

AETIOLOGY AND PATHOGENESIS OF FEMALE OSTEOPOROSIS

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GENERAL REMARKS

The definition of osteoporosis refers mainly to the increased frailty of the bone. Since this normally increases with increasing age, so that every second woman over the age of 75 presents with osteoporosis, the pathophysiological explanations for this disease include not only pathological processes, but also physiological events such as the menopause and age-related changes. Accordingly, high age and female gender are included among the "risk factors" for osteoporosis.

Whether osteoporosis will occur or not, depends mainly on the peak bone mass that is formed during the growth phase, and on the rate at which this bone mass is destroyed again after the menopause and in old age. In every phase of life, it is the ratio between osteoblast bone formation and osteoclast bone destruction that determines whether the bone mass remains unchanged, increases or decreases. It is not always known which of the factors that are known to cause osteoporosis tend to inhibit bone formation and which ones promote destruction. Formation and absorption are always closely linked with each other. Physical inactivity, for example, inhibits formation during adolescence, probably accelerates destruction in young adult years, and in old age it appears to be an

independent risk factor for osteoporosis and fractures of the femoral neck without any pathophysiological explanation for this. Therefore, the pathophysiology must be explained separately for every age, and always with a view to the multi-factorial influences. Those factors that have a stronger influence on the mechanical quality of bone and less on the bone mass are less well known.

GENETIC FACTORS

The genetic factors determine the variability of bone mass in adults to an extent of 50–80 %. This is indicated by the concordant bone density values in twin studies, or the correlation between the bone mass of young women and their premenopausal mothers. In general, the presence of osteoporotic fractures in a family history predicts osteoporosis in the progeny with a high probability. Thereby, the genetic body build plays an important role; a slight body build is associated with an increased risk of osteoporosis and fracture [1]. Some of these genetic factors have been researched, such as e.g. the influence of the allele of the gene for the vitamin D receptor and for collagen type I (COLIA1) on bone mass and on the rate of bone destruction [2]. Positive correlations between genotype and bone mass have been found mainly in

premenopausal women, since environmental influences and the influences of lifestyle tend to blur the genetic influence in later phases of life. The genotype for the vitamin D receptor may be noticeable only if calcium intake is very low, or it may be effective only if a certain estrogen receptor is present. The influence of genetic variants for other substances on bone density has also been shown, e.g. the genes for osteocalcin, TGF β 1 and IGF-1.

DISORDERS OF BONE FORMATION

An absolute or relative increase in bone absorption with reference to bone formation leads to deficient growth or loss of bone. Examples for weak bone formation include hypogonadism, corticoid therapies, reduced secretion of growth factors, age effects; examples for increased bone absorption include estrogen deficiency, hyperparathyroidism and hyperthyroidism. The sequence of bone absorption and bone formation is the same in trabecular and cortical bone. The destruction of unstressed horizontal trabeculae is specific to the trabecular bone, whereby the lateral support for the trabeculae is lost and the trabeculae are interrupted, which ultimately results in lower mechanical resistance. Thereby, failure of the vertebral bone is preceded by hundreds of microfractures that cannot all be repaired by the normal healing processes, as would be the case in healthy bone. In the cortical bone, deficient formation in the form of enlarged Haversian canals may occur, leading to increased porosity and frailty of the tubular bones in old age.

INFLUENCE OF BONE GEOMETRY

The geometry of the bone at risk of fracture plays a clear role, although it does not receive much attention in clinical practice. A long femoral neck has a higher fracture risk than a short one, since the vertical stress on the femoral neck increases and the adduction forces, which are already overdeveloped in the human body, are enhanced. Small vertebral bone is also associated with a higher risk of fracture, since smaller end plates are subject to higher pressure.

PATHOGENETIC FACTORS IN CHILDHOOD

Apart from the genetic factors, the development of bone mass during growth is also determined by nutrition, the presence of sex hormones and physical exercise, especially in childhood and adolescence [3]. Deficiencies in one or more of these factors lead to reduced bone mass in young adulthood, and thus to osteoporosis. This includes malnutrition, being bedridden for longer periods, both possible due to serious illness, and deficient gender development, in extreme cases even primary hypogonadism. Several such negative aspects are joined in anorexia nervosa, which is characterized by malnutrition, hypogonadism (primary or secondary amenorrhea) and stress-induced hypercortisolism. Thus, it inevitably results in osteoporosis. Excessive physical exercise can have the same effect, especially in top female athletes and ballet dancers.

