Racial differences in bone turnover rate and hyperparathyroidism in hemodialysis patients

Wendy Wei-Yue Lou
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RACIAL DIFFERENCES IN BONE TURNOVER RATE AND HYPERPARATHYROIDISM IN HEMODIALYSIS PATIENTS

Wendy W. Lou

Yale University

1994
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Racial Differences in Bone Turnover Rate and Hyperparathyroidism in Hemodialysis Patients

Thesis submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

Wendy W. Lou
1994
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Signature of Author

[Date]

Date

February 5, 1994
Dedicated with love to my parents
who have made tremendous sacrifices and
who have given me more love and support than
I can ever hope to return.
Acknowledgements

I would like to extend special thanks to Dr. Margaret J. Bia, my thesis advisor, for her unfailing guidance and encouragement throughout this project. Thanks are also due to Dr. Karl L. Insogna and Dr. Caren M. Gundberg for their invaluable help and insightful discussions. Additionally, I would like to acknowledge Dr. Pepita Yap and the Yale-New Haven Hospital Dialysis Unit staff for their help in the collection of patient data.

For their lifelong love and inspiration, I am forever indebted to my parents and my sister. Their belief in me has encouraged me through my every endeavor.

Finally, I am grateful to Siu-Sun Yao, my best friend, who with his love and patience has enriched my life for the past several years and will for many years to come.
RACIAL DIFFERENCES IN BONE TURNOVER RATE AND HYPERPARATHYROIDISM IN HEMODIALYSIS PATIENTS.

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This study was undertaken to determine whether there was a racial difference in bone turnover rates in hemodialysis patients. It was also done to confirm previous observations demonstrating a lower level of calcium tolerance in white compared to black hemodialysis patients. Fifty HIV-negative and HBsAg-negative subjects were grouped according to race: 31 black subjects (62%) and 19 white subjects (38%). Except for one patient who was not prescribed any phosphate binders, the rest of the patients were maintained on calcium carbonate, aluminum hydroxide, or both. The two groups were similar in mean age, duration on dialysis, dialysis membrane surface area, body mass index (BMI), serum albumin concentration, average serum bicarbonate concentration, percent females, percent wheelchair-bound/bed-ridden subjects, percent with diabetes mellitus, and percent with subtotal parathyroidectomy.

Bone turnover was examined indirectly with serum alkaline phosphatase, osteocalcin, tartrate-resistant acid phosphatase, and intact parathyroid hormone (iPTH) levels. The mean iPTH (273±56.5 pg/ml in black subjects vs 118±39.1 pg/ml in white subjects, p=0.0286) and mean tartrate-resistant acid phosphatase (4.4±0.28 U/l in black subjects vs 3.3±0.27 U/l white subjects, p=0.0166) levels were significantly higher among the black patients compared to white patients. The mean osteocalcin (81.32±12.82 ng/ml in black subjects vs 48.49±15.32 ng/ml in white subjects) and mean alkaline phosphatase (153±20.8 U/l in black subjects vs 114±22.0 U/l in white subjects) levels tended to be higher among the black subjects compared to the white subjects. In addition, a greater proportion of black patients had osteocalcin levels higher than the upper limits of normal range (77.42% of black subjects vs 47.37% of white subjects, p=0.0290; normal<25 ng/ml). The same was seen in average alkaline phosphatase (58.06% of black subjects vs 21.05% of white subjects, p=0.0180; normal<114 U/l) measurements. Taken as an aggregate, these results suggested that the black hemodialysis patients had a higher bone turnover rate than the whites.
The groups had similar dietary calcium and phosphorus intakes, oral 1,25-dihydroxyvitamin D dose, blood 1,25-dihydroxyvitamin D levels, dialysate calcium concentrations, ionized serum calcium levels, total serum calcium levels, serum phosphate levels, and number of hypercalcemic episodes. However, black subjects did have a significantly higher mean elemental calcium dose of calcium carbonate than the white subjects did (elemental calcium content for black and white subjects: 2330±366.4 vs 1273±312.9g/day, respectively, p=0.05). There was also a greater percentage of black subjects who were ingesting more than 1g of elemental calcium per day compared to the white subjects (74.19% of black subjects vs 42.11% of white subjects, p=0.023). This suggested that, in comparison to the white hemodialysis patients, the black patients had a greater tolerance for calcium carbonate without becoming hypercalcemic.

These results suggest that black hemodialysis patients did have a higher bone turnover rate than white patients and that this may explain black patients' ability to tolerate a greater daily dose of calcium carbonate. Since iPTH levels were significantly higher in black subjects, the results also suggest that black hemodialysis patients have a greater degree of secondary hyperparathyroidism than white patients, which may explain black patients' higher bone turnover rate.
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I. Introduction

Chronic renal failure (CRF) is defined as the condition in which the mass of functioning kidney tissue is insufficient to meet the demands for the excretion of wastes, regulation of plasma biochemistry, and normal synthetic functions. The severity of renal failure may be graded according to the reduction of glomerular filtration rate (GFR) (180) and may also be clearly reflected in the resulting systemic derangement.

Uremic Osteodystrophy

Among the many clinical manifestations of end-stage renal disease is the development of uremic osteodystrophy. This metabolic bone disease of these uremic patients is subdivided into four subtypes. Though all four are likely to be present in variable degrees, one may be more prominent clinically. Hyperparathyroidism is universal among end-stage renal disease patients and may lead to osteitis fibrosa cystica. Osteomalacia or rickets may result from the inability to convert vitamin D to its active metabolite, 1,25-dihydroxyvitamin D in advanced renal disease (high-turnover). Moreover, aluminum may accumulate in bone leading to a type of vitamin D-resistant rickets (low-turnover). With near complete inactivity at the bone surfaces, the aplastic characteristic marks the fourth type of uremic osteodystrophy. In addition, other factors such as chronic acidosis and poor nutrition contribute to osteoporosis in these patients.

That renal failure contributes multiple factors to the pathogenesis of these disease states is evident. Of particular interest here is hyperparathyroidism of chronic renal failure resulting from the kidney's inability to catabolize parathyroid hormone and phosphate retention as well as elevated serum calcium set point for parathyroid hormone secretion.

Phosphate Retention

As kidney disease progresses and GFR falls below 25 ml/min, hyperphosphatemia is common (37, 73). By means of multiple mechanisms, hyperphosphatemia is partially
responsible for the development of secondary hyperparathyroidism (166, 167, 168),
dialytic bone diseases (35), and soft tissue calcifications (132) all of which are widely seen
in hemodialysis patients. The involvement of phosphorus in hyperparathyroidism has been
demonstrated in studies of oral phosphorus loading (151), long-term feeding of a high-
phosphate diet (85), dietary phosphate restriction proportional to GFR reduction (168), and
other manipulations of a similar nature (97, 100). In fact, Fournier, et al. (63) found a
positive correlation between serum immunoreactive parathyroid hormone (iPTH) and the
degree of hyperphosphatemia in dialysis patients.

Hyperphosphatemia can lead to secondary hyperparathyroidism by decreasing
serum calcium concentration. Acute elevation of serum phosphate level tends to decrease
serum calcium level as the body attempts to maintain a constant calcium-phosphate product
(181). The resulting low serum calcium level acts as a stimulus for parathyroid hormone
(PTH) secretion. Phosphate retention also inhibits the activity of 25-hydroxyvitamin D-1-
alpha-hydroxylase of the kidney and therefore contributes to the already altered vitamin D
metabolism of renal disease (143). As shown by metabolic balance studies monitoring
fecal calcium loss (91, 174) as well as isotopic methods (36, 134), the decreased
production of 1,25-dihydroxyvitamin D is associated with low intestinal calcium absorption
and thus contributes to a low serum calcium level. In addition, 1,25-dihydroxyvitamin D
itself directly suppresses the secretion of PTH (25, 30, 52, 103, 125, 154, 163, 164, 169).
It follows that a low plasma level of 1,25-dihydroxyvitamin D can decrease the sensitivity
of parathyroid glands to the normal inhibitory effects at any given serum level of ionized
calcium (127), thus contributing to the pathogenesis of secondary hyperparathyroidism via
this abnormal calcium set point. Finally, deficiency in 1,25-dihydroxyvitamin D
production along with phosphate retention leads to skeletal resistance to the calcemic action
of parathyroid hormone (PTH) (56, 98, 108). Clearly, hyperphosphatemia, 1,25-
dihydroxyvitamin D deficiency, and skeletal resistance to the calcemic effects of PTH all
contribute to the decrease in serum calcium concentration which in turn stimulates PTH
secretion and leads to secondary hyperparathyroidism.

**Secondary Hyperparathyroidism** (Table 1)

Slatopolsky and colleagues (168) have suggested that secondary hyperparathyroidism in chronic renal disease begins with the first stage of renal functional impairment and worsens with increasing loss of nephron population. If phosphorus intake is not reduced during the progression of chronic renal disease, a transient hyperphosphatemia would result and would temporarily lower serum ionized calcium level, which would then stimulate PTH secretion. Through phosphaturia, the serum phosphorus and calcium concentrations are brought back to normal at the expense of an elevated serum PTH level. Postulating this vicious cycle as the generator of secondary hyperparathyroidism, Slatopolsky and co-workers found that the onset of secondary hyperparathyroidism in experimental chronic renal disease can be delayed or perhaps even prevented by reducing dietary phosphorus intake proportional to the decrease in GFR (168). These effects of dietary phosphorus restriction are also supported by the observation that blood levels of 1,25-dihydroxyvitamin D inversely and iPTH directly vary with dietary phosphorus intake and that 1,25-dihydroxyvitamin D increases and iPTH decreases under phosphorus intake restrictions (143).

The consequences of secondary hyperparathyroidism are numerous and complex. Among the conditions that result from this complication are soft tissue calcification (132) due to a high plasma calcium-phosphate product, and renal osteodystrophy (specifically osteitis fibrosa characterized by an increase in bone resorption, the number of osteoclasts, and marrow fibrosis) (35, 185).

