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Correlations Between Radiological, Histological and Metabolical
Findings in Osteoporosis, Osteomalacia and Paget's Disease.

by

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Osteoporosis, Osteomalacia 及び Paget's disease
に於るX線診断学的組織学的及び代謝の相関

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び慢性の骨の脱灰性の病変は、ある症例ではX線写真で判定出来る。その診断は、Looser's areaや bone cyst 等の典型的なX線像の存在により容易である。そして、その鑑別診断はradiocalcium kinetic study によつて判定する事が出来る。

radiocalcium dynamics が正常であると云う事は osteoporosis の存在を示し、又 radiocalcium

dynamics value が増加している場合には osteoporosisを除外する事が出来、むしろ osteoproloma lacia や osteolysis を意味するものである。

したがつて典型的なX線像の変化を示さない脱灰性骨病変の鑑別にこれが非常に重要であると考えられる。

Many authors use the term "osteoporosis" to indicate the loss of bone mineral in any way caused. This is unjustified because osteoporosis is the condition of the skeleton in which the bone present per unit volume is decreased in amount but normal in composition. Really X-ray diagnosis of rarefying bone disease is difficult as the characteristic radiological images (bone cysts, osteolytic areas, Looser's zones etc.) are not always present. In most cases X-ray show only a reduced bone opacity and the diagnostical problem is deferred to the laboratory. But the routine methods (Ca and P level in plasma and urine, serum alkaline phosphatase) may give useless data from the diagnostical point of view. Negative biochemical tests are common over all to the bordering metabolic bone disease.

A well defined differential diagnosis of diffuse demineralizing bone disease, in which pathognomonic radiological signs are lacking, can to-day be rationally formulated.

Which are the best means for a correct diagnosis? For this purpose in recent years it has become increasingly more necessary to obtain fragments of bone tissue from which diagnostic data on the condition of the skeleton may be reduced.

We have practiced the NEEDLE BIOPSY OF BONE according to the technique of MAZABRAUD (CANIGGIA et al., 1965). The advantage consists in its easy handling and its perfect tolerance. Such technique is suitable to the study of the bone as a whole, and allows the examination of the compact and cancellous bone.

Let me present, for instance two radiograms concerning two patients affected by a diffuse demineraliz-

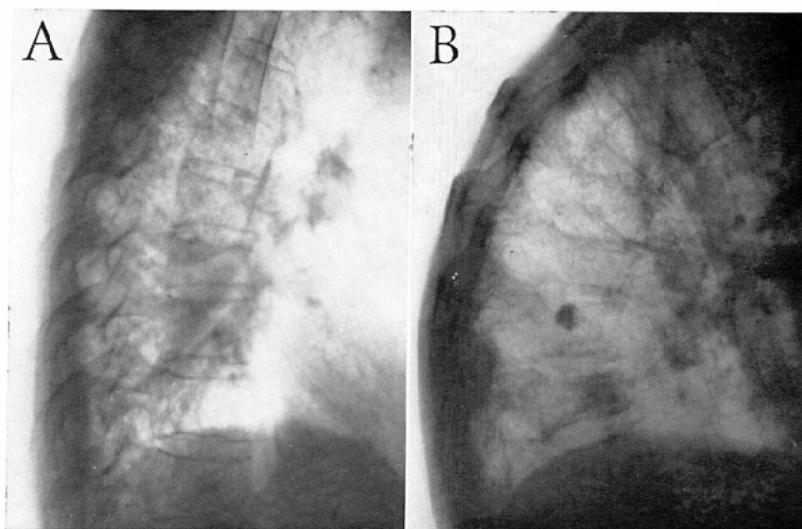


Fig. 1. Lateral spine X-ray in a case of severe osteoporosis (A) and in a case of nutritional osteomalacia (B). The radiologist's report had been of "osteoporosis" in both cases.