PATHOGENETIC FACTORS IN ADULTHOOD

The important factor for the occurrence of osteoporosis at a later age is the "peak bone mass", which is reached in young adulthood. The lower this peak bone mass, the greater is the risk of later osteoporosis, even if the bone destruction due to menopause and age is normal [4].

The peak bone mass is determined in more or less equal parts by the following five factors: body weight and height, which in a person with good nutritional status and good health are genetically determined, physical exercise in adolescence (effects on the spine) and as an adult (effects on the femoral neck), family history of osteoporosis, again genetically determined, calcium intake and genotype of the vitamin D receptor [5]. Accordingly, the cause of osteoporosis in a healthy postmenopausal woman may well lie in a too low peak bone mass that is the result of an unfavorable constellation of these factors, with subsequent normal postmenopausal bone destruction.

Naturally, premature bone destruction during this phase of life is possible and can cause osteoporosis. As perfect examples for this, premature menopause and ovariectomy without hormone replacement must be mentioned; the latter accelerates bone turnover and thus bone absorption due to the abrupt onset of estrogen deficiency, and almost always results in osteoporosis. Any other serious illness that impairs the nutritional status, reduces calcium absorption or accelerates bone destruction, can also lead to osteoporosis. This applies to gastrointestinal and endocrinological diseases. Lactase deficiency inhibits the absorption of cal-

cium from dairy products; malabsorption results in deficient calcium and vitamin D absorption; the status after partial gastrectomy also results in deficient calcium absorption; chronic polyarthritis through inflammatory factors and cortisone treatment; Crohn's disease also has an influence due to absorption disorders; hyperthyroidism causes accelerated bone turnover; diabetes probably leads to deficient bone formation; hypercortisolism – Cushing's syndrome or treatment with corticosteroids – acts mainly by inhibiting bone formation. Multiple myeloma not only stimulates the osteoclasts, there is also a lack of any osteoblast reaction, which quickly results in osteoporosis and pathological fractures.

Nicotine and alcohol abuse have a less serious but still significantly negative effect on bone mass. Since they are often associated with inadequate nutrition, lack of physical exercise, relatively low body weight and premature menopause, they act mainly as partial factors in a bundle of pathophysiological causes of osteoporosis, all of which have their mutual origins in a poor life hygiene. Here, too, a genetic predisposition for osteoporosis as discussed in explanation of low peak bone mass may be significant. An accumulation of lifestyle-related factors increases the risk of a genetic predisposition for osteoporosis taking effect and leading to osteoporosis. On the other hand, only optimal life hygiene allows a favorable genetic profile to take full effect.

PATHOGENETIC FACTORS IN THE POSTMENOPAUSE

With the almost total loss of estrogens (approx. 90%) associated with the meno-

pause, a physiological destruction of bone mass commences that is characterized by more intensive bone absorption. On the one hand, the osteoblasts are no longer stimulated by estrogen, which results in a decrease in growth factors (IGF1 and TGF β), and on the other hand the absorption-enhancing cytokines increase, e.g. interleukin 1. In the first five years, this process accelerates to a rate of about 3% per year in the trabecular bones. After that, it is similar to the rate in the cortical bone, which is 0.5–0.7% per year. In 25 % of women, the lab tests for bone absorption rise to significantly increased values compared with the premenopause. Thereby, there is a correlation between the intensity of bone absorption, measured using biological markers, and the subsequent bone loss, as well as the later risk of fracture. The higher the bone turnover and the faster the bone destruction is, the higher the risk of later osteoporotic fractures [6, 7]. Since the loss of estrogens may start before the menopause, there is also a possibility of premenopausal bone destruction. The faster the estrogen secretion decreases, the more the bone turnover and thus destruction increases. At greater body weights, a residual estrogen secretion is maintained due to the fatty tissue, which counteracts the increase in bone absorption. Thus, there is also a correlation between body weight, postmenopausal estrogen level and bone mass. Low body weight, on the other hand, accelerates the destruction of bone and the development of osteoporosis [8].

Postmenopausal bone destruction affects both trabecular and cortical bone, but in the case of the former it is accelerated during the first years. Osteoporotic fractures of the vertebral bone occur in the middle of the seventh decade, and are the classical frac-

ture in postmenopausal osteoporosis. Thereby, mainly trabecular bone is affected. Although estrogen deficiency is the predominant pathogenetic factor for bone loss during this phase of life, it alone cannot cause postmenopausal osteoporosis. At this point, attention must once more be drawn to the concurrence of several risk factors that either cause a low peak bone mass or help to accelerate bone destruction. However, nutrition, calcium intake and physical exercise play virtually no role in the early menopause; only a significantly low calcium intake of less than 400 mg per day could contribute additionally towards the acceleration of bone destruction.