**Reduction of Intestinal Phosphate Absorption**

Since phosphate retention can lead to secondary hyperparathyroidism, renal osteodystrophy, and extra-skeletal calcification, the prevention of hyperphosphatemia is
critical in the management of chronic renal failure patients. For patients with chronic renal failure, hemodialysis is usually conducted three times a week in the United States and may improve hyperphosphatemia. Although hemodialysis may serve as an adequate substitute for renal function with respect to the serum concentrations of many other ions, it is insufficient in maintaining an acceptable serum phosphate concentration on a daily basis. Therefore, a reduction in intestinal phosphate absorption is necessary and can be achieved by two methods: restriction of dietary phosphate content and use of phosphate-binding agents. Although it is possible to decrease dietary phosphorus intake to as low as 700-900mg/day (60% of normal) by a diet that is low in meats and dairy products (90), intakes lower than this are extremely difficult to achieve by dietary restriction alone. Therefore, for patients with advanced renal disease, orally administered phosphate-binding compounds are usually necessary to control hyperphosphatemia and to prevent secondary hyperparathyroidism (63, 64, 65).

For many years, various orally administered aluminum salts have been used as effective phosphate binders in the gastrointestinal tract. However, at a dose sufficiently high to prevent hyperphosphatemia in most patients, a small amount of aluminum is usually absorbed. Consequently, therapies with aluminum-containing compounds can often lead to an elevated plasma and tissue aluminum content (3, 38, 99), anemic conditions (24, 86, 113, 136, 184), dialysis encephalopathy (3, 51, 142, 162), and renal osteodystrophy (7, 29, 51, 59, 136, 141, 189) in these patients.

**Calcium Carbonate**

In a search of alternatives to aluminum-containing phosphate binders, various investigators have conducted trials using such compounds as magnesium hydroxide (75, 126), calcium carbonate (75), calcium citrate (44), and calcium acetate (44, 159). Though some controversies concerning their effectiveness and side effects remain (75, 120, 126, 159), the most popular and currently believed to be the best replacement for aluminum-
containing phosphate binders is calcium carbonate (65). High doses of calcium carbonate taken by uremic patients may have three potential positive effects: binding of phosphates in the gut so that less dietary phosphates are absorbed; increasing passive calcium absorption from the gastrointestinal tract by increasing total oral calcium intake; and possibly contributing to the correction of metabolic acidosis (9, 121).

Studies that support orally administered calcium carbonate as an effective phosphate binding agent are numerous. Clarkson and colleagues (33) demonstrated that patients with chronic renal failure taking high doses (20g/day) of oral calcium carbonate decreased their gastrointestinal absorption of phosphorus. Moriniere, et al. (122) observed that high dose calcium carbonate (5-20g/day) in hemodialysis patients can correct hyperaluminemia and control hyperphosphatemia. Studies undertaken by Addison, et al. (2), Fournier, et al. (66), Hercz, et al. (79), and Slatopolsky, et al. (170) all showed that calcium carbonate effectively controlled hyperphosphatemia and improved hypocalcemia, while Andreoli, et al. (6) and Salusky, et al. (156) published similar findings in their studies on children with chronic renal failure. Mak's crossover study of aluminum hydroxide or calcium carbonate therapy in children with chronic renal failure under dietary phosphate restriction revealed that both phosphate binding agents are able to suppress existing secondary hyperparathyroidism (104). In fact, Ramirez, et al. (146) concluded that calcium carbonate reduced gastrointestinal phosphorus absorption as much as aluminum hydroxide did.

Other investigators focused on the effects of high dose calcium carbonate on calcium homeostasis in patients with chronic renal failure. Clarkson, et al. (34) showed that patients with chronic renal failure receiving 20g of calcium carbonate per day had a positive calcium balance and a reduced phosphate absorption. However, the phosphate balance was positive because the decrease in urinary phosphate excretion greatly surpassed the decrease in gastrointestinal phosphate absorption. Thus, they suggested that the observed reduction in plasma phosphate could be due to the decreased phosphate absorption and the the precipitation of calcium phosphate extra-skeletally. However, other
investigators (43, 117) found that high-dose oral calcium carbonate actually decreased bone resorption without increasing soft tissue calcifications. In fact, recovery from aluminum-related bone disease was observed by Hercz, et al. (80) when calcium carbonate was substituted for aluminum-containing phosphate binders. Furthermore, Renaud, et al. (152) observed that the doses of calcium carbonate are not covariant with the severity of metastatic calcification, as would be expected according to Clarkson's explanation. These findings are consistent with the idea that calcium phosphate precipitates mainly in the bone rather than in the soft tissues.

Two other potential benefits of high dose calcium carbonate were demonstrated by Makoff and co-workers in their study of chronic calcium carbonate therapy in non-dialyzed uremic patients (105). As uremic patients usually suffer from chronic negative calcium balance and metabolic acidosis, the subjects received 3-7g/day of calcium carbonate for 3-12 months and showed a steady increase in serum calcium and bicarbonate levels. Symptomatically, several patients also noticed the disappearance of anorexia, nausea, fatigue, vomiting and neuromuscular irritability. The studies of Anelli, et al. (9), Berlyne (14), Clarkson, et al. (33), and Moriniere, et al. (121) revealed similar results dialysis patients, although the improvement in metabolic acidosis was not observed in Berlyne's investigation (14).

The above accounts for many of the beneficial effects of orally administered calcium carbonate in chronic dialysis patients. However, this phosphate binding agent is not without side effects. Three complications of calcium carbonate administration were suggested by Raine and Oliver (145): 1) potential rebound increase in gastric acid secretion after calcium carbonate administration 2) extraosseous calcification, and 3) calcium carbonate doses insufficient as phosphate binders still often resulted in significant hypercalcemia. The first possible effect is theoretically hazardous in patients with end-stage renal disease since they have an increased incidence of peptic ulceration.

Extraosseous calcification or soft tissue calcification and its many debilitating
sequelae had long been documented in hemodialysis patients (132). Calcium carbonate therapy may exacerbate the development and manifestations of soft tissue calcification (23). However, the majority today believe it to be a problem. Hypercalcemia as the main side effect of high dose calcium carbonate therapy has been noted by many investigators (66, 71, 79, 101, 102, 106, 122, 156, 170). During Stein's twelve month observation of approximately 150 hemodialysis patients on 1.5-4g of calcium carbonate per day (176), there were 11 cases of mild to severe hypercalcemia -- associated with pancolonic impaction in two patients and worsening hypertension in one patient. Increasing weakness, nausea, confusion, pruritis, and milder degrees of constipation were noted in the others. However, Fournier, et al. (66) reported that about half of the patients in whom calcium carbonate successfully controlled hyperphosphatemia encountered hypercalcemia. The reported incidence of hypercalcemia varies from 27 to 53 percent of dialysis patients on high-dose calcium carbonate therapy (66, 71, 101, 106, 122, 170).

**Hypercalcemia**

**Causes of Hypercalcemia** (Table 2)

Patients are usually considered hypercalcemic if their serum calcium levels rise above 10.5mg/dl (171). In the general population, the clinical manifestations of hypercalcemia depend partly on the underlying disease. Mild to moderate hypercalcemia is often asymptomatic, but there may be mild disturbances in renal, gastrointestinal, central nervous, or other systems (178). Confusion, obtundation, weakness, and dehydration may be features of more severe hypercalcemia (124). Population studies in England (124) and in the United States (78) showed similar incidences of hypercalcemia -- approximately 40 per 100,000 persons a year, of whom about 25 per 100,000 a year have primary hyperparathyroidism. Another study in England (62) revealed different figures for the causes of hypercalcemia among hospital patients: 47 percent had malignant disease, 13 percent had hyperparathyroidism, 15 percent were dialyzed, and 22 percent showed no
apparent cause. All other known causes amounted to less than 5 percent.

Parfitt (133) divided hypercalcemia into equilibrium types and disequilibrium types. Coburn and Slatopolsky (35) included a third group, the hyperabsorptive types, which share characteristics of both equilibrium and disequilibrium types. Equilibrium hypercalcemia, typified by chronic hyperparathyroidism, has a stable serum calcium concentration over time and a zero calcium balance. Since bone resorption may be normal, this hypercalcemia is not sustained by a net increase in calcium release from the bone, but by a PTH-induced shift in the plasma-bone equilibrium at quiescent bone surfaces, where the net calcium exchange remains zero. In hyperparathyroidism, calcitriol levels may be raised, leading to an increased calcium absorption from the gut. Moreover, PTH promotes tubular calcium reabsorption so that calcium excretion at the elevated serum calcium concentration balances the net intestinal absorption. In addition, tumors may also cause equilibrium hypercalcemia by producing PTH-like compounds which act to increase bone resorption and renal calcium reabsorption (88).

Disequilibrium hypercalcemia, on the other hand, is characterized by an unstable serum calcium concentration which tends to increase gradually. There is a pathologic increase in the net bone resorption which may be due to multiple myeloma (123) or metastatic carcinoma, for example. Furthermore, renal calcium excretion is decreased by reduced glomerular filtration rate (GFR) as a result of hypercalcemia, sodium depletion, and volume contraction. Thus, a vicious cycle of elevating plasma calcium levels proceeds. Severe hyperparathyroidism with extensive bone resorption (for example, as a result of large or malignant parathyroid tumors) or reduction in renal calcium excretion, as with volume depletion or the use of thiazide diuretics (17), can lead to disequilibrium hypercalcemia.

Finally, hyperabsorptive hypercalcemia may be associated with vitamin D intoxication (45, 157), sarcoidosis (10), the milk-alkali syndrome (87, 129), and hyperparathyroidism. Here, because of alkalosis, volume depletion, or perhaps the
elevated vitamin D level, intestinal calcium absorption is increased, renal calcium reabsorption is usually increased, and net bone resorption may also be increased (179).

A list of some clinical causes of hypercalcemia appears in Table 2.

**Hypercalcemia in Chronic Renal Failure**

The symptoms of hypercalcemia at a given serum calcium level may be more severe in uremic patients than in patients with normal renal function (35). Therefore, it is important to determine the causes of hypercalcemia in patients with chronic renal failure (Table 3). Persistent hypercalcemia is mainly a consequence of severe secondary hyperparathyroidism and/or aluminium-related bone disease, both of which are commonly seen in chronic dialysis patients. Hypercalcemia in patients with severe secondary hyperparathyroidism can develop within a few months or after several years of dialysis. One possible reason for the appearance of hypercalcemia may be that dialysis patients are more resistant to the suppression of PTH secretion by elevated serum calcium level (35). Brown and co-workers (19) observed that a marked elevation of calcium set point is common in patients with advanced renal failure and secondary hyperparathyroidism. The set point is defined by the calcium concentration necessary to suppress PTH secretion from parathyroid cells by 50-percent. The change in the set point may be responsible for the hypercalcemia. Another explanation for the high levels of PTH secretion may be the existence of massive parathyroid hyperplasia in the presence of an elevated serum calcium concentration.

