periosteal expansion is wider long bones in early adulthood. Structurally, this expansion places cortical bone mineral mass at a greater distance from the neutral axis of the bone in men than in women and in blacks than in whites. Placement of bone mineral mass at a greater distance from the neutral axis of the bone confers a mechanical advantage that enhances the strength of long bones, especially in resistance to torsional stress. One result of this increase in strength is a lowered risk of non-traumatic fracture. Consequently, at peak bone density, both racial and gender differences in bone strength are likely attributable to size and not BMD.

The loss of trabecular bone is similar in both sexes, but women experience greater loss of connectivity, the important relationship between the struts and plates that maintains the structural integrity of the trabeculae. In addition, endocortical resorption is greater in women. Men lose less cortical width for that reason and because of a greater amount of subperiosteal apposition during aging. Men who suffer fractures of the spine have smaller vertebral width[120] and men with hip fractures have a narrower femoral neck. Nonetheless, the average decline in density of the radius experienced by men between the ages of 29 and 76 is about 1% per year[145]. Ultrasound determinations of bone density in the calcaneus have proven effective in predicting fracture risk in men[146] despite the difference between the structural and functional characteristics of the bones of the forearm and the heel.

Materials and Methods

The Arizona Bone Density Study was initiated in 1982. The first cohort of subjects was drawn from the Volunteer Association of the Walter O. Boswell Memorial Hospital in Sun City, Arizona. These subjects were, by and large, retirees. Most owned their own homes and were financially independent. Almost all were of European ancestry. In order to broaden the demographics of the study, a second cohort was recruited from residents of publicly subsidized retirement housing in Tucson, Arizona. These subjects were, on the average, less affluent than those from Sun City. Also, most of the Tucson subjects had been Arizona residents for a longer period of time, often since birth, and roughly 30% of them were of Hispanic origin as compared to less than 5% in Sun

City. A small sample of African American subjects was also recruited in Tucson. From the outset, more women than men were recruited in both the Sun City and Tucson populations. This sampling bias reflected the belief, prevalent at the time, that osteoporosis was primarily a condition-affecting woman.

The primary objective of the study was to monitor changes in bone density over time. However, other changes were monitored as well. Height and weight were measured on each occasion for all subjects, and bioelectric impedance assessments of body composition were conducted on a sample of 451, (277 men and 174 women) who were enrolled in the wheat bran fiber and piroxicam clinical trials. Alkaline phosphatase levels and concentrations of serum calcium and other minerals were also determined through the analysis of blood samples from these subjects. On each occasion, all subjects were requested to complete questionnaires containing questions about bone fracture histories, medications, stress-inducing experiences, exercise patterns, milk consumption, and use of dietary supplements. On the occasion of their first visit, women were asked to complete an additional questionnaire concerning age at menarche and menopause and reproductive and breast-feeding histories.

Subjects

From 1982 through 1998 data were collected annually at both Sun City and Tucson. Since the average age of the subjects of the first cohort was 70 years, and the loss of subjects for various reasons could be expected, new subjects were added each year. By the end of 1998, the total sample was 5,475 (4,121 women and 1,354 men). One hundred and seventy three subjects, (126 women and 47 men) participated for 10 years or more. Over the course of the study, subjects from several rural communities in Pinal County, Arizona (Casa Grande, Eloy, and Florence) had been incorporated in the study population, as had subjects enrolled in wheat bran fiber and piroxicam colon cancer prevention clinical trials conducted in Sun City and Tucson.

Methods

Annual scans of the left radius were conducted using single-beam photon absorptiometry (Lunar Radiation SP-1 and SP-2 Bone Densitometers). While both dual-photon and dual-energy x-ray (DEXA) instruments provide more information about clinically-sensitive areas such as the lumbar spine and the femoral neck, the objective of comparing serial measurements of cortical bone density was satisfactorily achieved using the single photon devices. The portability of the single photon device was a major consideration in its favor, because in order to reach the target populations of the Arizona study, it was necessary to set up the equipment at a number of sites in several cities and in rural areas. Change in cortical bone density over time can be measured with a high degree of accuracy at the radial site using single-beam photon absorptiometry (SPA). Since cortical bone makes up more than 80% of the total bone mass of the adult, the SPA scanning of this bone as a surrogate for whole-body scanning yields useful results.

Within this limited context, SPA bone scans are a highly reliable method for effecting valid assessments of cortical bone density. When suitable safeguards are taken to assure that all scans are taken at precisely the same site; the method is ideal for the monitoring of bone density change through serial measurements. Thus, when used as a research method for a large sample, mixed longitudinal study of bone density change it is a very powerful tool. However, its clinical use as a predictor of fractures at sites where trabecular bone is more abundant cannot