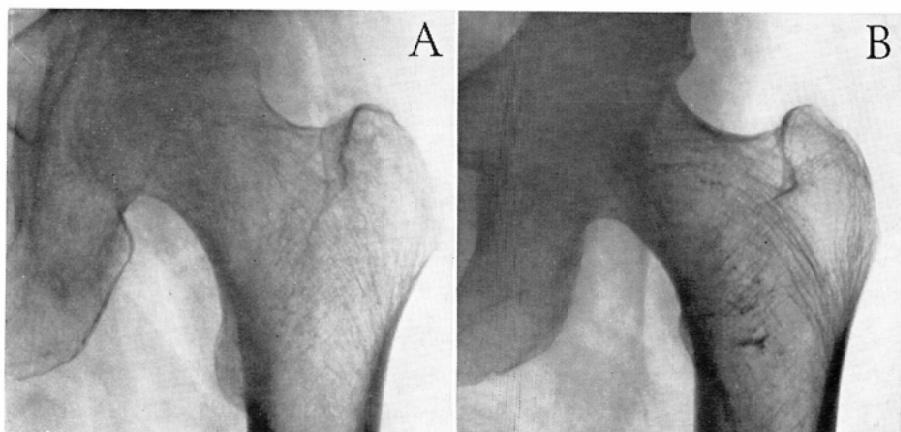


Fig. 2. Femur X-ray in the same cases of Fig. 1. (A: osteoporosis; B: osteomalacia). The trabecular pattern in case B is less blurred than in case A.

ing bone disease in which the radiologist's report had fatally been that of "osteoporosis" (Fig. 1). A more refined radiological study of the skeletal design has demonstrated that in case B the trabecular pattern was less blurred than in case A, despite case B was a nutritional osteomalacia patient and case A a senile osteoporosis (Fig. 2). Well, a histological study of bone by needle biopsy of the iliac crest allowed to confirm the diagnosis of osteoporosis in case A (Fig. 3): we can in fact see the reduction of the compact and of the trabeculae of the cancellous bone. In case B, instead, the needle biopsy of the iliac crest gave the distinctive histological feature of osteomalacia (Fig. 4): see the wide osteoid seams (yellow) with the hematoxylin, safranine, orange staining.

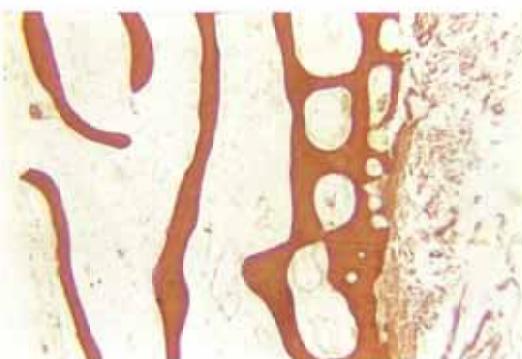


Fig. 3. Iliac crest needle biopsy in case A (senile osteoporosis) of Fig. 1 and 2: note the thinning of the trabeculae of the spongy tissue; because of the numerous re-absorption lacunae the compact has taken on a spongy appearance. (Haematoxylin-van Gieson staining; $\times 84$)



Fig. 4. Iliac crest needle biopsy in case B (nutritional osteomalacia) of Figures 1 and 2: note the wide osteoid seams yellow coloured. (Haematoxylin-safranine-orange staining; $\times 84$).

Of course with the needle biopsy of bone we can make a correct and safe diagnosis; but such procedure, even if not harmful, is not always accepted by the patient.

In recent years a new method has become available for the evaluation of bone metabolism: Kinetics of Radiocalcium to assess the skeletal mineral turnover. We have studied the kinetics of Ca^{45} and Ca^{47} in several pathologocal conditions using the simplified method of Aubert and Milhaud, which gives homogeneous and satisfying answers from the practical point of view.