A second condition that may lead to hypercalcemia in dialysis patients is aluminum-related bone disease (161). The deposition of aluminum in bone is associated with mineralization defects (60). Boyce and colleagues found that 14 of their 16 patients with aluminum-related osteomalacia were hypercalcemic. They also suggested that the aluminum at calcification sites interferes with the proper mineralization of osteoid. Since calcium can not be incorporated into bone, the body's largest reservoir of calcium
(normally containing over 99% of the total body calcium) (92), it remains extra-skeletally and causes hypercalcemia.

Transient hypercalcemia may also occur or preexisting hypercalcemia may be aggravated in patients who receive large doses of calcium salts during vitamin D sterol treatment and after being dialyzed against a calcium concentration of 7-8mg/dl (149).

Other causes of hypercalcemia in dialysis patients may include the use of calcium-containing cation-exchange resins (131), thiazide diuretics (89), hypophosphatemia due to phosphate restriction, excessive vitamin D, and immobilization (69, 130, 177).

In addition, the frequency of hypercalcemia appears to vary with different types of renal osteodystrophy. Cochran, et al. (40) studied twenty-two dialysis patients according to the presentation of bone disease: 12 patients had atypical osteomalacia and had fractures most likely resulting from aluminum toxicity. All patients were prescribed 600mg oral calcium carbonate per day (except in those who developed hypercalcemia) but no vitamin D supplements. The average plasma phosphorus level was lower in the fracture group, though not statistically significant, compared to the other group. Members of the fracture group also had greater fluctuations in the plasma calcium concentration and more frequent spontaneous hypercalcemic episodes than those with secondary hyperparathyroidism. This difference in plasma calcium levels was believed to stem from the difference in the bone turnover rates. As reflected in the elevated alkaline phosphatase levels, the secondary hyperparathyroidism group had a higher bone formation rate compared to the fracture group. When the plasma calcium level is elevated, for example, from dialysis or gastrointestinal absorption, the reduced mineralization activity in the fracture group is not capable of rapidly incorporating the excess plasma calcium into bone and thus allows hypercalcemia to persist.

A study conducted by Piraino and co-workers (139) compared the nature of bone disease in 30 normocalcemic dialysis patients against 10 dialysis patients with spontaneous hypercalcemia who were receiving neither calcium nor vitamin D supplements. There was
no significant difference between the two groups in the mean age, sex, race ratios, duration of dialysis, type of dialysis, percent of patients with mineralization defects, and serum albumin, phosphorus, alkaline phosphatase, and parathyroid hormone levels. Bone pain as rated by a disability scale was more severe in hypercalcemics than normocalcemics; and osteomalacia and bone aluminum staining were more dramatic in the hypercalcemic patients. Moreover, the stainable bone aluminum level correlated negatively with mineralization activity and positively with serum calcium concentration. In hypercalcemics, polycystic kidney disease and other congenital-hereditary diseases were more common causes of chronic renal failure (80%) than in normocalcemics (20%). Although 1,25-dihydroxyvitamin D levels were not measured in their study, the investigators suggested that more 1,25-dihydroxyvitamin D may be produced by polycystic kidneys than other end-stage disease kidneys and may explain the difference.

Piraino, et al. (141) compared 21 hypercalcemic dialysis patients without vitamin D or calcium therapy and 28 non-hypercalcemic dialysis patients. Bone biopsies determined that two-thirds of the hypercalcemia patients had low-turnover osteodystrophy (mostly osteomalacia), and hypercalcemic patients with osteitis fibrosa had a significantly lower mean N-terminal PTH level than the non-hypercalcemics with osteitis fibrosa did.

**Hypercalcemia Associated with Calcium Carbonate Therapy**

Hypercalcemia during calcium carbonate therapy has been observed by numerous investigators. When calcium carbonate was started or increased in hemodialysis patients, Gonella, et al. (74) observed that significant hypercalcemia especially in patients who had normal predialysis serum phosphate levels and who did not receive aluminum hydroxide before the calcium carbonate therapy. It was suggested that these patients may have had a higher level of 1,25-dihydroxyvitamin D, whose formation would be inhibited by hyperphosphatemia, although vitamin D levels were not reported. This greater availability of 1,25-dihydroxyvitamin D may allow increased gastrointestinal calcium absorption and
thus hypercalcemia to occur. In a year-long study of 12 children with chronic renal failure, Mak and co-workers (104) did not observe hypercalcemia until several months after the initiation of calcium carbonate therapy and did not find it to be more common with calcium carbonate than with aluminum hydroxide. Therefore, the investigators suggested that the altered vitamin D metabolism as a consequence of controlling phosphate retention is responsible for the hypercalcemic episodes.

From a study of 10 hemodialysis patients receiving 3.2-6.4g calcium carbonate (or 1.28-2.56g elemental calcium) per day for 4-8 weeks, Ginsburg, et al. (72) concluded that the hypercalcemia resulted from the intestinal absorption of calcium because they observed a prompt recovery from hypercalcemia and remission of symptoms upon the withdrawal of calcium carbonate therapy. Moreover, Slatopolsky and colleagues noted that hypercalcemia occurred mainly in those patients who received high oral calcium carbonate doses (>12g calcium carbonate/day, or >4.8g elemental calcium carbonate) because of their high phosphorus intake. This observation suggests that high calcium carbonate doses are responsible for the elevated serum calcium concentration.

In contrast, Mactier and co-workers (101) found that hypercalcemic patients did not receive higher calcium carbonate doses and did not have a higher serum aluminum or parathyroid hormone levels than the other hemodialysis patients in their study.

Hercz, et al. (81) studied 29 dialysis patients on 3-10g calcium carbonate (with 40% elemental calcium) per day and found hypercalcemic episodes in 12 patients. Of these, 10 had bone biopsies and 9 showed aluminum-related bone disease. Andreoli, et al. (6) reported improvement in a case of calcium carbonate intolerance manifesting hypercalcemic symptoms in an infant after the resolution of his severe aluminum-induced bone disease.

Bia and Meric's Study of Hypercalcemia in Dialysis Patients

Meric and Bia (116) set out to characterize the risk factors of hypercalcemia in
dialysis patients on high-dose calcium carbonate therapy. Fourteen hypercalcemic patients were compared with 14 eucalcemic patients matched for age, sex, duration of dialysis, and etiology of kidney disease. The two groups were similar in terms of calcium carbonate dosage, dietary calcium intake, plasma levels of vitamin D metabolites, and aluminum burden; but compared to the eucalcemics, the hypercalcemics had significantly lower bone turnover rates as reflected by their lower serum osteocalcin, intact PTH, and alkaline phosphatase levels. Thus, there was no evidence that the hypercalcemics had greater active intestinal calcium absorption, although the latter was not directly measured. However, the results did show an association between hypercalcemia and low bone turnover rate, therefore supporting the notion that patients with low bone turnover rates are less able to move calcium out of the circulation quickly enough to prevent hypercalcemia. Another observation noted by the investigators is of special interest: While the dialysis unit at which the study was conducted consisted of 36% white patients, 64% of the hypercalcemic patients were white while only 14% of the eucalcemic patients were white. Therefore, there appeared to be a significant difference in bone turnover rate and calcium tolerance level between black and white hemodialysis patients.

Racial Differences of Bone Metabolism in the Healthy Population

Racial differences in bone density and metabolism have been documented (42). Black subjects tend to have a higher bone density than white subjects by 5-10%. (This difference is also observed in the population with chronic renal failure) (110). In the healthy population, this is attributable to a greater increase in bone growth during the pubertal spurts in black individuals than in white individuals (70), and to the lower bone turnover rate (only about 35% of that in white subjects) in the black subjects (191). Higher PTH levels have been found in normal black subjects compared to white subjects (11), but similar levels were observed in other studies (115). The higher PTH levels in these black
subjects were associated with lower osteocalcin levels suggesting resistance to the effects of PTH.

Aside from the observations in Bia and Meric's study, there have not been any reports on racial differences in bone turnover or on calcium tolerance on chronic dialysis patients at the time of this study.
II. Purpose

Meric and Bia observed that hypercalcemia occurred more commonly in hemodialysis patients with low bone turnover. Furthermore, their results suggest that this phenomenon occurred more commonly in white versus black hemodialysis patients. The current investigation was designed to determine whether there actually is such a racial difference in indirect measures of bone turnover rate in hemodialysis patients. In the process, this study would also confirm or disprove their previous observation that calcium tolerance is greater in black than in white hemodialysis patients.
III. Materials and Methods

**Patient Population** (Table 4)

At the time of this investigation, the Yale-New Haven Dialysis Unit was treating a total of 58 patients with chronic hemodialysis, who were potential candidates for this study. Chronic hemodialysis was defined as having been on dialysis for at least one month before this investigation and having no expectation of recovering physiological renal function. Because of the nature of our question and hypothesis, only white and black patients were chosen; the numbers of Asians, Hispanics, or patients of other descents were too small to be included. In addition, those with HIV-positive or HBsAg-positive status were also excluded. The unit had three Hispanic patients, one of whom was HBsAg-positive, and one HIV-positive patient. Of the 54 remaining patients, 50 gave oral consent to participate and formed the patient population of this investigation. None of these patients had any evidence of metastatic cancer which might be a confounding cause of hypercalcemia. Therefore, fifty HIV-negative, HBsAg-negative, and white or black chronic hemodialysis patients were evaluated for their bone turnover rate in this study.

The following summary of the patient characteristics was true not only at the time of this study but also for at least one month immediately prior to it. All, except one, of the 50 subjects underwent hemodialysis three times a week at Yale-New Haven Hospital. One white, male patient diagnosed with renal failure required only two dialysis treatments per week, but he was not expected to recover his own physiologic renal function and therefore will continue to rely on hemodialysis. The patients at the unit were dialyzed against a calcium bath of either 2.5mEq/l or 3.5mEq/l. Oral phosphate binders (aluminum-containing binder(s) and/or oral calcium-containing binders) were taken by all subjects except one who was not on any phosphate binders. The only form of oral vitamin D supplement for the patients was 1,25-dihydroxyvitamin D, and the patients were prescribed daily doses of 0.25μg, or 0.50μg. Postdialysis intravenous 1,25-dihydroxyvitamin D was
also prescribed when necessary as described in “Results” section of this thesis.

