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The Fetal Origins of Osteoporotic Fracture

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Preventive strategies against osteoporosis may be aimed at either increasing the peak bone mass attained or reducing the rates of bone loss [1]. There is evidence to suggest that peak bone mass is inherited, but current genetic markers are able to explain only a small proportion of the variation in individual bone mass or fracture risk [2]. It is likely that environmental influences during early life interact with the genome in establishing the functional level of a variety of metabolic processes involved in skeletal growth. This review addresses the role played by such environmental influences during intrauterine or very early postnatal life.

Fetal Origins of Chronic Disease

Epidemiological studies have revealed that men and women who were undernourished during intrauterine life, and therefore had low birthweight, have an increased risk of coronary heart disease, hypertension, non-insulin-dependent diabetes, and hypercholesterolaemia [3,4]. These associations are explained by a phenomenon known as programming [5]; this term describes lasting changes in structure and function caused by environmental stimuli acting at critical periods during early development. During embryonic life, the basic form of the human body is laid down in miniature. However, the body does not increase greatly in size until the fetal period when a rapid growth phase commences, which continues until after birth [4]. The main feature of fetal growth is cell division. Different tissues of the body grow during periods of rapid cell division, so called ''critical'' periods. Their timing differs for different tissues; for example, the kidney has one in the weeks immediately before birth, while the long bones accelerate their rate of growth during the second trimester of gestation. The main adaptive response to a lack of nutrients and oxygen during this period of growth is to slow the rate of cell division, especially in tissues that are undergoing critical periods at the time. This reduction in cell division is either direct or mediated through altered concentrations of growth factors or hormones (in particular, insulin, growth hormone, and cortisol).

It is not in question that the human skeleton can be programmed by undernutrition. Rickets has served as a long-standing example of undernutrition at a critical stage of early life, leading to lasting changes in structure. What is new is the realization that some of the body's ''memories'' of early undernutrition become translated into pathology and thereby determine disease in later life. Evidence has now accumulated that such intrauterine programming contributes to the risk of osteoporosis in later life.

Programming of Osteoporosis

Evidence that the risk of osteoporosis might be modified by environmental influences during early life stems from four groups of studies: (1) bone mineral measurements undertaken in cohorts of adults whose detailed birth and/or childhood records have been preserved; (2) studies relating growth in infancy and childhood to the later risk of hip fracture; (3) detailed physiological studies of candidate endocrine systems which might be programmed (GH/IGF-1; hypothalamic–pituitary–adrenal (HPA); gonadal); and (4) studies characterizing the nutrition, body build, and lifestyle of pregnant women and relating these to the bone mass of their newborn offspring.

Epidemiological Studies

The first epidemiological evidence that osteoporosis risk might be programmed came from a study of 153 women born in Bath between 1968 and 1969 who were traced and studied at age 21 years [6]. Data on childhood growth were obtained from linked birth and school health records. There were statistically significant ($P < 0.05$) associations between weight at one year and bone mineral content (BMC), but not density, at the lumbar spine and femoral neck; these relationships were independent of adult weight and body mass index. The data suggested a discordance between the processes which govern skeletal growth and those which influence mineralization. They also provide direct evidence that

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the trajectory of bone growth might be programmed, an assertion previously supported only by inference from measurements of body height.

The association between weight in infancy and adult bone mass was replicated in a second cohort study of 238 men and 201 women aged 60–75 years, who were born and still lived in Hertfordshire [7]. In this study, there were highly significant relationships between weight at 1 year and adult bone area at the spine and hip ($P < 0.005$); the relationships with BMC at these two sites were weaker but remained statistically significant ($P < 0.02$). They also remained after adjustment for lifestyle characteristics in adulthood which might have influenced bone mass (physical activity, dietary calcium intake, cigarette smoking, and alcohol consumption). Evidence of a gene-early environment interaction was observed for the gene for the vitamin D receptor (VDR) [8]. Thus, the relationship between lumbar spine BMD and VDR genotype varied according to birthweight. Among individuals in the lowest third of birthweight, spine BMD was higher ($P = 0.01$) in individuals of genotype BB after adjusting for age, sex, and weight at baseline. In contrast, spine BMD was reduced ($P = 0.04$) in individuals of the same genotype who were in the highest third of the birthweight distribution. A significant ($P = 0.02$) statistical interaction was found between VDR genotype and birthweight as determinants of BMD. These observations suggest that genetic influences on adult bone size and mineral density may be modified by undernutrition *in utero*.

Childhood Growth and Later Risk of Hip Fracture

Most evidence relating the intrauterine environment to later osteoporosis stems from studies utilizing noninvasive assessment of bone mineral. The clinically important consequence of reduced bone mass is fracture, and data are now available which directly link growth rates in childhood with the risk of later hip fracture [9]. Studies of a unique Finnish cohort, in whom birth and childhood growth data were linked to later hospital discharge records for hip fracture, have permitted followup of approximately 7000 men and women who were born in Helsinki University Central Hospital between 1924 and 1933. Body size at birth was recorded and an average of 10 measurements were obtained of height and weight throughout childhood. Hip fracture incidence was assessed in this cohort using the Finnish hospital discharge registration system. After adjusting for age and sex, there were two major determinants of hip fracture risk: tall maternal height ($P < 0.001$) and low rate of childhood growth (height, $P = 0.006$; weight, $P = 0.01$). The effects of maternal height and childhood growth rate were statistically independent of each other and remained after adjusting for socioeconomic status. The data are compatible with endocrine programming influencing the risk of hip fracture. In addition, the observation that fracture subjects were shorter at birth but of average height by age 7 years suggests that hip fracture risk might be particularly elevated among children in whom growth of the skeletal envelope is forced ahead of the capacity to mineralize, a phenomenon which is accelerated during pubertal growth.

