PAPERS AND ORIGINALS

Clinical Significance and Pathogenesis of Osteoporosis*

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Summary

The development of osteoporosis with advancing age in man is a widespread if not a universal phenomenon. The average loss between youth and old age amounts to about 15% of the skeleton but involves a much larger proportion of trabecular than of cortical bone.

The principal clinical manifestation of osteoporosis is fracture, and three osteoporotic fracture syndromes can be defined: the lower forearm fracture, which predominantly affects women between the ages of 50 and 65; the fracture of the proximal femur, which affects both sexes over the age of 70; and the relatively rare vertebral crush fracture syndrome, which may present at any age but is most common in elderly women.

The lower forearm fracture rate is inversely related to the mean normal lower forearm x-ray "density" of the wrist, which falls by about 30% in the 15 years following the menopause. This process, which is associated with corresponding trabecular bone loss elsewhere in the skeleton, is associated with a corresponding rise in the fasting urinary calcium excretion. Some degree of negative calcium balance, and consequent bone resorption, probably occurs in everyone during the later part of the night because calcium absorption is completed within about three to five hours of a meal. In postmenopausal women, however, the sensitivity of the bone to parathyroid hormone appears to be increased, and their nocturnal negative calcium balance therefore comes to exceed the positive balance which can be achieved during the waking hours.

Femoral neck fractures in old people reflect the further progression of osteoporosis with advancing age since the fracture rate is inversely correlated with the mean thickness of the metacarpal cortex in the normal population. This progressive osteoporosis is associated with and could well result from a steady decline in calcium absorption which is at least partially attributable to vitamin-D deficiency and reversible on vitamin-D treatment.

The vertebral crush fracture syndrome represents a severe degree of spinal osteoporosis which may be associated with relatively normal peripheral bones. It probably results from an accelerated negative calcium balance which mobilizes trabecular bone preferentially. Some of the factors which may contribute to this accelerated negative balance have been identified and include a reduced rate of bone turnover, impaired calcium absorption, and low oestrogen activity as judged by vaginal smears, but there may well be others as yet unidentified.

Introduction

The term "osteoporosis" signifies a reduced volume of bony tissue per unit volume of anatomical bone. Osteoporotic bone differs in no other respect from normal, and occasional reports to the contrary (Little *et al.*, 1962) must at the present time be treated with reserve.

This working definition is satisfactory so far as it goes, but its practical implementation requires the existence of normal bone standards against which a reduction in bone volume can be established, and the definition of such standards is in turn complicated by the loss of bone that apparently accompanies ageing in both sexes and all races (Garn *et al.*, 1967). It is therefore necessary in any study of osteoporosis to consider first of all the nature, extent, and significance of the loss of bone that accompanies ageing.

Ageing and Osteoporosis

The first quantitative assessment of age-related bone loss was made by Trotter *et al.* (1960), when they determined the weight/volume ratio of young and old, male and female, white and negro skeletons and reported an overall skeletal loss between youth and old age of about 15%, slightly more in females than in males and slightly more in whites than in negroes. The variation between the different bones studied was considerable, but the downward trend occurred in all of them.

Many workers have subsequently confirmed this general observation by various techniques, including physical and

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histological measurements on bones at necropsy (Lindahl and Lindgren, 1962; Sissons *et al.*, 1967) and radiological measurements in life (Baylink *et al.*, 1964; Nordin *et al.*, 1965; Garn *et al.*, 1967). These data suggest that trabecular bone loses about 50% of its tissue during the ageing process, whereas the cortices of the long weight-bearing bones lose only about 5%. Since about 80% of the skeleton is composed of cortical bone and only 20% of trabecular bone (Gong *et al.*, 1964) these observations are compatible with the original data of Trotter *et al.*, (1960) that the overall skeletal loss with ageing is about 15%.