Data Collection

The following blood chemistry levels pertinent to our evaluation were obtained. These parameters were all measured predialytically on the same day for any given patient in this cross-sectional study.

* Serum bicarbonate: a measure of the degree of metabolic acidosis in dialysis patients;
* Plasma albumin: a sensitive measure of constitutional illness
* Ionized calcium: the biologically active portion of total calcium;
* Total calcium;
* Total phosphate;
* Intact parathyroid hormone: a measure of steady state parathyroid hormone level (112, 173);
* Plasma 1,25-dihydroxyvitamin D;
* Alkaline phosphatase: an estimate of osteoblastic activity and thus of bone formation rate (28, 112);
  ** Alkaline phosphatase cleaves, or hydrolyzes, pyrophosphate which is an inhibitor of bone mineralization (92)
* Total serum acid phosphatase;
* Prostatic acid phosphatase;
  ** Tartrate-resistant acid phosphatase (bone fraction acid phosphatase) level was calculated by subtracting prostatic acid phosphatase level from total serum acid phosphatase level. It is released from osteoclasts during bone resorption (48, 119, 128) (The validity of this subtraction method was confirmed by comparing the results of 10 random samples calculated by our method and obtained by direct measure of TRAP from the Jerry Pettis VA Medical Center endocrinology laboratory at Loma Linda, CA. A good correlation of these two methods was
evidence by linear regression analysis with $R^2 = 0.638$ and $p<0.0056$.

* Osteocalcin: a product of osteoblasts and a measure of bone formation rate (20, 28)

In addition to single serum measurements of these electrolytes, enzymes, and hormones for each of the 50 subjects, a chart review was performed to obtain serum levels of bicarbonate, albumin, alkaline phosphatase, total calcium, and total phosphate during the three months just before this study. Levels at the time of study are compared with the corresponding three-month averages to verify that the current values are reflective of the patient's general long-term status which ultimately affects her/his bone turnover rate.

Furthermore, the record was reviewed for the following additional information about each patient:

* Daily dietary calcium content calculated from a 24-hour dietary recall (138) by the Yale-New Haven Dialysis Unit dietician within the past six months;
* Daily dietary phosphate content calculated from a 24-hour dietary recall (138) by the Yale-New Haven Dialysis Unit dietician within the past six months;
* Dialyzer membrane surface area for at least one month just prior to this study;
* Calcium concentration in the dialysate bath for at least one month just before to this study;
* Daily oral intake of calcium from calcium-containing phosphate binders as prescribed for at least one month immediately prior to the time of this study unless specified; (Patients were given calcium carbonate, oyster shell calcium, Oscal500®, and/or Tums®.)
* Daily oral intake of aluminum from aluminum-containing phosphate binders as prescribed for at least one month immediately prior to the time of this study unless specified; (Patients were given Amphojel® and/or Basaljel®.)
* Daily oral intake of 1,25 dihydroxyvitamin D (Rocaltrol®) as prescribed for at least one month just before the time of this study;
* Intravenous dose of 1,25 dihydroxyvitamin D (Calcijex®) administered for at least one
month just before the time of this study;

Furthermore, the patients' activity levels were assessed with the assistance of Dr. Pepita Yap, the chief physician for the Yale-New Haven Dialysis Unit. For the purpose of this study, each subject was categorized as either being wheelchair-bound/bed-ridden or ambulatory.

The review also provided each patient's age, length of time on dialysis, race, sex, dry weight, height, as well as identified those with diabetes mellitus and those with parathyroidectomy (subtotal). Body mass index (BMI) was determined for each patient by dividing the dry weight (kg) by the squared height (m²).

**Laboratory Analyses**

The Yale-New Haven Chemistry Laboratory measured the serum levels of bicarbonate, albumin, ionized calcium, total calcium, phosphate, alkaline phosphatase, total acid phosphatase, and prostatic acid phosphatase.

Intact parathyroid hormone (Nichols Institute Allegro Intact PTH Immunoassay -- two-site immunoradiometric assay) and 1,25-dihydroxyvitamin D (Reinhold Method) levels were determined by Yale University, Mineral Metabolism Laboratories.

Osteocalcin levels were measured by the \( ^{125} \text{I} \) Radioimmunoassay (bovine) in Dr. Caren M. Gundberg's laboratory, Yale University School of Medicine, Department of Orthopedics and Rehabilitation.

After all the data were obtained, the 50 subjects were divided according to race, white or black, and the groups were then analyzed for their bone turnover rates, various calcium tolerance parameters, and episodes of hypercalcemia. Therefore, those performing the laboratory analyses were blinded to the subjects' demographic background.
**Statistical Analyses**

Differences between the races in the parameters which consisted of continuous values were analyzed by the 2-tail Student's t-test (unpaired). In addition, using the respective upper limits of normal range as cutoff points, the parameters that reflect bone turnover rates were then converted to dichotomous variables for the 2x2 chi-square table and were also analyzed by chi-square analysis (or Fisher's exact test where appropriate). For the parameters that were originally dichotomous or nominal, only chi-square analysis (or Fisher's exact test) was used. Linear regression analysis was performed to determine the relationships between the various parameters measured. All data are presented as mean ± SEM or as percentages.

In addition, multivariate analyses were performed by general linear modelling procedures in IBM-PC SAS. This allowed for a closer look at the associations among variables and the factors that account for the predictable variabilities of certain parameters in the study.

The student arranged for all the blood drawings, reviewed medical records, and collected current data of the subjects. She performed all data entry and statistical analyses according to the design of the study with consultations from James Jekel, MD, MPH of Yale University School of Epidemiology. With the guidance of her thesis advisor, Margaret Bia, MD, the results were further interpreted and thesis manuscript written.
IV. Results

Demographic Data (Table 5)

Fifty HIV-negative, HBsAg-negative chronic hemodialysis patients participated in this study: 31 blacks and 19 whites (i.e., 62% blacks and 38% whites). The subjects were divided into two groups according to race: blacks and whites.

As shown in Table 5, the black and white patients were similar in their mean age, mean body mass index (BMI), mean length of time on dialysis, percent of subjects on dialysis longer than 6 months, that longer than 12 months, percent females, percent wheelchair-bound/bed-ridden subjects, percent with diabetes mellitus, and percent with subtotal parathyroidectomy.

The Yale-New Haven Dialysis Unit dietician obtained a 24-hour dietary recalls from 47 subjects. Twenty-one (67.74%) of 31 blacks and 12 (63.16%) of 19 whites actually provided recalls, and these percentages were not statistically different. Of the remaining, one black patient had psychiatric problems preventing her from giving an accurate 24-hour recall, and the rest of the patients reported themselves as poor historians who could not recollect their daily dietary intake.

The patient groups also had comparable mean serum albumin levels (4.32 ± 0.08g/dl in black vs. 4.06 ± 0.17g/dl in white patients). All women, except one white patient, were amenorrheic either due to their normal physiological menopause or due to their chronic renal failure and dialysis treatments; none received estrogen replacement therapy. The most recent subtotal parathyroidectomy in the unit was completed four months before this study. Although white patients had a slightly higher mean bicarbonate level (20.0 ± 0.55mmol/l in black subjects vs. 21.9 ± 0.74mmol/l in white subjects; p=0.0398), the two groups had similar mean values for the 3-month average (21±0.442mmol/l in black subjects vs. 22.2±0.542mmol/l in white subjects; p=NS).
Parameters of Bone Turnover Rate (Table 6, Figures 1, 2, 3, 4, & 5)

The four key measurements of bone turnover rate in this study were serum alkaline phosphatase, osteocalcin (serum bone Gla-protein, S-BGP), tartrate-resistant acid phosphatase levels, and intact parathyroid hormone. Statistically higher concentrations of serum tartrate-resistant acid phosphatase (4.4 ± 0.28U/l in black subjects vs. 3.3 ± 0.27U/l in white subjects; p=0.0166) (Figure 1) and intact parathyroid hormone (273 ± 56.5pg/ml in black subjects vs. 118 ± 39.1pg/ml in white subjects; p=0.0286) (Figure 2) were found among the black subjects compared to that the white subjects. Although the mean serum alkaline phosphatase (153 ± 20.8U/l in black subjects vs. 114 ± 22.0U/l in white subjects) (Figure 3) and osteocalcin (81.32 ± 12.82ng/ml in black subjects vs. 48.49 ± 15.32ng/ml in white subjects) (Figure 4) concentrations tended to be higher in the black patients than in the white patients, the differences did not reach statistical significance. However, the proportion of patients with serum osteocalcin levels above 25ng/ml was significantly higher among the black subjects than the white subjects (77.42% vs. 47.37%, respectively; p=0.0290) (Figure 5). The level of 25ng/ml was used since it is the upper limit of normal postmenopausal women, the group expected to have the highest levels in our subject population. There was a significantly higher percent of black patients having a 3-month average serum alkaline phosphatase levels higher than normal as compared to the whites (58.06% vs. 21.05%, respectively; p=0.0180).

Each of the above four parameters reflecting bone turnover rate was statistically higher in blacks than in whites, either by t-test or chi-square analysis. Since the two groups had similar mean dialyzer membrane surface areas, these differences were probably not the result of filtration variability, but rather a reflection of difference in bone turnover rate.

As mentioned above, plasma 1,25-dihydroxyvitamin D, known to have complex interactions with other bone turnover parameters, may activate bone resorption and may
exert a direct anabolic effect on the osteoblasts (181). The two patient groups had similar mean plasma 1,25-dihydroxyvitamin D levels (Table 7).

**Serum Calcium and Phosphate-P Levels** (Table 6)

The total serum calcium concentration on the day of study was representative of each patient's average total serum calcium concentration for the 3 months of review. When the means for serum ionized calcium and total serum calcium concentrations were compared between the two patient groups, no significant difference was found.

Likewise, there was also no significant difference in the means of these concentrations between the two patient populations. The serum phosphate-P level on the day of study was representative of the 3-month average serum phosphate-P level for each patient in the study.