TABLE 6
FINAL BONE DENSITIES AND BODY MASS INDEX VALUES FOR TUCSON AND SUN CITY WOMEN AND MEN

	Bone density				Body mass index	
Age	Women	(N)	Men	(N)	Women	Men
< 50	0.6591	(369)	0.7803	(50)	25.79	26.12
50–55	0.6532	(142)	0.7468	(20)	27.36	29.30
55–60	0.6188	(202)	0.7553	(38)	26.97	27.58
60–65	0.5908	(332)	0.7502	(84)	26.17	27.40
65–70	0.5585	(684)	0.7279	(208)	26.16	26.91
70–75	0.5295	(808)	0.7157	(286)	25.79	26.70
75–80	0.4946	(708)	0.7054	(295)	25.34	26.92
80–85	0.4773	(497)	0.6763	(183)	24.94	25.17
85–90	0.4512	(246)	0.6341	(81)	24.31	24.21
90–95	0.4161	(69)	0.5817	(18)	23.58	24.72
95–100	0.3966	(11)	0.4106	(1)	23.26	23.30

be recommended. Since the objectives of the present study did not include estimates of trabecular bone density or changes thereof, the advantages of SPA methodology considerably outweighed its disadvantages. Results of a comparative study involving subjects drawn from the Arizona Bone Density Study, yielded a correlation of 89% between the values for whole-body bone density attained by DEXA measurement and the values for bone density of the distal one-third site of the radius attained through SPA measurement[147]. An additional advantage of the SPA method is that the highly collimated photon stream emitted by its 200 mC[125] I source produces a very low radiation dose for the subject, and its low scatter minimizes the risk of radiation to both subjects and investigators.

The measurement of stature to the nearest millimeter was done using a free-standing field anthropometer with the subject shoeless. Weight in kilograms was taken using a portable medical scale. The same anthropometrist took each of these measurements on each scanning occasion throughout the study. Body mass index was calculated using the equation: BMI = weight (kg)/ height $(m)^{2.}$ More than 14,000 records of these measurements as well as bone scan reports, human subjects' consent forms and questionnaires remain on file in The Biological Anthropology Laboratory at the University of Arizona.

Results

Table 6 shows the values for bone density and body mass index arranged by five-year categories for a sample of 4,036 women and 1,264 men for whom complete records are available. The values that appear in this table represent those obtained at each subject's final examination. In some instances, this may be the last of 16 such measurements and in others it is the first and only one. The values shown in this table therefore represent a purely cross-sectional database.

As the values in Table 6 indicate, average cortical bone density declines steadily from age 50 onwards in women. The relatively small sample of men in the 50–55 year age group would appear to experi-

TABLE 7
INITIAL AND FINAL PERCENT CORTICAL AREA – SEXES COMPARED

Age	Women		Men	
	Initial PCA	Final PCA	Initial PCA	Final PCA
50–55	64.6	63.5	61.0	61.0
55–60	59.5	58.6	59.3	59.1
60–65	58.0	57.4	59.1	59.1
65–70	54.5	53.3	58.0	57.3
70–75	52.4	50.5	57.9	56.6
75–80	49.0	47.0	57.4	55.7
80–85	48.7	45.5	54.8	52.8
85–90	46.0	43.1	54.3	49.8
90–95	42.6	39.1	50.4	45.9

ence a sharp decrease in bone density, but it is probable that the apparent acceleration of bone density decrease is an artifact of small sample size in this age group. Succeeding age groups exhibit a rate of decline similar to that seen in the values for women. The decline in bone density in both sexes is sufficient to dispel the widely held notion that bone density decrease is primarily a women's problem. However, the lower average bone densities characteristic of women throughout early adulthood, coupled with a period of accelerated bone loss at menopause make them susceptible to bone fractures at an earlier age than men.

Bone density values obtained through single SPA are expressed as grams of bone mineral per square centimeter of area. However, these values can be used to estimate the three-dimensional configuration of the radial diaphysis, and, by applying certain assumptions, the cross-sectional areas of the cortex and medullary cavity can be estimated. The method used in making these estimates is described in detail elsewhere[148]. Normal remodeling of the diaphysis of long bones such as the radius usually involves resorption at the endosteal surface and appositional growth at the subperiosteal surface. With increasing age, the deposit of new bone at the subperiosteal surface declines while resorption at the endosteal surface continues. The result is a thinning of the cortex. In its earlier stages, the increased cross sectional area of the diaphysis may confer an advantage in withstanding torsional stress. However, thinning of the cortex eventually leads to increased vulnerability to fractures produced by buckling of the cortex. Therefore, estimation of changes in the ratio of cortical area to total cross sectional area (PCA) of the radius provides a useful means of estimating the risk of fracture in the radius. Table 7 shows the average initial and final values for PCA for women and men.

As can be seen from the values for PCA in Table 7, women enter the postmenopausal period with PCA values as high or higher than those of men. However, they are already experiencing a decline in cortical area in the 50–55 year age interval, while men show little change until the 65–70 year interval. Because of the differences in age of onset and rate of decrease in PCA, initial values for men in the 80–85 year age group are higher than those for women in the 65–70 year age group. The rate of loss in the later years of life, however, is very similar in both sexes.

Relationships between body mass index and PCA at various ages are shown in Table 8. In Table 8, BMI values conventionally used to assign the designations »obese« (BMI>28.0), and »excessively lean« (BMI<20.0) were applied to average values in the 10-year age categories: 60–70, 70–80, and 80–90, to assess the relationship between extreme BMI values and PCA. Along with the aforementioned decline in PCA with age, the PCA values for subjects of both sexes with high BMI values are seen to be substantially higher than for those with low BMI values.

