Scintigraphic Bony changes in chronic renal failure patients using Tc-99m MDP(Methylene Diphosphonate)

Thesis submitted for Partial Fulfillment of M.Sc Degree In Internal Medicine

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List of abbreviations

B/ST: bone to soft tissue ratio

BAP: bone alkaline phosphatise

BMD: bone mineral denisity

BMP-7: bone morphogenetic protein 7

BMPs: bone morphogenetic proteins

BSU: bone structural unite

Ca calcium

CARE 2: calcium acetate renagel evaluation

CaSR: calcium sensing receptors

CKD: chronic kidney disease

CT: computed tomography

DFO: deferoxamine challenge

DPD: deoxypyridinoline

ESRD: end stage renal disease

F/S: bone to soft tissue ratio of the femoral neck

F-GF-23: natural circulating phosphaturic factor elevated in patients wih chronic renal failure

GFR: glomerular filtration rate

H/S: bone to soft tissue ratio of the skull

HMDP: hydroxyl methylene diphosphonate

IHH: Indian hedgehog genes

IL-6: iIL-6:interleukin 6

Ipth: intact parathyroid hormone

K/DOQI: kidney dialysis outcome quality initiatives

L/S: bone to soft tissue ratio of the lumbar spine

MRI: magnetic resonance imaging

NKF/DOQI: national kidney foundation dialysis outcome quality initiatives

NKF: national kidney foundation

ODF: osteoclast differentiating factor

P: serum inorganic phosphate

PTH: parathyroid hormone

PTHrp: parathyroid hormone related peptide

RANKL: receptor activator of NF kappa B ligand

ROIs: regions of interest

ROD: renal osteodystrophy

SHP: secondary hyperparathyroidism

SPSS: statistical package for social science

Tc-99m MDP:technetium-99-labelled methylene diphosphonate

TGF-beta

TRANCE: tumour necrosis factor related activation induced cytokines

VDR: vitamine D receptors

Intoduction and Aim of the work

INTRODUCTION

Changes in mineral metabolism and bone structure are an almost universal concomitant of progressive renal failure ,there are several types of renal bone disease, with many patients showing evidence of more than one defined disorder (called mixed osteodystrophy):

- Osteitis fibrosa cystica, in which bone turnover is increased due to secondary hyperparathyroidism.
- Osteomalacia, in which bone turnover is low in combination with an increased volume of unmineralized bone (osteoid); this problem was due primarily to aluminum deposition in bone in most, but not all, patients. The mineralization lag time is prolonged in osteomalacia: greater than 100 days, in comparison to less than 35 days in normal subjects and those with pure osteitis fibrosa.
- Adynamic bone disorder, in which bone turnover is low. Although aluminum deposition may cause this disorder, most current cases result from excessive suppression of the parathyroid glands. This represents the major bone lesion in peritoneal dialysis and hemodialysis patients.
- Mixed osteodystrophy, in which elements of both high and low bone turnover may be observed. This is also characterized by marrow fibrosis and increased unmineralized osteoid.

Symptoms due to these disorders, such as fractures and bone pain, generally do not occur until the patient is already on maintenance dialysis,however subclinical changes in bone remodeling begin early. A different type of uremic bone disease, with a unique pathogenesis, occurs in patients on prolonged dialysis: bone cysts due to beta2-microglobulin-associated amyloid deposits**(Hruska *et al*, 2006).**

In a 2006 position statement, the National Kidney Foundation (NKF) stated that the term, renal osteodystrophy, should be exclusively used to define bone morphology alterations observed in chronic kidney disease.

By comparison, they defined the term: chronic kidney disease-mineral and bone disorder, to define a broader syndrome in patients with chronic kidney disease, in which abnormalities in bone and mineral metabolism and/or extra-skeletal calcification are observed**(Moe *et al*,2006).**

Aim of work :

Our aim is to study the bone scintigraphic changes not only in chronic hemodialysis patients,but also in patients with chronic renal failure stage 3-5 who did not start dialysis considering the duration of dialysis ,the levels of serum calcium,phosphorus,PTH.

Review OF Literature

Normal skeletal development and regulation of bone formation and resorption

Physicians tend to regard the skeleton as an inert organ. In fact, the skeleton is metabolically active and constantly remodeling, and both processes are regulated by many local and systemic factors.

The skeleton has both structural and metabolic functions:

- Its structural function is critical for locomotion, respiration, and protection of internal organs. The structural connection between the skeleton and the hematopoietic system is particularly intimate; these two systems share both cells and local regulatory factors.

- Its metabolic function is largely as a storehouse for calcium, phosphorus, and carbonate, and it can contribute to buffering changes in hydrogen ion concentration. The enormous mineral surface of the skeleton can also bind toxins and heavy metals, thereby minimizing their ability to cause cellular damage**(Seeman *et al*,2006).**

Skeletal Devolopment

The processes of cellular differentiation that give rise to the skeleton are regulated by genes that first establish the pattern of skeletal structure in the form of cartilage and mesenchyme and then replace them with bone through the differentiation of osteoblasts. Bone can be formed directly from the mesenchyme (membranous bone formation) or on the surface of cartilage that has calcified (endochondral bone formation).The initial formation of the skeleton, first as cartilage and then as bone, requires the sequential activity of a large number of developmental regulators.

A complex interaction involving parathyroid hormone-related peptide (PTHrP) and the Indian hedgehog (IHH) genes is critical for the development and regulation of the cartilage growth plate . Bone morphogenetic proteins (BMPs) stimulate bone formation, but orderly growth requires that there also be periods when growth is inhibited or unwanted skeletal tissue is removed**(Blin-Wakkach *et al*,2001).**

Types of bone

Replacement of cartilage by more rigid bone begins early in fetal life. As the skeleton grows, not only in fetal life but also during childhood and adolescence, modeling, (the formation of new bone at sites where none previously existed and the removal of old bone at other sites) is critical for the formation of normal skeletal structures. However, even during fetal life much of the cellular activity is devoted to remodeling (removing and replacing skeletal structures already present). This becomes the dominant form of bone cell activity after puberty.