**Parameters of Calcium Tolerance** (Table 7, Figures 6 & 7)

As mentioned above, the two racial groups in this study had similar mean serum ionized calcium and total serum calcium concentrations. However, black subjects had a significantly higher mean prescribed elemental calcium dose than white subjects (2330 ± 366.4mg/day vs. 1273 ± 312.9mg/day, respectively; p=0.05) (Figure 6). Chi-square analysis showed a statistically greater proportion of black patients who ingested calcium carbonate doses containing more than 1g of elemental calcium per day as compared to white patients (74.19% vs. 42.11%, respectively; p=0.023) (Figure 7). The percent of blacks whose doses contained more than 2g of elemental calcium per day also tended to be higher than that of whites, though the difference did not reach statistical significance (41.94% of black subjects vs. 15.79% of white subjects; p=0.0678). The two groups did not differ statistically on the percentages receiving oral aluminum hydroxide or the dose received. Likewise, the percentages receiving no phosphate binders were similar. The mean aluminum dose per day was similar in both groups as is the percentages receiving
more than 1g of elemental aluminum per day in the form of aluminum hydroxide, and percentages receiving more than 2g of elemental aluminum per day.

The two groups had comparable mean dietary calcium intakes, dialysate calcium concentrations, oral 1,25-dihydroxyvitamin D doses, and serum oral 1,25-dihydroxyvitamin D level. Similarly, the percent dialyzed against a 3.5mEq calcium per liter of bath (as opposed to a 2.5mEq/l bath), percent receiving oral 1,25-dihydroxyvitamin D supplementation, percent receiving greater than 0.25µg/day of oral 1,25-dihydroxyvitamin D, and percent with plasma 1,25-dihydroxyvitamin D level above 65pg/ml were not different between the two subject populations. Only one black patient received 1µg of Calcijex® (intravenous 1.25-dihydroxyvitamine D) twice a week postdialysis. Each patient group had two cases of hypercalcemia (6.45% of black subjects vs. 10.53% of white subjects; p=NS). [Hypercalcemia was defined as two or more measurements > 10.7mg.dl (2.7mmole/l), or a single value over 10.7mg/dl if it represented an increase of 1mg/dl (0.25mmol/l) over the average calcium value of the other 2 months of the 3-month review.] Lastly, the two groups also had similar mean dietary phosphorus intake

**Regression Analyses (Table 8)**

Osteocalcin was positively correlated with intact parathyroid hormone levels (r=+0.65484; p=0.0001), tartrate-resistant acid phosphatase (r=+0.59522; p=0.0001), and alkaline phosphatase (r=+0.40372; p=0.0036). There was also significant positive correlation between tartrate-resistant acid phosphatase and intact parathyroid hormone (r=+0.41709; p=0.0032). Furthermore, intact parathyroid hormone level was positively correlated with body mass index (BMI) (r=+0.41623; p=0.0033).

In addition, the patients' dietary calcium intake tended to correlate negatively with their serum calcium level (r=−0.33471; p=0.0569). Doses of elemental calcium doses as calcium carbonate correlated positively with serum 1,25-dihydroxyvitamin D levels.
(r=+0.47367; p=0.0005) and negatively with doses of oral 1,25-dihydroxyvitamin D
(r=+0.45854; p=0.0008), but not with any measure of bone turnover. There was also
positive correlation between serum 1,25-dihydroxyvitamin D levels and total serum calcium
concentrations (r=+0.34120; p=0.0153). However, no correlation was observed between
serum calcium level and elemental calcium dose or dietary calcium intake.
V. Discussion

This study examined bone turnover rate and degree of calcium tolerance in black versus white hemodialysis patients from the Yale-New Haven Hospital Dialysis Unit. Bone turnover was analyzed indirectly via serum intact parathyroid hormone, tartrate-resistant acid phosphatase, osteocalcin, and alkaline phosphatase levels. Mean levels of intact parathyroid hormone and tartrate-resistant acid phosphatase were significantly higher and mean levels of osteocalcin and alkaline phosphatase tended to be higher in the black compared to the white patients. Additionally, a greater percentage of black subjects than white subjects had levels greater than upper limits of normal range for osteocalcin and alkaline phosphatase.

On estimate of calcium ingestion, black patients had a significantly higher mean elemental calcium dose of calcium carbonate and a greater percentage ingesting more than 1g/day of elemental calcium than white patients did. The two groups had similar ionized calcium levels, total serum calcium levels, number of hypercalcemic episodes, serum phosphate levels, dietary calcium and phosphate intakes, oral 1,25-dihydroxyvitamin D doses.

Bone Turnover Rate

The key question raised in the study was whether there was appreciable difference in bone turnover rates of black versus white hemodialysis patients. In order to examine this hypothesis, parameters which provided indirect measures of bone remodeling were examined: serum intact parathyroid hormone, serum alkaline phosphatase, serum osteocalcin, and serum tartrate-resistant acid phosphatase concentrations as well as plasma 1,25-dihydroxyvitamin D level to some extent. Plasma 1,25-dihydroxyvitamin D appears to function in the dynamics of bone turnover (48, 119, 128), in addition to promoting
calcium absorption in the intestine. The black and white subjects in this study had similar mean plasma 1,25-dihydroxyvitamin D levels.

Black patients were found to have a significantly higher mean intact parathyroid hormone level than the white patients in this study. High parathyroid hormone levels tend to associate with high bone turnover rates with increased osteoblast and osteoclast numbers and increased bone formation and resorption (15, 35, 96). In the early stages of chronic renal disease, hyperphosphatemia and hypocalcemia are corrected at the expense of an elevated parathyroid hormone level (15, 83, 168, 172) which leads to phosphaturia and skeletal calcium release. As this cycle progresses, the parathyroid glands become less sensitive to the inhibitory effects of serum ionized calcium level (15, 168). As the negative feedback regulation between ionized calcium level and parathyroid secretion becomes less effective, massive hypertrophy or autonomy of the parathyroid glands tends to occur giving rise to high parathyroid hormone concentrations in the presence of hypercalcemia (175). Nevertheless, serum intact parathyroid hormone level is a indication of bone turnover.

In this study, black subjects tended to have a higher mean serum alkaline phosphatase level and had a significantly greater percentage with serum levels above the upper limit of normal range in comparison to white subjects. Serum alkaline phosphatase originates primarily in the bone, liver, and placenta. In terms of bone metabolism, the bone fraction of this enzyme rises in proportion to osteoblastic activity (28, 61). Accordingly, elevated serum alkaline phosphatase concentrations are seem in high bone turnover conditions such as osteitis fibrosa (5), whereas low levels were found in low bone turnover osteomalacia (16, 26, 40, 51, 182). In fact, serum alkaline phosphatase concentration correlates positively with the activity level at bone turnover surfaces (53). In this study, none of the subjects were pregnant, and all had been watched for liver disease from their routine liver enzyme tests of ALT (SGPT), AST (SGOT), and bilirubin (direct and total) concentrations. Thus, elevations of serum alkaline phosphatase levels were interpreted as increases in bone formation in this study.
Black subjects also tended to have a higher mean serum osteocalcin level and had a significantly greater percentage with levels above the upper limit of normal range compared to the white subjects in this study. As a result of impaired renal clearance of osteocalcin (49) and increased osteoblastic (28) and osteoclastic activities (26, 57, 76, 107, 158), chronic renal failure patients are known to have an elevated serum osteocalcin (serum bone gamma-carboxyglutamic acid-containing protein, serum Gla-protein, S-BGP) level. Having been identified as a more accurate marker of bone formation than serum alkaline phosphatase and parathyroid hormone levels in dialysis patients (27, 41, 107, 144, 158), serum osteocalcin levels were compared and found to be different between the two groups as described above. Serum osteocalcin levels correlated positively with parathyroid hormone and alkaline phosphatase levels in this study as in other studies. In accordance with previous studies (27, 41, 55, 107, 158), serum osteocalcin levels were not correlated with ionized calcium, or total serum calcium levels in this investigation.

Mean serum tartrate-resistant acid phosphatase level was significantly higher in black versus white patients in this study. This enzyme is released by osteoclasts during bone resorption (48, 119, 128). Therefore, it was used as an indirect marker of bone resorption. In this study, black patients had a higher mean tartrate-resistant acid phosphatase than the white patients. Furthermore, tartrate-resistant acid phosphatase levels correlated positively with osteocalcin and PTH levels. Therefore, our results are consistent with the fact that bone formation and bone mineralization are usually closely coupled.

Taken together, these results suggest that black patients have a higher bone turnover rates than white patients (Table 7). The mean values for all four major bone turnover parameters in black subjects were nearly two standard deviations above the white subjects' means. Furthermore, in every bone turnover parameter measured, there was a higher percentage of black subjects with values above the upper limit of normal range than white subjects. These differences reached statistical significance for serum osteocalcin and average serum alkaline phosphatase levels. At this point, we have no evidence that there
are differences in the clearance of these molecules between the two racial groups. Therefore, these findings, taken as an aggregate, suggest that the black dialysis patients had higher bone turnover rates than white dialysis patients. This difference is likely to be in part due to black patients’ greater degree of secondary hyperparathyroidism.

Possible Explanations of Higher iPTH levels in Black Patients

Whether the greater degree secondary hyperparathyroidism is due to biological / genetic predisposition or to socioeconomic factors or both warrants further investigation. In this investigation, it is possible that the PTH secretion in black patients has a higher calcium set point or is more resistant to the suppressive effects of vitamin D. Racial differences in bone metabolism of normal subjects without renal failure have been studied. In the healthy population, black people in general have a 5-10% higher bone density (due to greater bone mineral content) than white people do (42), a difference which persists even in patients with chronic renal failure (110). This is partly due to a greater increase in bone growth during the pubertal spurt in black individuals than in white individuals (70). Because of the higher parathyroid hormone levels (11) and a lower bone turnover rate in normal black subjects (about 35% of that in white subjects), Bell, et al. suggested that the black people are more resistant to the bone resorptive effects of parathyroid hormone compared to white people (191). They further proposed that the greater bone mass developed during adolescence is preserved by a lower rate of bone turnover throughout adulthood (191). Moreover, normal black individuals also have a higher 1,25-vitamin D level and a lower osteocalcin level (11). Unfortunately, whether this relative resistance increases or decreases in chronic dialysis patients is unclear, and the exact link between genetics and bone metabolism remains to be proven and elaborated in this patient population.