In order to establish more precisely the age and sex pattern of bone loss in the metacarpal we have carried out a study of normal men and women between the ages of 30 and 80. Cortical thickness and total diameter were measured with calipers on the x-ray film at the midpoint of the second metacarpal of the right hand (Barnett and Nordin, 1960) and the cortical and total areas were calculated on the assumption that the bones were tubular. The results are expressed as cortical area/total area ratios because this value is a function of bone "density" rather than bone mass and has a much smaller standard deviation than either of its components (see Table). This study shows that young women have higher cortical area/total area ratios than young men. After the age of 45 to 50 the values fall steeply in women but slightly, if at all, in men, so that the two lines cross over at about the age of 60 (Figs. 1 and 2). Male values are definitely reduced above the age of 70.

Mean and Ranges of Metacarpal Cortical Area and Total Area Measurements in Normal Young Men and Premenopausal Women

Variable	Mean	Standard Deviation	Coefficient of Variation
<i>Females</i>			
Metacarpal cortical area	43.1 mm ²	5.26 mm ²	12.2%
Metacarpal total area	50.7 mm ²	7.53 mm ²	14.9%
Cortical area/total area	0.856	0.067	7.9%
<i>Males</i>			
Metacarpal cortical area	57.1 mm ²	7.62 mm ²	13.3%
Metacarpal total area	72.3 mm ²	11.19 mm ²	15.5%
Cortical area/total area	0.795	0.07	8.8%

Thus osteoporosis develops with age in the whole population, at least in the Western world, though at different rates in men and women. It is far from clear, however, whether this process should be regarded as a disease in its own right or simply as part of the "ageing process," whatever that may be. One way to answer this question is by considering the clinical significance of bone loss. A disease can be defined as a condition which impairs the physical or mental health and well-being of the subject. A rising blood pressure is a feature of ageing, but there is ample evidence that this hypertension is associated with an increased morbidity and mortality, particularly from cardiovascular and renal disorders, and it is therefore surely a "disease." So also with the osteoporosis of ageing; it too increases morbidity and mortality by predisposing the subject to certain fractures, and it therefore seems reasonable to regard it as a disease.

Osteoporosis and Fractures

It has been known for a long time, and certainly since 1824 (Cooper), that fractures in the aged are attributable to a loss of bone strength with ageing, but it is only recently that good epidemiological data have become available to show the precise relationship between age and fracture rate. Two such studies in Sweden and Great Britain (Alffram and Bauer, 1962; Knowelden *et al.*, 1964) have shown that the rate of fracture of the lower end of the forearm rises steeply in women over the age of 45, with a possible levelling off at about the age of 70. As Newton-John and Morgan (1968)

FIG. 1—Metacarpal cortical/total area ratios in normal premenopausal and postmenopausal women (mean $\pm$ standard error).

FIG. 2—Metacarpal cortical/total area ratios in normal men (mean $\pm$ standard error).

pointed out, if there is a general loss of bone with age in the population as a whole, and if this loss of bone produces structural weakening then there might be expected to be a critical bone level below which the fracture risk would be significantly increased, and the fracture rate in the population would then rise as more and more individuals fell below this critical level. It has now become possible to test this general hypothesis with specific data.

In order to test the relation between the mean bone status of the population and the fracture rate we first compared the metacarpal cortical area/total area ratios of normal men and women at different decades (derived from the data in Figs. 1 and 2) with the annual age-specific wrist fracture rate derived from the data of Knowelden *et al.* (1964). Though there was an inverse relation between the metacarpal cortical area/total area ratio and the wrist fracture rate in women, the same relationship did not exist in men. This meant either that the hypothesis was wrong or that the metacarpal cortical area/total area ratio was not an adequate model to represent the degree of osteoporosis of the lower forearm.

We have therefore compared the ulna and radius "density" values in our normal men and women (Nordin *et al.*, 1970a) with the wrist fracture rates and found the relationships shown in Fig. 3. It is clear that the fracture rate in the normal population is inversely related to the mean "density" of the lower end of the radius. Only one value is indicated for the males because neither the wrist fracture rate nor the

forearm "density" changes much with age in the male sex. This one value, however, indicates that the relation between fracture rate and lower forearm bone "density" is comparable in men and women, as would be expected if "density," strength, and fracture rate were simply related.