If we inject a small dose of radiccalcium intravenously, this tends to accumulate primarily in the neo-deposition zones of bone tissue which are not yet completely mineralized. This poorly mineralized areas, rapid exchanging with tracer, constitute the greatest amount of the Exchangeable Calcium Pool (P) and may be determined by the study of the blood radiocalcium level. With a further calculation it is possible to evaluate also the Bone Accretion Rate (V_{0+}); taking into consideration the urinary and fecal losses of the tracer we can evaluate tracer which has been fixed in bone. From the accretion rate value (V_{0+}) and calcium balance, we get the Resorption Rate (V_{0-}). The bone accretion rate correlate directly with pool values. This correlation, that is considered a constant characteristic in radioisotopic studies of bone, arises partially from the mathematical elaboration of experimental data (Heaney and Whedon, 1958; Gennari, 1964).

Fig. 5 presents bone accretion rate values in over 100 studies performed in our laboratory, plotted as a function of exchangeable calcium pool, and demonstrates the close coupling that exists between these two parameters: the patients represented had a wide spectrum of bone diseases, from Paget's disease on the high end to hypoparathyroidism on the low end.

The study of the decline curves of radiocalcium demonstrates two opposite behaviours as compared with normal subjects. In Fig. 6 you can seen such curve in a case of hypoparathyroidism (above) where

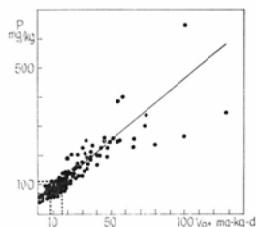


Fig. 5. Correlation between exchangeable calcium pool (P) and accretion rate (V_{0+}) values, as determined with the radiocalcium kinetic method of Aubert and Milhaud, in 104 patients with different bone diseases.

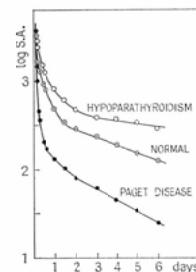


Fig. 6. Semilogarithmic plot of ^{47}Ca plasma specific activity curves against the time in a case of hypoparathyroidism and in a case of Paget's disease, as compared with a normal subject.

the fall of the plasmatic specific activity is very slow, and in a case of Paget's disease (below), in which there is a faster decline in plasma specific activity. In the first case the exchangeable calcium pool and the accretion rate are reduced, in the second one they are greatly increased.

In hypoparathyroidism the bone at kinetic examination behaves as a hypoactive, inert bone as confirmed by the histological finding which shows closed osteonic systems without reabsorption lacunae. On the contrary in Paget's disease, the biopsy shows, an evident mosaic structure and the signs of a very active remodeling.

Let us examine now the two parameters P and V_{0+} of the radiocalcium kinetics in the diffuse demineralizing bone diseases (Fig. 7): the histologically ascertained osteoporosis cases present pool and accretion values more or less normal, and this agrees with the histological findings. On the contrary the osteomalacia cases present increased pool and accretion values: in these cases we see a great amount of osteoid tissue. Osteoid tissue is a poorly mineralized bone that may exchange more readily than usual with the plasma, thus explaining both the large pool and the elevated accretion rate. To a great osteoid space correspond high values of P and V_{0+} . As we have previously demonstrated (Caniggia and Gennari, 1965) this finding is common to all types of osteomalacia. Let us stress how mixed forms of osteoporosis and osteomalacia behave as osteomalacia cases from Ca^{47} kinetics point of view: the histologic study shows thinner osteoid seams bordering slender trabeculae. This condition is frequently found in so-called gastrectomy "osteoporosis" (Caniggia et al., 1964).

The histological-radioisotopic comparison convinced us that high pool and accretion values correlate with osteoid amounts. The osteoid tissue is therefore an important factor in producing elevated values of radiocalcium kinetics, in as much as it determines an increase of the rapidly exchanging osseous spaces. That does not mean that elevated values of radiocalcium dynamics signify large amounts of osteoid tissue only.

In some metastatic osteolysis we have demonstrated the presence of osteoid seams (Caniggia and Gennari, 1965); increased amount of osteoid tissue is present also in Paget's disease. Nevertheless in these cases the elevated values of P and V_{0+} (Fig. 8) are not accountable for by osteoid tissue only: there is an increase of the resorption surfaces by the active breakdown of bone with disaggregation of the mineral archi-

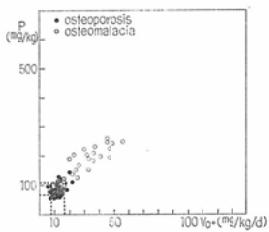


Fig. 7. Correlation between exchangeable calcium pool (P) and accretion rate (V_{0^+}) values in 31 senile osteoporosis and 24 osteomalacia cases.