On the other hand, well known in this society is that socioeconomic factors can affect preventive care and early intervention, as well as patient education and compliance,
which in turn have major impacts on the progression of diseases to renal failure (32, 67, 77, 150). In general, black subjects, compared to white subjects, in this patient population may be less educated about the health care system, thus diseases in black patients may be brought to the attention of medical professionals much later (67). In addition, black patients may be less educated about their diseases leading to poorer compliance (67). For instance, in hypertension and diabetes mellitus, the two most common causes of renal failure, early medical intervention and good patient compliance may delay the progression to renal failure and may perhaps influence further complications once the patient is on renal dialysis. Thus, it is possible that the greater degree of hyperparathyroidism observed in black subjects in our study is due to socioeconomic factors leading to less frequent use of measures to prevent hyperparathyroidism in black subjects as end stage renal disease develops or after starting on dialysis.

Other Explanations

Several possible confounding factors were considered in this comparison of the racial groups. There was no evidence that the groups differed in terms of age, length of time on dialysis, serum albumin level, average serum bicarbonate concentration, percent females, percent with low activity, percent with diabetes mellitus, or percent post subtotal parathyroidectomy.

Aging has a large impact on calcium metabolism (21, 68, 153), and age is the most important determinant of bone density in a normal population. The decrease in bone density with increasing age may be a consequence of several age-related processes: decreased osteoblast function, decreased calcium absorption in both sexes especially after 70 years of age, and increase in serum immunoreactive parathyroid hormone. The increased bone turnover at the tissue level with increasing age actually enhances bone loss because of the decreased osteoblastic function at the cellular level. In other words, although the number of bone remodeling units in the skeleton is increased, more bone is
removed than is subsequently replaced. However, the two group in our study had similar mean age.

In recent years, the sex differences of bone metabolism and bone characteristics in the general population have been examined intensely. Compared to women within the same race, men tend to reach a higher peak bone density at skeletal maturity and maintain a heavier skeleton throughout life (111, 137). In addition, menopause accelerates bone loss in women. In our patient population, all women, except one white patient, were amenorrheic and were not receiving estrogen replacement therapy. Although men do not undergo the rapid physiological changes equivalent to menopause, gonadal function does decline gradually in some older men. Such hypogonadism is often associated with vertebral fractures. In light of these differences, this study took account the sex ratios in the two racial groups and showed no evidence of a statistical difference.

The physical activity level relevant to this study was assessed by the percent of wheelchair-bound/bed-ridden subjects in each group because mechanical forces have been shown to promote osteoblast growth and activity, and prolonged inactivity immobilization to cause secondary osteoporosis as a result of remodeling imbalance (96). Therefore, wheelchair-bound/bed-ridden are expected to have a relatively lower bone turnover rate. However, the two groups in our study had similar average activity levels, as measured by percentage of patients that were wheelchair-bound/bed-ridden.

Body mass indices of the two groups were considered since obese people are believed to have a slower rate of bone loss (95) and fewer spine fractures (114). Bell, et al. (12) also found that the obese non-dialysis subjects tended to have higher osteocalcin, plasma 1,25-dihydroxyvitamin D, and PTH levels and a lower serum 25-hydroxyvitamin D level. The two groups had similar body mass indices.

The results cannot be explained by greater diabetic osteopenia in white patients since the black patients actually had a greater percentage with diabetes mellitus, though this difference did not reach statistical significance. As bone mass has been variously reported
to be increased (114), normal (47), or decreased (94, 95, 183) in the older, adult diabetic population, there is no consensus in the literature. In addition, these diabetics are usually obese. In a study of 79 white, postmenopausal, type II diabetics with age, 59.9±6.6 years (mean ± SD), similar to the age of our patient population, Johnston, et al. (84) found that compared to normals, postmenopausal white type II diabetics lost bone at a slower rate and had higher bone mass compared to normals not explained by obesity or glucose control alone, although the diabetics did have a higher mean body weight than the controls. However, more recently, Chew (31) found that in the adult population, generalized osteoporosis may accompany insulin-dependent diabetes mellitus if obesity is absent. Moreover, Andress, et al. (8) observed that diabetes is often associated with the failure of PTH to promote bone mineralization. Thus, the current thinking is that osteopenia is more often seen in diabetes mellitus than in the normal population. In this investigation, the difference in the percentages of diabetes mellitus in black (54.84%) and white (31.84%) subjects was considerable, although it did not reach statistical significance. Therefore, if either one group were to have a lesser degree of diabetic low bone turnover, the black patient group is more likely. Our results are therefore even more impressive in demonstrating that bone turnover was higher in black patients despite a greater number of diabetic patients in this group.

Also important to consider was the percentage of subjects with subtotal parathyroidectomy in each group, since those with subtotal parathyroidectomy are expected to have a lower parathyroid hormone level than they would had without this surgical intervention. Short term effects of parathyroidectomy include alterations in plasma alkaline phosphatase activity and plasma osteocalcin level (187). Weinstein, et al. (190) found that the decrease in intact parathyroid hormone level after subtotal parathyroidectomy is associated with decreased mineralization and increased nonosteoblastic osteoid formation. After subtotal parathyroidectomy, some hemodialysis patients may convert osteitis fibrosa
Calcium Ingestion

In our study, the overall frequency of hypercalcemic episodes among the patients in our study was only 8% as compared to 36% in Meric and Bia's investigation at the same dialysis unit three years ago. This difference might lead one to think that either the patient characteristics of the unit had changed since that time or that some other factors had played a role in decreasing the incidence of hypercalcemia in this unit. After reviewing the characteristics of our patient population, we did not find any major difference. For example, our subject population was 38% white subjects, compared to their 36% white subjects. Thus, the first of the two possibilities did not seem likely.

However, the current management of the dialysis patients is very different from that at the time of Meric and Bia's study. They analyzed patients who had just been initiated on the high-dose calcium carbonate therapy and who had only minor or temporary modifications of their calcium doses in order to control their serum phosphate levels or to treat hypercalcemia if it occurred. Since then, management has changed to make hypercalcemic episodes less likely. For example, more than half of the patients in the unit are now on a low calcium bath (2.5 rather than 3.5 mEq/l). Furthermore, vitamin D supplements are not initiated until the patient is on a dose of calcium supplement that provides adequate phosphate binding. Because of these practices, the frequency of hypercalcemic episodes appears to be markedly reduced. In contrast to the patient population in Meric and Bia's study, ours reflect the success of such clinical manipulations to avoid hypercalcemia.

From this perspective, it was not surprising to find a lower incidence of hypercalcemia in our study compared to their study. However, this does not imply that the ability to tolerate ingested calcium is necessarily similar in black and white dialysis patients.
in our study. The two groups did have similar mean levels of serum calcium, ionized calcium, and serum phosphate-P. However, a look at the more subtle parameters of calcium tolerance revealed that there were differences in total calcium intake.

Although the two groups had similar dietary calcium intakes, dialysate calcium concentration, oral 1,25-dihydroxyvitamin D doses, and plasma 1,25-dihydroxyvitamin D levels, the black patients were able to tolerate significantly higher elemental calcium doses (in the form of calcium carbonate) than the white patients. The results suggest that black patients had either lesser passive reabsorption of oral calcium or lesser sensitivity of the action of vitamin D. The fact that the mean dietary phosphate intake and mean serum phosphate levels were comparable in the two racial groups implied that the two dialysis patient groups required similar amounts of phosphate-binding. At this time, calcium carbonate is preferred as a phosphate binder over aluminum hydroxide to avoid aluminum overload. During the present investigation, the first medical intervention in hypercalcemic patients taking calcium carbonate was to discontinue or lower the dose of calcium carbonate. The fact that elemental calcium doses from calcium carbonate tended to correlate negatively with elemental aluminum doses in the form of aluminum hydroxide among the subjects in this study suggests that patients on relatively lower doses of calcium carbonate are most likely to be those who cannot tolerate a higher dose. Therefore, these results suggest that black hemodialysis patients, compared to white patients, have greater ability to tolerate ingested calcium without becoming hypercalcemic (although the frequency of hypercalcemia is the same).

Slatopolsky, et al. (170) proposed that hypercalcemia on calcium-containing phosphate binders resulted from the high doses (greater than 12g) of calcium carbonate used. Gonella, et al. (74) suggested that those who developed hypercalcemia while on calcium carbonate had higher levels of vitamin D metabolites which would enhance calcium absorption. However, hypercalcemic episodes in other studies were often not related to high calcium carbonate doses (66, 71, 101, 116). Of the 41 dialysis patients on high-doses
of calcium carbonate in Mactier's study (101), the 11 who became hypercalcemic did not receive a higher dose than the rest. This observation suggests that the difference in the ability to tolerate calcium carbonate might not stem directly from difference in calcium absorption from the gut. In order to examine this issue, we looked at several factors relevant to calcium absorption.

Plasma level of 1,25-dihydroxyvitamin D is regarded as a major factor in the active absorption of calcium (50). While some studies have found that the decreased plasma 1,25-dihydroxyvitamin D level in chronic renal failure patients reduces calcium absorption in the gut (18, 39, 188), others have shown that intestinal calcium absorption is preserved in a rather unpredictable fashion from one patient to the next and perhaps supranormal absorption in the presence of severe uremia (118, 148). Therefore, variability in plasma 1,25-dihydroxyvitamin D levels may be present to account for the difference in calcium absorption. In the healthy population, black subjects appeared to have resistant to the intestinal calcium absorption effects of 1,25-dihydroxyvitamin D in one study (46), but such resistance was not found in another study comparing black and white adolescents (13). Whether this difference occurs in the chronic hemodialysis patients is unknown, and whether it holds true for calcium carbonate ingested as phosphate binders is also unclear. Studies have shown that a low calcium meal can nearly saturate the vitamin D-dependent active absorption of calcium in the gut of hemodialysis patients (135), so this difference found in the healthy subjects may not apply to this current study. Although their active calcium absorption abilities may be impaired, passive calcium absorption in chronic renal failure patients is believed to be intact (34, 135). Since the two groups in the present investigation were similar in their dietary calcium intake and the black patients had a higher elemental calcium dose in the form of calcium carbonate, there is no evidence in this study that the black patients absorbed less calcium via the vitamin D-dependent active process, although that possibility still exists. Many studies have suggested that the increased calcium absorption during calcium supplementation may be attributable to vitamin D-
independent mechanisms (72, 135, 175). Shiekh, et al. (160) found that passive calcium absorption correlated linearly with luminal calcium concentration which varied with calcium intake. With large doses of calcium carbonate (20g), absorption was the same in patients with and without renal disease (34). Therefore, the average amounts of calcium passively absorbed by the subjects were expected to correlate roughly with their mean calcium doses. Since the black patients in our study tolerated a higher calcium dose from calcium carbonate, their overall intestinal calcium absorption was probably greater than white patients' on the basis of passive absorption alone. Thus, neither intestinal calcium absorption nor calcium carbonate dosage is likely to account for the greater ability to tolerate ingested calcium in the black compared to the white patients.