The same procedure has been applied to the hip fractures. The mean metacarpal cortical area/total area ratios in our normal men and women by decades were compared with the corresponding hip fracture rates derived from the data of Knowelden *et al.* (1964) (Fig. 4) and an inverse relation observed between the fracture rate and metacarpal cortical thickness. It will be noted that the male and female data are comparable, though there is a slight tendency for the hip fracture rate to be higher in males than in females for any given cortical area/total area ratio.

These data suggest that the metacarpal cortex reflects the bone loss which predisposes to fractures of the proximal femur, and this tends to be confirmed by the low metacarpal cortical area/total area ratios found in actual hip fracture cases (Fig. 5). Most hip fractures seem to occur in elderly subjects with a severe degree of osteoporosis, though some fractures occur with normal bones and are no doubt attributable to genuine trauma.

It has proved difficult to find any quantitative way of expressing the bone loss in the femur itself in a manner which reflects the fracture rate. It is clear, however, from the study of Nordin *et al.* (1965) that the rise in fracture rate with age is not associated with any substantial thinning of the femoral cortex, nor have we found the femoral cortex to be abnormally thin in hip fracture cases. There is no fall with age in the thickness of the calcar femorale (the condensation of bone at the inferior cortex of the femoral neck immediately above the lesser trochanter), though it is significantly reduced in proximal femur fracture cases compared with age-matched controls (Nordin, 1966). This does not necessarily mean that the fracture of the proximal femur should be directly attributed to weakness of the calcar femorale; perhaps subjects with a thin calcar are more liable to femoral neck fracture when ageing osteoporosis has depleted the bone of internal trabeculae.

These data leave little room for doubt that the rise in fracture rate which accompanies ageing is attributable to age-related osteoporosis, and imply that this bone loss should be regarded as a disease, the cause of which deserves further investigation. Moreover, since fracture is presumably a function of absolute bone quantity and bone strength, it seems reasonable to assess the bone status of the elderly relative to that of normal young persons, whose fracture rate is low, and not to regard bone status as "normal" simply because it falls within the normal range for the age of the individual concerned (Smith *et al.*, 1970).

Crush Fracture Syndrome

In addition to the long-bone fractures, there is also the syndrome of vertebral biconcavity and compression, which is the only one that most clinicians recognize as osteoporosis. It is not certain what is the relation between this condition and the osteoporosis of the elderly described above, or what terminology can appropriately be used to distinguish it from simple osteoporosis, if indeed such a distinction is necessary. Is this a more severe form of age-related bone loss or a different disease?

The measurement of peripheral bone status in patients with the crush fracture syndrome has yielded inconclusive results. Whether the measurements are applied to the radius, ulna, or metacarpal, we find that though young patients with the crush fracture syndrome have values below the normal range for their age, older subjects generally fall within the normal range for their age, though often in the lower half (Fig. 6). If these

bone measurements reflect the degree of osteoporosis in the vertebral bodies it would be difficult to understand the compression fractures, for Weaver and Chalmers (1966) have shown that the strength of vertebrae is directly related to the amount of bony tissue they contain. Spinal densitometry, however (Nordin *et al.*, 1968), does suggest that crush fracture cases generally suffer from a more severe degree of spinal osteoporosis than other individuals of the same age (Nordin *et al.*, 1970b). Moreover, crush fracture cases according to

FIG. 3—Relation between ulna and radius "density" values in normal men and women by decades compared with the corresponding annual lower forearm fracture rates.

FIG. 4—Relation between the mean metacarpal cortical/total area ratios by decades in normal men and women and the corresponding intertrochanteric hip fracture rates.

FIG. 5—Metacarpal cortical/total area ratios in women with hip fractures compared with the normal range.

Schenk (personal communication) show severe osteoporosis on iliac crest biopsy; and it is known that iliac crest and vertebral status are related (Bell *et al.*, 1967).