Although the fracture risk can be evaluated with a bone density measurement, this does not fully register the loss in mechanical quality of the bone. In fact, an existing fracture of a vertebral bone doubles the risk of further fracture regardless of the bone density, since it indicates a reduction in mechanical resistance, although the pathogenetic mechanism is not fully explored yet [9]. Estrogen deficiency appears to be involved in this process, since replacement therapies and even raloxifene therapy reduce the incidence of fracture much more than might be predicted by the modest effect on bone density.

PATHOGENETIC FACTORS IN OLD AGE

With increasing age, there are new pathogenetic mechanisms that apply equally to both sexes and no longer affect primarily the trabecular bone. First, the osteoclast function is reduced, partly as a result of age-related de-

creases in growth hormone. This slows down the permanent healing process that corrects the countless microscopic and asymptomatic fatigue fractures, which results in a deterioration of mechanical resistance.

In addition, an increase in vitamin D deficiency is observed, which was initially found among the inhabitants of old people's homes and explained by a lack of sunshine. Later, it was then discovered that even healthy older persons and younger adults can have fairly low vitamin D levels without any associated signs of osteomalacia [10]. However, there is a negative correlation with the PTH level, which starts to increase continuously as soon as the 25-OH vitamin D level drops below 100 nmol/l [11], and which reaches a pathological level if the latter drops to below 10 nmol/l. This trend, which is referred to as "secondary hyperparathyroidism", is probably the result of reduced calcium absorption, but it has also been attributed indirectly to estrogen deficiency [12], and it contributes towards acceleration of bone destruction. The age-related decrease of 1 α -hydroxylase in the kidney may also be a contributing factor. Thus, both the reduced vitamin D level and the increased PTH level show a significant correlation with the bone density of the femoral neck and the risk of fractures of the femoral neck in some studies [13].

The typical osteoporotic fracture in this phase of life is the femoral neck fracture. It occurs mainly at an age of over 80, and it is primarily the result of the degeneration of cortical bone, which is associated with a tendency towards reduced vitamin D levels and secondary hyperparathyroidism, referred to as osteoporosis type II [14].

The relative vitamin D deficiency becomes particularly noticeable if the

calcium intake is low, as is more and more the case with increasing age. The protein intake, which is often inadequate, would also appear to be important. Proteins stimulate the secretion of growth factors such as IGF, and thus the formation of bone. A nutrition lacking in protein thus decreases the production of IGF and the activity of the osteoblasts; on the other hand, protein supplements increase the bone density of the femoral neck. A diet that is deficient in proteins, calcium, vitamin D and presumably other nutritional constituents as well must be viewed as a major pathogenetic factor for osteoporosis in old age [15]. The well-known correlation between body weight and bone density can also be regarded from this viewpoint.

With increasing age, the incidence of concurrent illnesses that not only deteriorate the nutritional status but are also involved in the destruction of bones increases, as is the case in chronic polyarthritis or malignant disorders that accelerate bone absorption with the secretion of cytokines and PTHrP.

Another, less well-known factor that is still involved in this phase of life is the estrogen deficiency, which also affects men. A relatively high postmenopausal estrogen level – statistically associated with increased body weight – correlates with a lower osteoporosis risk, whilst a low body weight and low estrogen level again increases the risk [12]. In any case, body weight and height still play a significant role in this age group [16].

Whereas normally half of the bone mass is lost up to the age of 70–80 (in women up to two thirds), the mechanical resistance is reduced eight-fold in the same period of time. This age-related reduction in mechanical strength starts in the young adult, and is the

main cause of the fracture risk in old age. The fact that is impossible to measure it clinically limits the risk assessment to measurement of the bone density and the search for fractures that are already present. It also makes it more difficult to identify those pathogenetic mechanisms that weaken the mechanical resistance in particular.

The occurrence of an osteoporotic fracture of the proximal femur or humerus requires a fall; spontaneous fractures in a standing position are extremely rare. Therefore, the age-related fall risk is one of the pathogenetic factors of osteoporotic fractures in old age. It is due to the following factors: physical inactivity, disturbances of gait and vision, use of sedatives, medication with more than 4 drugs, urinary incontinence etc. [17]. Life in an old people's home appears to be particularly unfavorable, since it combines several factors in addition to the age-related bone loss: physical inactivity, lack of sunshine and thus vitamin D deficiency and secondary hyperparathyroidism, often inadequate nutrition, co-morbidity and medication.

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