In the chronic hemodialysis patients, it remains possible that differences in intestinal calcium absorption contribute to the greater calcium ingestion tolerated by black patients. This question is best answered by measuring calcium absorption directly with stringent records of intake and output or with oral $^{45}$Ca studies, rather than from the less reliable dietary recalls by patients.

In summary, the black hemodialysis patients in this study appear to have a greater degree of secondary hyperparathyroidism and a higher bone turnover rate than the white patients. Whether this difference is due to biological/genetic predisposition or is due to socioeconomic factors affecting preventive care and early intervention warrants further investigation.

The association between high bone turnover rate and decreased likelihood of hypercalcemia in dialysis patients has been documented (116). The fact that black patients in our study had a greater calcium tolerance may well be explained by their higher bone turnover rate, which allowed serum calcium to be deposited into bone more quickly. The lack of linear correlation between elemental calcium dose and parameters of bone turnover does not disprove this explanation, as the relationship between the two may not be strictly
linear. Of course, further confirmation of this explanation rests on bone biopsy, the definitive measure of bone turnover. In any case, the black hemodialysis patients appear to be able to tolerate a higher dose of calcium carbonate than white patient without succumbing to the side effect of hypercalcemia.
VI. Conclusion

In comparison to the white hemodialysis patients, black patients had a higher bone turnover rate as reflected by a higher mean serum tartrate-resistant acid phosphatase level and mean intact parathyroid hormone level (suggesting a greater degree of secondary hyperparathyroidism), as well as by a greater percentage of the group having an elevated osteocalcin level and a greater percentage of the group having an elevated average alkaline phosphatase level. Moreover, the high degree of positive correlation between osteocalcin and tartrate-resistant acid phosphatase levels suggests that the bone formation and reabsorptions rates of these hemodialysis patients were closely coupled as seen in normal bone metabolism and in high turnover states of hyperparathyroidism. These results are consistent with the explanation that the higher bone turnover rates in black patients make available their bones as a reservoir for any excess calcium in the circulation, rather than allowing them to become hypercalcemic. Whether the greater bone turnover rate and greater degree of secondary hyperparathyroidism in blacks are the results of genetic predisposition or the results of social factors affecting preventive care and early intervention warrants further research.

While requiring similar amounts of phosphate-binding, the two patient group ingested different amounts of calcium carbonate, which is preferred over aluminum hydroxide as a phosphate binder. Compared to the whites, black patients tended to have a higher mean elemental calcium dose (in the form of calcium carbonate) and did have a significantly higher percentage receiving over 1 gram of elemental calcium in the form of calcium carbonate. However, the two groups had similar mean total serum calcium, ionized calcium, and dialysate calcium concentrations. It appeared then that the black patients had a greater tolerance for calcium carbonate (without becoming hypercalcemic or
having to lower the dialysate calcium concentration) than the white patients. This greater
calcium tolerance in black patients was probably not a result of a decreased intestinal
absorptive capacity because 1) there was no evidence to show that the groups differed in
terms of dietary calcium intake and plasma 1,25-dihydroxyvitamin D level, 2) vitamin D-
dependent calcium absorption tends to be saturated at low calcium intakes in chronic renal
failure so that any vitamin D resistance at the gut level in black patients probably plays a
minor role, if any, and 3) the black patients had a higher mean calcium dose from calcium
carbonate than the white patients suggesting a greater amount of calcium absorbed via
passive vitamin D-independent mechanism. Therefore, the black patients' higher tolerance
for the calcium from calcium carbonate probably cannot be attributable to a reduction of
intestinal calcium absorption and certainly not to a lower calcium carbonate dose.
However, these results are consistent with the idea that the blacks' higher bone turnover
rate renders them the greater calcium tolerance.

At this time, there have not been any reports on racial differences in bone turnover
and calcium tolerance in chronic hemodialysis patients. The findings of this study remain
to be confirmed and extended by future research. Whether the greater degree of
hyperparathyroidism in the black patient group is a consequence of genetic or social factors
also deserves further investigation.
VII. Tables

Table 1: Factors Contributing to the Development of Secondary Hyperparathyroidism in Renal Insufficiency (35)

<table>
<thead>
<tr>
<th>1. Phosphate retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Altered vitamin D metabolism</td>
</tr>
<tr>
<td>3. Skeletal resistance to the calcemic action of parathyroid hormone</td>
</tr>
<tr>
<td>4. Altered feedback regulation between ionized calcium level and parathyroid secretion</td>
</tr>
<tr>
<td>5. Impaired degradation of parathyroid hormone by the kidneys.</td>
</tr>
</tbody>
</table>
Table 2: Causes of Hypercalcemia (178)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>2.</td>
<td>Cancer-associated hypercalcemia</td>
</tr>
<tr>
<td>3.</td>
<td>Hypervitaminosis D</td>
</tr>
<tr>
<td>4.</td>
<td>Sarcoidosis and other granulomatous diseases</td>
</tr>
<tr>
<td>5.</td>
<td>Idiopathic hypercalcemia of infancy</td>
</tr>
<tr>
<td>6.</td>
<td>Hypervitaminosis A</td>
</tr>
<tr>
<td>7.</td>
<td>Hypercalcemic periostitis</td>
</tr>
<tr>
<td>8.</td>
<td>Milk-alkali syndrome</td>
</tr>
<tr>
<td>9.</td>
<td>Immobilization (extensive skeletal immobilization in normal young people and prolonged bed rest in patients with osteolytic metabolic bone disease)</td>
</tr>
<tr>
<td>10.</td>
<td>Recovery from acute renal failure</td>
</tr>
<tr>
<td>11.</td>
<td>Thiazide diuretic-associated hypercalcemia</td>
</tr>
<tr>
<td>12.</td>
<td>Other endocrine causes of hypercalcemia (Hyperthyroidism, Adrenal insufficiency, etc)</td>
</tr>
<tr>
<td>13.</td>
<td>Low turnover osteomalacia due to aluminum accumulation (Dialysis osteomalacia, total parenteral nutrition)</td>
</tr>
<tr>
<td>14.</td>
<td>Familial Hypocalcuric hypercalcemia</td>
</tr>
<tr>
<td>15.</td>
<td>Other mechanisms: theophylline, lithium, etc</td>
</tr>
</tbody>
</table>
Table 3: Causes of Hypercalcemia in Dialysis Patients (35)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Severe secondary hyperparathyroidism</td>
</tr>
<tr>
<td>2.</td>
<td>Low turnover osteomalacia due to aluminum accumulation</td>
</tr>
<tr>
<td>3.</td>
<td>Treatment with calcium-containing phosphate binders (calcium carbonate, calcium acetate, calcium citrate) and/or with vitamin D sterols*</td>
</tr>
<tr>
<td>4.</td>
<td>High dialysate calcium concentration</td>
</tr>
<tr>
<td>5.</td>
<td>Endogenous production of 1,25-dihydroxyvitamin D (sarcoidosis, tuberculosis, or other granulomatous diseases)</td>
</tr>
<tr>
<td>6.</td>
<td>Malignancy or neoplasms</td>
</tr>
<tr>
<td>7.</td>
<td>Immobilization*</td>
</tr>
</tbody>
</table>

* often coexists with #1 and #2 and may be the precipitating or aggravating event in the manifestation of hypercalcemia.
Table 4: Selection of Subject Population and Its Sex and Racial Distributions

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td>Fifty-eight patients chronically hemodialyzed at the Yale-New Haven Dialysis Unit.</td>
</tr>
<tr>
<td>-2</td>
<td>Two patients were Hispanic but were HIV-negative and HBsAg-negative.</td>
</tr>
<tr>
<td>-1</td>
<td>One patient was HBsAg-positive and Hispanic.</td>
</tr>
<tr>
<td>-1</td>
<td>One patient was HIV-positive.</td>
</tr>
<tr>
<td>-4</td>
<td>Four patients did not give oral consent to participate in this study.</td>
</tr>
<tr>
<td>50</td>
<td>Fifty HIV-negative and HBsAg-negative, black and white patients who were chronically hemodialyzed at the Yale-New Haven Dialysis Unit gave oral consent and participated in this study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black females</td>
<td>16</td>
</tr>
<tr>
<td>Black males</td>
<td>15</td>
</tr>
<tr>
<td>Black subjects</td>
<td>31</td>
</tr>
<tr>
<td>White females</td>
<td>6</td>
</tr>
<tr>
<td>White males</td>
<td>13</td>
</tr>
<tr>
<td>White subjects</td>
<td>19</td>
</tr>
</tbody>
</table>
Table 5: Demographic Data compared by Student's t-test or chi-square analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Blacks</th>
<th>Whites</th>
<th>p value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years) (mean ± SE)</td>
<td>57.2 ± 2.5</td>
<td>62.6 ± 3.0</td>
<td>—</td>
</tr>
<tr>
<td>body mass index (BMI) (kg/m&lt;sup&gt;2&lt;/sup&gt;) (mean ± SE)</td>
<td>26.0 ± 1.9</td>
<td>24.2 ± 1.3</td>
<td>—</td>
</tr>
<tr>
<td>years on dialysis (mean ± SE)</td>
<td>3.8 ± 0.8</td>
<td>3.0 ± 1</td>
<td>—</td>
</tr>
<tr>
<td>% on dialysis &gt; 6 months</td>
<td>87.1</td>
<td>89.5</td>
<td>—</td>
</tr>
<tr>
<td>% on dialysis &gt; 12 months</td>
<td>80.7</td>
<td>57.9</td>
<td>—</td>
</tr>
<tr>
<td>% female</td>
<td>51.6</td>
<td>31.6</td>
<td>—</td>
</tr>
<tr>
<td>% wheelchair-bound or bedridden</td>
<td>16.1</td>
<td>10.5</td>
<td>—</td>
</tr>
<tr>
<td>% with diabetes mellitus</td>
<td>54.8</td>
<td>31.6</td>
<td>—</td>
</tr>
<tr>
<td>% with subtotal parathyroidectomy</td>
<td>12.9</td>
<td>5.3</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>1</sup> p values greater than 0.05 are not listed.
<sup>2</sup> measured in 18/19 white patients.
Table 6: Parameters of Bone Turnover Rate compared by Student's t-test and chi-square / Fisher's exact test