The crush fracture syndrome therefore represents a severe degree of osteoporosis in the spine not necessarily associated with an equivalent degree of osteoporosis in the peripheral bones. If the hypertension analogy invoked above is extended, this syndrome is perhaps comparable with malignant or accelerated hypertension. Accelerated may be a particularly appropriate term because the relation between the vertebral and the peripheral bone status may well depend on the rate at which osteoporosis develops. If osteoporosis is in fact a disturbance in calcium homeostasis, as Nordin (1960, 1961) and Heaney (1965) have suggested, it might be expected that trabecular bone, with its large surface/volume ratio, would be mobilized preferentially in response to the calcium demands of the organism. The vertebral bodies, which consist almost entirely of trabecular bone, would be particularly vulnerable in this situation. This would also explain why the crush fracture syndrome is occasionally seen in relatively young women with a high urinary calcium, very severe spinal osteoporosis, and normal peripheral bones. Such cases probably go on to develop peripheral osteoporosis, but in the early stages peripheral bone loss lags behind the resorption of the vertebral bodies.

Pathogenesis

Though osteoporosis had been recognized as a histological entity for at least 50 years, it was Albright *et al.* (1941) who first clearly defined the crush fracture syndrome which is recognized today and which they attributed to a reduced rate of new bone formation associated with osteoblastic insufficiency and inadequate synthesis of the collagenous component of bone. Their reasoning was clearly based on the assumption that calcium deficiency must cause osteomalacia and could not therefore be the cause of osteoporosis.

Nordin (1960, 1961) subsequently pointed out that experimental data available in the literature indicated that simple calcium deficiency caused osteoporosis (not osteomalacia) in animals and that for osteomalacia to occur there must be severe vitamin-D deficiency or some other reason for lowered plasma calcium and/or phosphorus levels. This has since been re-confirmed in animal experiments performed by a number of different workers—for example, Scott *et al.* (1961) and Campbell and Douglas (1965). The question is, of course, whether these animal experiments are relevant to the osteoporosis which develops in women over the age of 50, the osteoporosis that affects both sexes over the age of 70, and the crush fracture syndrome (clinical osteoporosis) which occurs at all ages but mainly in elderly women. Is there any evidence of low calcium intake, malabsorption of calcium, or obligatory hypercalciuria in any of these syndromes?

POSTMENOPAUSAL OSTEOPOROSIS

It is reasonably certain that the loss of bone experienced by women between about 50 and 65 years of age is related to the menopause. This cannot be conclusively established by metacarpal x-ray morphometry because the loss of bone from the metacarpal is relatively slow (Fig. 1) and the technique relatively insensitive. It is strongly suggested by spinal x-ray densitometry, however (Nordin *et al.*, 1968), and has been confirmed by Meema (1966), Davis *et al.* (1966), and others using peripheral bone densitometry.

The cause of this osteoporosis is not simple dietary insufficiency (Garn *et al.*, 1967; Smith *et al.*, 1968), but this would hardly be expected since there is no reason to suppose that women consume less calcium immediately after the menopause than before it. Nor is there a sufficient fall in calcium

FIG. 6—Metacarpal cortical/total area ratios in normal women and women with crush fractures.

FIG. 7—Fasting urinary calcium excretion in mg/100 ml of glomerular filtrate (approximately equal to mg/minute) in normal premenopausal and postmenopausal women.

FIG. 8—Fasting urinary calcium excretion in mg/100 ml of glomerular filtrate (approximately equal to mg/minute) in normal men.

absorption in women at this time to account for a significant negative calcium balance (Bullamore *et al.*, 1970).

So far as obligatory calcium loss is concerned, the 24-hour urine calcium of postmenopausal women does not differ significantly from that of premenopausal women (Bulusu *et al.*, 1970). The fasting urinary calcium of postmenopausal women, however, is significantly raised (Fig. 7) and no corresponding rise in calcium excretion occurs in men (Fig. 8). Though this "hypercalciuria" is only slight, it is sufficient to explain the