Physiological Studies of Endocrine Programming

To explore further the potential role of hypothalamic–pituitary function and its relevance to the pathogenesis of osteoporosis, profiles of circulating GH and cortisol were compared with bone density among groups of men and women whose birth records had been preserved. These studies revealed that birthweight and weight in infancy were predictors of basal levels of GH and cortisol during late adult life [10–12]. The levels of these two skeletally active hormones were also found to be determinants of prospectively determined bone loss rate. The data are compatible with the hypothesis that environmental stressors during intrauterine or early postnatal life alter the sensitivity of the growth plate to GH and cortisol. The consequence of such endocrine programming would be to reduce peak skeletal size, perhaps also to reduce mineralization, and to predispose one to an accelerated rate of bone loss during later life [10–12].

Maternal Nutrition and Neonatal Bone Mass

The fourth piece of epidemiological evidence that osteoporosis might be programmed stems from investigation of a series of mothers through pregnancy; maternal anthropometric and lifestyle characteristics were related to the bone mineral of their newborn offspring [13]. After adjusting for sex and gestational age, neonatal bone mass was strongly and positively associated with birthweight, birth length, and placental weight. Other determinants included maternal and paternal birthweight and maternal triceps skinfold thickness at 28 weeks. Maternal smoking, maternal energy intake at 18 weeks gestation, and high maternal physical activity, were negatively associated with neonatal BMC at both the spine and whole body. The independent effects of maternal and paternal birthweight on fetal skeletal development support the notion that paternal influences, for example, through the imprinting of growth-promoting genes such as IGF-2, contribute strongly to the establishment of the early skeletal growth trajectory, while maternal nutrition, body build, and lifestyle modify fetal nutrient supply and subsequent bone accretion, predominantly through influences on placentation.

Animal Models of Programming

Numerous animal experiments have shown that hormones, undernutrition, and other influences that affect development during sensitive periods of early life permanently program the structure and physiology of the body's tissues and systems. A remarkable example is the effect of temperature on the sex of reptiles [14]. If the eggs of an American alligator are incubated at 30°C, all the offspring are female. If incubated at 33°C, all the offspring are male. At temperatures between 30°C and 33°C, there are varying proportions of females and males. It is believed that the fundamental sex is female, and a transcription factor is required to divert growth along a male pathway. Instead of the transcription factor being controlled genetically by a sex chromosome, it depends on the environment, specifically temperature.

Organ systems in the body are most susceptible to programming during periods when they are growing rapidly. During the first two months of life, the embryonic period, there is extensive differentiation of progenitor cells, without rapid cell replication. Thereafter, in the fetal period, the highest growth rates are observed. Growth slows in late gestation and continues to slow in childhood. The high growth rates of the fetus compared with the child are mostly the result of cell replication; the proportion of cells which are dividing becomes progressively less as the fetus becomes older. Slowing of growth is a major adaptation to undernutrition. Experiments on rats, mice, sheep, and pigs have demonstrated that protein or calorie restriction of the mother during pregnancy and lactation is associated with smaller offspring. In general, the earlier in life that undernutrition occurs, the more likely it is to have permanent effects on body size [15]. Early in embryonic life, growth is regulated by the supply of nutrients and oxygen. At some point shortly after birth, growth begins to track. In humans, tracking is demonstrated by the way in which infants grow along centile curves. Once tracking is established, it is no longer possible to make animals grow faster by offering them unlimited food. The rate of growth has become set, homeostatically controlled by feedback systems. After a period of undernutrition, they will regain their expected size. This contrasts with the effects of undernutrition during intrauterine life, in which skeletal development is slowed and the peak skeletal proportions attained following the completion of linear growth are reduced.

The feeding of a low-protein diet to pregnant rats produces offspring that exhibit growth retardation in late pregnancy. This modulation of the maternal diet has been demonstrated to yield adult offspring who have lower bone mineral content and bone area compared with normal control offspring [16]. In addition, the low-protein diet *in utero* was associated with changes in the appearance of the growth plates among the aged male offspring. Studies on bone marrow stromal cells from the offspring of female rats maintained on normal or low protein have demonstrated alterations in total colony formation, alkaline phosphatase-specific activity, and responsiveness to growth hormone, IGF-1, and 1,25-$(OH)_2$ D_3.

Summary

Undemutrition and other adverse influences arising in fetal life or immediately after birth have a permanent effect on body structure, physiology, and metabolism. The specific effects of undernutrition depend on the time and development at which it occurs; rapidly growing fetuses and neonates are more vulnerable. Its effects include altered gene expression, reduced cell numbers, imbalance between cell types, altered organ structure, and changes in the pattern of hormonal release and tissue sensitivity to these hormones. Evidence is now accumulating from human studies that programming of bone growth might be an important contributor to the later risk of osteoporotic fracture. Body weight in infancy is a determinant of adult bone mineral content, as well as of the basal levels of activity of the GH/IGF-1 and HPA axes. Epidemiological studies have suggested that maternal smoking and nutrition during pregnancy influence intrauterine skeletal mineralization. Finally, childhood growth rates have been directly linked to the risk of hip fracture many decades later. Further studies of this phenomenon are required in order that effective preventive strategies against osteoporosis throughout the life course may be delineated and more effectively applied.

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