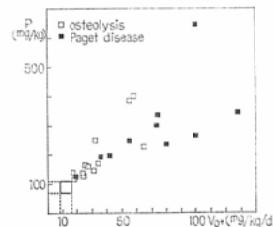


Fig. 8. Correlation between exchangeable calcium pool (P) and accretion rate (V_{0^+}) values in 12 osteolysis and 10 Paget's disease cases.

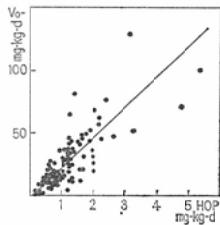


Fig. 9. Correlation between radioisotopic "resorption rate" (V_{0^-}) values and 24 hrs urinary excretion of hydroxyproline (HOP) in 93 cases.

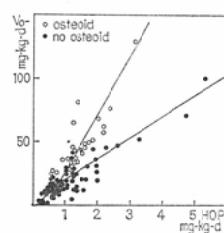


Fig. 10. Correlation between resorption rate (V_{0^-}) and hydroxyprolinuria (HOP) values: the open circles represent patients with large osteoid seams. The correlation lines of the two groups are very different.

structure that favours a greater radiocalcium uptake by ion exchange.

Another metabolic data can be introduced to support this latter hypothesis: the measurement of daily urinary excretion of Hydroxyproline, the unique iminoacid found almost exclusively in bone collagen, and that has a catabolic significance (Lenzi et al., 1962). If we correlate hydroxyprolinuria with the radioisotopic parameters, accretion and resorption rates, we will find the most significative correlation between hydroxyprolinuria and resorption rate (Fig. 9).

The most complete correlation between hydroxyprolinuria and resorption rate was evident in skeletal disease when bone activity was normal (viz., senile osteoporosis). When bone activity was increased the spectrum of correlation was divided in two groups (Fig. 10): a first one with resorption rate more elevated than urinary excretion of hydroxyproline, characterized by wide osteoid seams from the histological point of view; a second one including most of the cases of Paget disease and osteolysis. In these cases the urinary hydroxyproline values were often more elevated than the resorption rate. This gives an interesting contribution to a proper interpretation of calcium kinetic data.

Elsewhere (Caniggia and Gennari, 1965) we have pointed out some of the main limits of the radiocalcium kinetic studies: radiocalcium methods provide a measure of mineral transport in and out of the bone. It is a helpful index of bone formation and resorption but it is not a direct measure of osteoblastic and osteoclastic activities: both are in fact influenced by the amounts of osteoid tissue and by the increase of the resorption surfaces as well. On the contrary urinary excretion of hydroxyproline is a true expression of

resorption processes, as the "resorption rate" is accounted for by resorption and exchange processes as well.

In summary, the type of diffuse demineralizing bone disease can be stated by X-ray only in a limited number of cases. The diagnosis may be properly formulated in the presence of typical radiological images: Looser's areas, bone cysts and so on. A differential diagnosis can be forwarded by radiocalcium kinetic studies (Fig. 11). Normal radiocalcium dynamics values are indicative of osteoporosis. Increased radio-

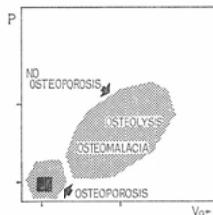


Fig. 11. Correlation between exchangeable calcium pool (P) and bone accretion rate (V_{0+}): osteoporosis and osteolysis + osteomalacia areas (the black square is the normal range).

calcium dynamics values, do exclude osteoporosis and are indicative of osteoporomalacia, osteomalacia or osteolysis.

One can easily understand that this is particularly important in those demineralizing bone disease patients who did not have typical radiological images.

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