bone loss which follows the menopause in the normal female population. Thus if the average skeletal loss between the ages of 50 and 70 is 10% of the skeleton, this would represent about 100 g of calcium over 20 years, or 5 g per annum. This is equivalent to 100 mg per week or about 15 mg per day. It is not surprising that this small increase in calcium excretion cannot be detected in 24-hour urine collections or in calcium balance studies, but it does appear to show up in the fasting state and is compatible with the increased fasting calcium excretion by postmenopausal women shown in Fig. 7. Moreover, since it is reasonably certain that the absorption of calcium after an average meal of 250 to 300 mg is completed within about three to five hours (Birge *et al.*, 1969), it is clear that calcium excretion during the later part of the night and early morning must represent a net loss from the body. This could come from the extracellular fluid, but we have been unable to detect any overnight fall in plasma calcium in any sex or age group. It therefore seems that most of the calcium excreted in the urine during the night must constitute a net loss from the tissues, and probably represents the amount of calcium resorbed from bone by the parathyroid hormone in order to maintain the plasma calcium concentration during the night.

In young men and women this overnight loss is reduced to a minimum by the action of the parathyroid hormone on the renal tubular reabsorption of calcium (Nordin and Peacock 1969); the net loss of calcium from the body is therefore small and the bone resorbed during the night is probably replaced by day. The so-called nutritional "steady state" is in fact a continuous ebb and flow of calcium, and presumably other nutrients, in and out of the body. If the overnight or early morning loss of calcium is increased, however, it may exceed the amount that can be restored to the skeleton during the day, and this is probably what happens in the postmenopausal period. Even if bone resorption can be completely suppressed (which is unlikely) the maximum positive calcium balance that can be achieved by day must be limited by the rate of bone mineralization—which is about 100-150 mg per 12-hour period. This is therefore the maximum negative calcium that can safely be incurred at night and which we suspect is exceeded in postmenopausal women.

To explain the increased nocturnal bone resorption of postmenopausal women, one has to understand the crucial role of the parathyroid hormone in the production of osteoporosis. Burkhardt and Jowsey (1967) and Jowsey and Raisz (1968) showed that osteoporosis cannot be produced in parathyroidectomized animals either by immobilization or calcium deficiency, and it is therefore inherently probable that parathyroid hormone is also involved in the slow bone resorption which characterizes postmenopausal osteoporosis. It is well known that oestrogenic hormones tend to inhibit bone resorption (Lindquist *et al.*, 1960), and it is possible that this is due to an inhibition of the effect of parathyroid hormone on bone. In tissue culture experiments with five-day mouse calvaria Nisbet and Nordin (unpublished) found that stilboestrol diphosphate inhibits the bone-resorbing action of parathyroid hormone (Nordin *et al.*, 1970b). If this can be confirmed with the natural oestrogens it will support the suggestion of Heaney (1965) that osteoporosis is in a sense attributable to an altered end-organ sensitivity to parathyroid hormone. In other words, postmenopausal osteoporosis is due to increased bone resorption in the fasting state attributable to loss of the protective action of oestrogenic hormones against parathyroid hormone-induced bone resorption. This explains the rise in plasma calcium after the menopause and its reduction by oestrogenic hormones (Young and Nordin, 1967; Young *et al.*, 1968; Riggs *et al.*, 1969). It is central to this concept that oestrogens should not inhibit the stimulating action of parathyroid hormone on calcium absorption from the gut or calcium reabsorption by the renal tubule, nor do they appear to do so.

SENILE OSTEOPOROSIS

After the age of about 70 bone loss not only continues in women but develops in men as well (Figs. 1 and 2). It might be argued that the postmenopausal factors mentioned above continue to operate in women, and that the gonadal insufficiency is at this time operating in the male sex as well. This is possible, but since the 24-hour urine calcium tends to fall rather than rise in this age group (Bulusu *et al.*, 1970) we think this explanation unlikely. We have noted, however, a pronounced fall in calcium absorption in normal men and women over 70 (Bullamore *et al.*, 1970), and this appears to be the most likely explanation of senile osteoporosis at the present time.

