Osteoporosis: The Orientation of Future Basic Research

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INTRODUCTION

In the past 10 years there has been a significant increase in the interest in osteoporoses of various types. This is manifested by a large increase in the number of publications concerning the clinical and fundamental aspects of the disease. Out of this mass of work a pattern is emerging. The pattern reveals the route which future productive work will follow and, in fact, is already following. The orientation of this presentation is histopathophysiologically. Significant clinical aspects of interests to many will be omitted.

In order to present the emerging pattern briefly and pungently some basic ground must be reviewed so that the writer and the reader are semantically in tune. This is necessary because the very term, osteoporosis, means different things to different people. We will be concerned from now on with a limited aspect of the problem of genesis of the osteoporoses: the relative alterations in bone formation and resorption that are immediately responsible. The more fundamental factors which are in turn responsible for the immediate factors are more capably handled by other investigators.

First the concept of skeletal balance must be presented.

SKELETAL BALANCE

A) Consider all the bone in a single human skeleton. If the volume of the marrow spaces, the vascular channels and the lacunar and canalicular spaces were subtracted, the remainder will be the total absolute bone volume of this skeleton. In a so-called standard man this volume amounts to about 1400 cc. It is preferable that the total amount of bone in any given skeleton be thought of as a volume rather than as a weight because in a given unit volume of bone the weight may vary as the result of variations in the amount of mineral deposited in the bone matrix. As far as is known the amount of matrix in a unit volume of bone does not vary throughout the life history of the unit volume.

The result of these facts is that a given absolute unit volume of bone implies a proportional amount of matrix present in the unit volume, and implies that regardless of how much variation there may be in the degrees of mineralization, the matrix is constant both in volume and in mass.

B) Bone is formed through the actions of cells known as osteoblasts. The osteoblasts form bone matrix. Mineral is subsequently deposited in the matrix, but the prior existence of the matrix is essential for this. Therefore, the direct result of osteoblastic activity is bone matrix. An indirect and necessarily subsequent event is mineralization of that matrix.

If we wish to measure the result of osteoblastic activity, we must measure the volume of bone matrix formed in unit time. This is a true measure of osteoblastic
activity and is not subject to unpredictable variations or qualifications by disease states which affect the degree of mineralization of matrix.

C) Bone is destroyed by cells known as osteoclasts. Just as bone formation is the direct result of osteoblastic activity, and of no other type of biological activity, so bone destruction is the direct result of osteoclastic activity and of no other type of activity.

D) Osteoblastic activity is therefore skeletal anabolic activity and osteoclastic activity is skeletal catabolic activity. This may be simply written as the A/C ratio.

E) Skeletal balance is the dynamic state of the total bone volume. As with nitrogen balance, a positive skeletal balance means net accretion of bone matrix and a negative skeletal balance means net loss of bone matrix. Skeletal balance is therefore more than unity, or less than unity. While shifts in the mass of bone mineral of like sign usually accompany shifts in skeletal balance, they do not

![Schematic of skeletal balance](image)

**Figure 1**

Skeletal balance: A schematic representation of skeletal balance. The amount of fluid in the container represents the amount (absolute bone volume) of bone in the skeleton. When new material is constantly being poured in (anabolism) and old material is constantly flowing out (catabolism), then the total amount of fluid — or bone — is the result of the past state of balance between inflow and outflow. Whether the volume of fluid is changing or constant at any one time depends on the balance between inflow and outflow at that time. This is the idea embraced by the term: skeletal balance.

Too little fluid (analogous to osteoporosis) may occur as the result of increased outflow, of decreased or arrested inflow, or of unequal increase in both.
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always do so. Therefore methods which measure the total volume of bone matrix will always be correct indicatrixes of skeletal balance. Methods that measure the mineral skeletal mass on the other hand will sometimes be in error. (Fig. 1,2).

![Diagram showing the components of bone](image)

**Figure 2**

Schematic representation of a unit volume, or standard quantity of bone. Note that in all four cases illustrated the organic fraction of bone (collagen and cement substance) is the same in volume. The amounts of mineral and of water vary widely however. Water content is at its largest in newly formed osteoid, while mineral content is at its largest in micropetrotic bone. Because mineral is appreciably heavier than either water or the organic part of bone, an attempt to illustrate the present situations in terms of density lead only to confusion and obscure the true situation.

The volume of bone in a skeleton is the correct parameter of measurement for expressing and considering the events involved in the osteoporoses. This volume is dependent on the volume of organic matrix within very narrow limits and is not affected by differences in degree of mineralization.

**NEGATIVE SKELETAL BALANCE**

In the above terms a negative skeletal balance will, given sufficient time, lead to a decreased total absolute bone volume (as well as a decreased total bone mass). The mechanism by which skeletal balance may be negative is of interest, because there is more than one.

A) There may be increased catabolism with normal anabolism.
B) There may be decreased anabolism with normal catabolism.
C) There may be a simultaneous decrease in anabolism and increase in catabolism.
D) There may be unequal increase in both anabolism and catabolism.
E) There may be unequal decreases in both anabolism and catabolism.

**OSTEOPOROSIS**

As a working definition, let us define osteoporosis in morphological terms: a decreased total absolute bone volume. This of necessity also constitutes a decrease in total bone mass because matrix cannot be absorbed without absorption of the mineral normally found in the matrix.