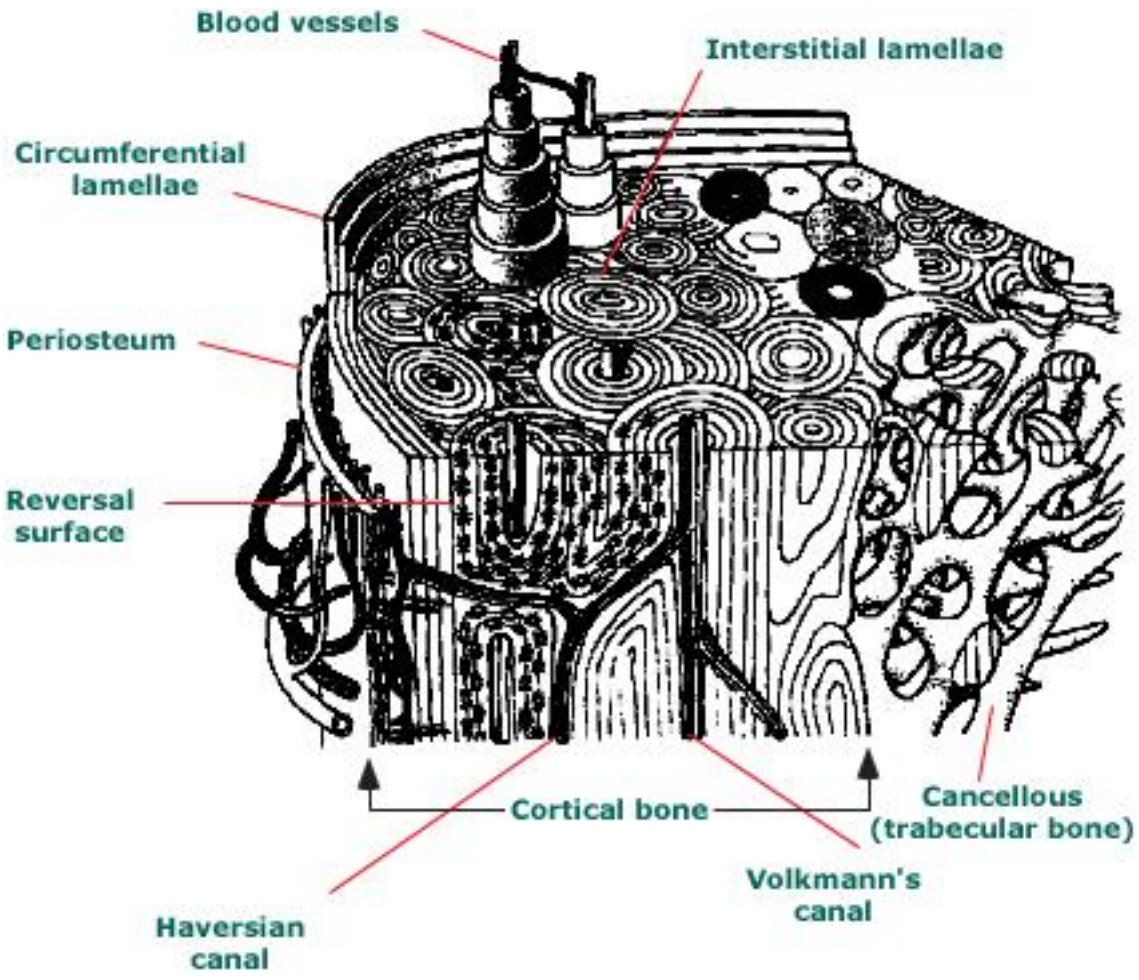
The first bone formed from mesenchyme in early development as well as bone formed during rapid repair may have a relatively disorganized pattern of collagen fibers in the matrix and is termed "woven" bone. However, all other bone is laid down in an orderly fashion with successive layers of well-organized collagen, and is termed lamellar bone(**Kobayashi *et al*,2002).**

There are two major types of bone in the adult skeleton; cortical and trabecular or cancellous:

- **Cortical bone** is dense and compact. It constitutes the outer part of all skeletal structures. The lamellae may be extensive (circumferential) or tightly packed in concentric circles in osteons. Cortical bone comprises 80 percent of the skeleton. Its major function is to provide mechanical strength and protection, but it can participate in metabolic responses, particularly when there is severe or prolonged mineral deficit.

- **Trabecular bone** is found inside the long bones particularly at the ends, throughout the bodies of the vertebrae, and in the inner portions of the pelvis and other large flat bones. Trabecular bone is an important contributor to mechanical support, particularly in the vertebrae. It is also more metabolically active than cortical bone and provides the initial supplies of mineral in acute deficiency states**(Seeman *et al*,2006).**

Anatomy of cortical bone : Figure (A)



Schematic diagram of diaphysial cortical bone showing the transverse and longitudinal arrangement of osteons.(sandos pharma ltd. Basal Switzerland)

Modeling

Growth of the skeleton and changes in bone shape are produced by modeling. Linear growth during childhood and adolescence occurs by growth of cartilage at the end plates, followed by endochondral bone formation. The width of the bones increases by periosteal apposition. During childhood, this is accompanied by endosteal resorption. The endosteal (or inner) surface is in contact with the marrow; thus, endosteal resorption results in a concomitant enlargement of the marrow cavity.