When the values for PCA, bone mineral content and bone density for subjects drawn from the low BMI (n=370) and high BMI (n=1228) categories are compared, the differences for all three of these indicators of bone fracture risk are highly significant ($p<0.0001$). This is true of all age categories whether calculated by sex or with sexes combined. Analysis of variance to test the relationship of PCA to BMI at all ages yields an F value of 91.9 ($p<0.0001$), sexes combined. Separate analyses of variance for the male and the female samples yield F values of 15.5 and 65.9 respectively, both also significant at the $p<0.0001$ level.

TABLE 8
PCA VALUES IN THREE AGE GROUPS AND BY BMI CATEGORY

	Female X (N)	Male X (N)
Age group 60–70		
Average BMI	26.1	26.7
Average PCA	54.6 (928)	57.9 (212)
PCA (BMI > 28)	56.9 (288)	58.7 (62)
PCA (BMI < 20)	50.4 (60)	54.5 (5)
Age group 70–80		
Average BMI	25.6	26.8
Average PCA	48.9 (1,423)	56.2 (418)
PCA (BMI > 28)	51.2 (348)	56.7 (147)
PCA (BMI < 20)	45.8 (115)	52.9 (12)
Age group 80–90		
Average BMI	24.8	24.8
Average PCA	44.7 (732)	51.9 (250)
PCA (BMI > 28)	47.8 (144)	53.6 (36)
PCA (BMI < 20)	41.4 (86)	45.1 (15)

Normative bone density values, developed from a number of studies conducted in various geographic areas of the United States, are consistently higher than the averages for each age group for both sexes in the Arizona study. When the mean percent of the national normative values for Arizona subjects is compared to their mean BMI values, a t-test yields a 2-tailed significance <0.0001, similar to the level of significance for the comparison of means for body mass index and percent of peak bone density.

Discussion

The physiological roles of vitamin D are many and varied. Indeed, its original function may well have had nothing to do with the maintenance of bone. Vitamin D is a steroid hormone, and it should come as no surprise that some of its effects may differ in males and females. There is no question that the maintenance of the integrity of the skeleton is important to survival. But the skeleton's role as a reservoir of calcium is sometimes more important than its structural one. Therefore, the demands of reproduction may on occasion require the sacrifice of bone mass even though the risk of fractures is increased. The demands of pregnancy and lactation experienced by women have no parallel in men. »Osteoporosis of pregnancy« and a surprisingly rapid recovery of normal bone density is a well-known occurrence. The mobilization of bone calcium is necessary to support the needs of the fetus and infant. When adequate calcium is available in the diet, increased intestinal absorption efficiency can compensate for the increased demand. However,

calcium intake frequently falls short, with the result that skeletal calcium must be mobilized. That the skeleton can contribute a substantial amount of calcium at this critical stage in the reproductive process should come as no surprise. What is surprising is the rapid recovery that often occurs. Clearly, adaptations at the endocrine level are invoked.

When menopause occurs, the finely-tuned mechanisms that make this recovery possible no longer occur. Consequently, the ability to resorb bone mineral that is adaptive early in life becomes maladaptive after the endocrinological changes associated with menopause have occurred. These are the characteristics expected of antagonistic pleiotropy. The detailed pathways of these adjustments are complicated and subject to considerable inter-individual variability. Nevertheless, efforts to understand them more fully should yield both practical and theoretical rewards. In a future where the leading causes of mortality are no longer cardiovascular diseases and cancer, conditions that arise from such senescent changes will be a major concern for health delivery systems around the world.

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SPOLNE RAZLIKE U GUBITKU KOŠTANE MASE: EVOLUCIJSKE PERSPEKTIVE JEDNOG KLINIČKOG PROBLEMA

S A Ž E T A K

Dramatičan porast stanovništva u svijetu koji se pojavio tijekom zadnjih stotinu godina u najvećoj je mjeri posljedica pada smrtnosti od infektivnih bolesti. Epidemiološka tranzicija uzroka smrti prema degenerativnim stanjima, kao što su kardiovaskularne bolesti i karcinomi, javlja se u industrijaliziranim zemljama, kao i u zemljama u razvoju. U industrijaliziranim zemljama, demografski profili danas odražavaju porast u očekivanom trajanju života za oba spola. No, očekivano trajanje života kod žena je veće od onog za muškarce za 6 i više godina. Daljnje promjene u uzorku mortaliteta pratit će uspjeh u redukciji smrtnosti prouzrokovane degenerativnim stanjima kao što su kardiovaskularne bolesti i tumori. U 21. stoljeću, stanja koja su povezana sa starenjem bit će od sve veće važnosti. Adaptivne strategije koje su pojačavale reproduktivan uspjeh tijekom najvećeg dijela evolucije čovjeka mogu se sada pokazati štetnima za ljudsko zdravlje kako prosječno očekivano trajanje života dosiže besprimjernu dužinu. U takvom okolišu, razlike u mehanizmima preživljavanja koje su razvili muškarci u odnosu na žene postat će sve važnije.