Osteoporosis as defined above may then occur, in theory, by any of the five mechanisms outlined above.
How is osteoporosis supposed to occur in actuality? Obviously this depends on the disease in question. In osteogenesis imperfecta there is a congenital decrease in lamellar bone anabolism, while in hyperthyroidism there is an acquired increase in skeletal catabolism. In postmenopausal osteoporosis and in senile osteoporosis there is — supposedly — a decrease in skeletal anabolism. One current theory holds that a major factor accelerating skeletal anabolism is the supply of protein anabolic hormones, exemplified by testosterone and estrogen. Since the endogenous supply of these hormones is known to decrease with advancing age it was postulated that a related decrease in skeletal anabolic activity — meaning formation of bone matrix — necessarily follows, and this leads to the clinical syndromes termed postmenopausal and senile osteoporosis. This same theory holds that the protein catabolic hormones — the cortisone group — do not decrease, or do not decrease in proportion to the protein anabolic hormones. Since the protein catabolic hormones are supposed to be one of the factors affecting skeletal catabolism, osteoporosis would, in theory, be the inevitable result of these combined hormone shifts and effects.

This theory has not been proved. The related facts are these:

A) Estrogens do cause an increase in bone mass in mice and some birds, and originally analogy was made between these animals and man. The original observations were accepted without realizing that the increase in bone mass in these animals was due mostly to an increase in fibrous bone, not lamellar bone; while the disease of osteoporosis in man is the result of insufficient lamellar bone in the skeleton. Recently it was learned that there are major differences in the local and homoeostatic controls of fibrous and lamellar bone formation in man, so that an effect of a governing factor on one type does not necessitate a similar effect on the other type of bone.

B) Finally, and conclusively, the majority of humans given anabolic hormones do not produce more bone in their skeletons even after several years of continuous treatment; some humans treated with these hormones continue to become more severely osteoporotic; rarely does a case produce a demonstrable increase in bone volume and mass. Newer theories based on protein and calcium intake effects are now current and enjoy some clinical success.

C) Methods of measuring the quality of osteoporotic bone have had designed into them sufficient insensitivity to prevent recognition of at least two recently recognized bone diseases which are characterized by under- or over-mineralization of matrix. These diseases are feathering and micropetrosis. The methods referred to also had designed into them an inability to recognize a bone composed in part of overly mineralized and in part of undermineralized bone matrix, a combination which has been repeatedly found in aged adult axial skeletons in this laboratory with sensitive methods of evaluating bone quality. A number of other qualitative variables which might exist in osteoporotic skeletons have not been evaluated as yet — too new.

Accordingly the statement that the quality of bone found in human osteoporosis is normal cannot be critically accepted. The quality of osteoporotic bone may not be as grossly abnormal as it is in severe human osteomalacia, but it may be and often is abnormal to lesser degrees and in different respects.
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D) It is widely believed that a human osteoporotic patient must be in negative skeletal balance and thus in negative calcium balance. In spite of this belief, accurate balance studies are increasingly revealing that this is not necessarily so. Osteoporotic patients may be in negative calcium balance, or they may be in the balance region of unity, or they may actually be in positive calcium balance. Tracer studies have frequently revealed that calcium turnover is increased or normal, and less frequently indicated that calcium balance was negative as postulated. The essential fact overlooked is that skeletal balance as defined here need not always vary with calcium balance since calcium balance is affected by factors in addition to the state of skeletal balance.

AGE AND MEASURED OSTEOBLASTIC ACTIVITY

This laboratory is publishing the results of measurement of human osteoblastic activity in a series of cases from birth to over age 70. Osteoblastic activity is at a minimum at age 30 or so and thereafter increases. Osteoblastic activity is increasing during the time in life when most people are gradually losing absolute bone volume. Since the measurements reveal increasing osteoblastic activity at a time when the endogenous supply of protein anabolic hormone is known to be decreasing, there is only one conclusion: the protein anabolic hormones do not accelerate osteoblastic activity. On the other hand by similar measurements it has been possible to show that the cortisone group of hormones does indeed depress osteoblastic activity, often profoundly.

The measurements quoted, while not in agreement with the protein anabolic theory of the genesis of osteoporosis, are in agreement with the observed clinical behavior of patients’ skeletons under the influence of exogenous anabolic and catabolic hormones.

OSTEOPOROSIS: A SIGN, NOT A DISEASE

It is necessary to face the fact that not as much is known about osteoporosis as we thought. In fact, relatively little is known about the genesis, therapy, and nature of the disease when one strips speculation away to find the underlying core of hard facts.

It has been shown that there are at least five basic mechanisms by which a skeleton can go into negative balance.

Available data indicate that at least in so-called senile osteoporosis the cause must be an increase in osteoclastic activity. This increase is out of proportion to the measured increase in osteoblastic activity occurring after age 30.

It is probable that examples of each of the five possible mechanisms of osteoporosis exist in clinical practice. Their recognition will require that the individual interpreting data be aware of these possibilities and aware of the fact that the possibilities are definitely open. Methods need to be devised to investigate the mechanisms actually existing in a given case of osteoporosis.

Osteoporosis is not a disease. Instead it is a sign, the net result of some effect on skeletal balance. This effect is due to an alteration in osteoblastic activity,
osteoclastic activity, or both. These alterations in turn are caused by more subtle and more fundamental physiological alterations and it is the latter alterations and their causes that we must attempt to detect in the future. Otherwise we will not understand what causes the sign known as osteoporosis.

THE FUTURE OF OSTEOPOROSIS

When the fundamental factors governing osteoblastic and osteoclastic activities are found, osteoporosis will assume its proper place in our texts as the result of a disease rather than as a disease entity unto itself. Consideration of osteoporosis as a disease entity will die out. With its recognition as a sign will come the realization that the sign is due to a spectrum of etiologies rather than one, or two or such.

To understand the causes of osteoporosis attention must be directed in the future to quantitative osteoblastic and osteoclastic activity. It will be necessary to develop methods of measuring skeletal accretion and resorption, first under laboratory conditions, then under clinical conditions. It is likely that such methods will reveal a spectrum of osteoporoses of unexpected variety and complexity.

REFERENCES


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