In the elderly subjects we have so far treated with quite small doses of vitamin D calcium absorption has risen in nearly every case, which indicates that this malabsorption is probably due to vitamin-D deficiency. This deficiency no doubt arises because there is so little vitamin D in any food except fish oils and fortified margarine, which many people do not eat. Solar irradiation of the skin is of course believed to be the main source of vitamin D, but there is not much sunlight in our northern industrial cities, and in any case people become increasingly housebound as they grow older. This country has virtually abolished rickets by fortifying baby foods but has done nothing similar for old people, among whom vitamin-D deficiency is probably widespread. At present it passes unnoticed until severe enough to cause osteomalacia, which is not uncommon among old people in Scotland at least (Anderson *et al.*, 1966; Chalmers *et al.*, 1967), but in the meantime it is probably responsible for or at least aggravates the steady deterioration in bone status which we tend to accept as an ageing process.

CRUSH FRACTURE SYNDROME

It remains to consider the special type of osteoporosis characterized by spinal crush fractures and biconcavity, which is so widely recognized as a clinical syndrome and which is really a particularly severe and relatively rare form of a common disorder. In seeking the cause of this accelerated form of osteoporosis we have measured dietary calcium intake, calcium absorption, bone turnover, and calcium excretion. Neither calcium intake nor calcium excretion generally differs in these cases from the corresponding values in normal individuals of the same age and sex, though young patients with severe spinal osteoporosis may have a very high urine calcium. Both calcium absorption and bone mineralization, however, appear to be reduced in crush fracture cases.

The fractional hourly rate of calcium absorption after the administration of an oral dose of radiocalcium in 20 mg of calcium carrier (Bullamore *et al.*, 1970) to women with crush fractures is shown in Fig. 9. It is clear that many of these cases have malabsorption of calcium, as reported by Caniggia *et al.* (1963), and we have confirmed this repeatedly by balance studies. The rate of bone mineralization calculated by the method of Burkinshaw *et al.* (1969) in elderly women with and without crush fractures, compared with the normal mean value, is given in Fig. 10. These data show that the mineralization rate also tends to be low in crush fracture cases, at least in women; which recalls the original suggestion of Albright *et al.* (1941) that osteoporosis was associated with a low rate of bone formation.

Both malabsorption of calcium and a low rate of bone formation will contribute to the development or acceleration of osteoporosis. Malabsorption of calcium must tend to produce negative calcium balance and increased bone resorption, and a low rate of bone formation must reduce the skeleton's ability to replace bone that is destroyed. These factors are probably sufficient to explain the crush fracture syndrome, but there may also be an element of gonadal insufficiency in

FIG. 9—Fractional hourly calcium absorption measured with radiocalcium in women with osteoporosis and crush fractures.

FIG. 10—Bone mineralization rates (in mg Ca/kg/day) in crush fracture and non-crush fracture men and women. The horizontal line represents the normal mean.

these cases, since we have also found (Nordin *et al.*, 1970b) that the vaginal cornification index is often very low. In fact one might make the general statement that negative calcium balance is unlikely to occur in the presence of normal gonadal function at any but the lowest calcium intakes because bone resorption is kept by the gonadal hormones to a minimum and the parathyroid hormone acts mainly on gut and kidney. It is the combination of calcium deficiency with reduced gonadal function that so easily leads to bone resorption, as Ferguson and Hartles (1970) found in experimental animals.

Low gonadal activity may even be responsible for the low rate of bone formation we observed in the crush fracture cases (as Albright and his colleagues originally predicted in 1941), but this does not mean that the osteoporosis is due to impaired osteoblastic activity. Rather, persons with low bone formation rates are more vulnerable than others when bone resorption has occurred, but postmenopausal bone resorption at least is due to an increased sensitivity of the bone to parathyroid hormone secretion rather than to "calcium deficiency." Just as iron-deficiency anaemia is seldom due to dietary iron deficiency per se but generally to blood loss or malabsorption of iron, so osteoporosis is probably seldom due

to simple dietary deficiency of calcium but generally arises because of excessive calcium loss from the body (in the post-menopausal period) or malabsorption of calcium (in old age). None the less, osteoporosis is probably due to "negative calcium balance" in the widest sense of that term.

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