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Blacks mean ± SE</th>
<th>Whites mean ± SE</th>
<th>p value&lt;sup&gt;1&lt;/sup&gt;</th>
<th>% of Blacks</th>
<th>% of Whites</th>
<th>p-value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialyzer membrane surface area (m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>1.16 ± 0.01</td>
<td>1.18 ± 0.02</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ionized calcium (mg/dl)</td>
<td>4.81 ± 0.09</td>
<td>4.81 ± 0.13</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total calcium (mg/dl)</td>
<td>9.4 ± 0.18</td>
<td>9.2 ± 0.23</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hypercalcemia during the 3 months of review</td>
<td>6.45</td>
<td>10.53</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phosphate-P (mg/dl)</td>
<td>5.48 ± 0.40</td>
<td>5.87 ± 0.68</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>153 ± 20.8</td>
<td>114 ± 22.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alkaline phosphatase level &gt; 114U/l</td>
<td>54.84</td>
<td>31.58</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml)</td>
<td>81.32 ± 12.82</td>
<td>48.49 ± 15.32</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Osteocalcin level &gt; 25 ng/ml</td>
<td>77.42</td>
<td>47.37</td>
<td>0.0290</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tartrate-resistant acid phosphatase&lt;sup&gt;2&lt;/sup&gt; (U/l)</td>
<td>4.4 ± 0.28</td>
<td>3.3 ± 0.27</td>
<td>0.0166</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tartrate-resistant acid phosphatase&lt;sup&gt;2&lt;/sup&gt; &gt; 4.2U/l</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>273 ± 56.5</td>
<td>118 ± 39.1</td>
<td>0.0286</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Intact PTH level &gt; 65pg/ml</td>
<td>64.52</td>
<td>47.37</td>
<td>0.0290</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serum 1,25-(OH)&lt;sub&gt;2&lt;/sub&gt;D level (pg/ml)</td>
<td>30.7 ± 2.69</td>
<td>25.6 ± 1.25</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serum 1,25-(OH)&lt;sub&gt;2&lt;/sub&gt;D level &gt; 65pg/ml</td>
<td>3.23</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>1</sup> p values greater than 0.05 are not listed.

<sup>2</sup> N for tartrate-resistant acid phosphatase is 30/31 for blacks and 18/19 for whites.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intact PTH level</th>
<th>Intact PTH level &gt; 65pg/ml</th>
<th>1,25-(OH)2 D level (pg/ml)</th>
<th>1,25-(OH)2 D level &gt; 65pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>intact PTH (pg/ml)</td>
<td>273 ± 56.5</td>
<td>64.52</td>
<td>30.7 ± 2.69</td>
<td>3.23</td>
</tr>
<tr>
<td>intact PTH level &gt; 65pg/ml</td>
<td>118 ± 39.1</td>
<td>47.37</td>
<td>25.6 ± 1.25</td>
<td>0.00</td>
</tr>
</tbody>
</table>

1. p values greater than 0.05 are not listed.
2. N for tartrate-resistant acid phosphatase is 30/31 for blacks and 18/19 for whites.
Table 7: Parameters of Calcium Tolerance compared by Student's t-test and chi-square / Fisher's exact test

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Blacks mean ± SE</th>
<th>Whites mean ± SE</th>
<th>p-value</th>
<th>% of Blacks N=31</th>
<th>% of Whites N=19</th>
<th>p-value</th>
<th>chi-square / Fisher's exact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Calcium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ionized calcium (mg/dl)</td>
<td>4.81 ± 0.09</td>
<td>4.81 ± 0.13</td>
<td>0.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>serum calcium (mg/dl)</td>
<td>9.4 ± 0.18</td>
<td>9.2 ± 0.23</td>
<td>0.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypercalcemia during the 3 months reviewed</td>
<td>6.45</td>
<td>10.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysate Calcium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dialysate calcium concentration (mEq/l)</td>
<td>3.1 ± 0.09</td>
<td>3.0 ± 0.18</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with dialysate calcium conc = 3.5mEq/l</td>
<td>54.84</td>
<td>52.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium Intake²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dietary calcium (mg/day)</td>
<td>493 ± 56.0</td>
<td>522 ± 71.7</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>dietary calcium intake &gt; 600mg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elemental calcium dose (mg/day)</td>
<td>2330 ± 366.4</td>
<td>1273 ± 312.9</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% on dose &gt; 1g elemental calcium³ per day</td>
<td>74.19</td>
<td>42.11</td>
<td>0.0230</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% on calcium-containing phosphate³ binder</td>
<td>80.65</td>
<td>68.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oral 1,25-dihydroxyvitamin D dose (µg/day)</td>
<td>0.15 ± 0.03</td>
<td>0.09 ± 0.03</td>
<td>0.74</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% on oral 1,25-dihydroxyvitamin D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% on oral vitamin D dose &gt; 0.25 µg/day</td>
<td>48.39</td>
<td>31.58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plasma 1,25-(OH)₂ D level (pg/ml)</td>
<td>30.7 ± 2.69</td>
<td>25.6 ± 1.25</td>
<td>0.28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plasma 1,25-(OH)₂ D level &gt; 65pg/ml</td>
<td>3.23</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphate Intake⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dietary phosphorus (mg/day)</td>
<td>867 ± 53.2</td>
<td>926 ± 111</td>
<td>0.24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminum Intake⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elemental aluminum dose (mg/day)</td>
<td>405.7 ± 107.6</td>
<td>673.4 ± 201.4</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% on aluminum-containing phosphate binder</td>
<td>38.71</td>
<td>47.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% on dose &gt;1g elemental aluminum per day</td>
<td>25.81</td>
<td>42.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% on dose &gt;2g elemental aluminum per day</td>
<td>3.23</td>
<td>5.26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no phosphate binder</td>
<td>3.23</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 p values greater than 0.05 are not listed.
2 Dietary calcium intakes were obtained for 21/31 black patients and 12/19 white patients.
3 Administered in the form of calcium carbonate
4 Dietary phosphorus intakes were obtained for 21/31 black patients and 12/19 white patients.
5 Administered in the form of aluminum hydroxide
Table 8: Linear Correlations

<table>
<thead>
<tr>
<th>Parameter 1</th>
<th>Parameter 2</th>
<th>Pearson correlation coefficient</th>
<th>p value</th>
<th>sample size (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>osteocalcin</td>
<td>&amp; intact PTH</td>
<td>+0.65484</td>
<td>0.0001</td>
<td>50</td>
</tr>
<tr>
<td>osteocalcin</td>
<td>&amp; TRAP</td>
<td>+0.59522</td>
<td>0.0001</td>
<td>48</td>
</tr>
<tr>
<td>osteocalcin</td>
<td>&amp; alkaline phosphatase</td>
<td>+0.40372</td>
<td>0.0036</td>
<td>50</td>
</tr>
<tr>
<td>TRAP</td>
<td>&amp; intact PTH</td>
<td>+0.41709</td>
<td>0.0032</td>
<td>48</td>
</tr>
<tr>
<td>intact PTH</td>
<td>&amp; body mass index</td>
<td>+0.41623</td>
<td>0.0033</td>
<td>50</td>
</tr>
<tr>
<td>elemental calcium dose</td>
<td>&amp; serum 1,25-dihydroxyvitamin D</td>
<td>+0.47367</td>
<td>0.0005</td>
<td>50</td>
</tr>
<tr>
<td>elemental calcium dose</td>
<td>&amp; oral 1,25-dihydroxyvitamin D</td>
<td>+0.45854</td>
<td>0.0008</td>
<td>50</td>
</tr>
<tr>
<td>serum 1,25-dihydroxyvitamin D</td>
<td>&amp; total serum calcium</td>
<td>+0.34120</td>
<td>0.0153</td>
<td>50</td>
</tr>
</tbody>
</table>

Elemental calcium doses of calcium carbonate did not correlate with any parameter of bone turnover.

Serum calcium level is not correlated with either elemental calcium dose or dietary calcium intake.

Table 9: Correlations found by Meric, F., et al. (116)

<table>
<thead>
<tr>
<th>Parameter 1</th>
<th>Parameter 2</th>
<th>Pearson correlation coefficient</th>
<th>p value</th>
<th>sample size (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>osteocalcin</td>
<td>&amp; PTH</td>
<td>+ 0.8</td>
<td>&lt; 0.001</td>
<td>28</td>
</tr>
<tr>
<td>serum calcium</td>
<td>&amp; alkaline phosphatase</td>
<td>- 0.38</td>
<td>0.045</td>
<td>28</td>
</tr>
<tr>
<td>osteocalcin</td>
<td>&amp; alkaline phosphatase</td>
<td>+ 0.46</td>
<td>&lt; 0.001</td>
<td>28</td>
</tr>
</tbody>
</table>

Osteocalcin levels did not correlate with mean or peak serum calcium concentration on calcium carbonate therapy.
Figure 1: Distributions and Means of Serum Tartrate-Resistant Acid Phosphatase Levels of Black and White Patients

$\text{p = 0.0166}$
Figure 2: Distributions and Means of Serum intact Parathyroid Hormone (PTH) Levels of Black and White Patients

\[ p = 0.0286 \]
Figure 3: Distributions and Means of Serum Alkaline Phosphatase Levels* of Black and White Patients

* Plotted are values and calculations from the patients' serum alkaline phosphatase levels at the time of study.
Figure 4: Distributions and Means of Serum Osteocalcin Levels of Black and White Patients

- Females
- Males
- Mean of Blacks
- Mean of Whites

Serum Osteocalcin Level (ng/ml)
Figure 5: The Percentages of Black and White Patients with Elevated* Serum Osteocalcin Levels

* Serum osteocalcin levels above the upper limit for normal range (25ng/ml) were considered elevated.
Figure 6: Distributions and Means of Daily Elemental Calcium Dose* of Black and White Patients

\[ p = 0.05 \]

* Daily elemental calcium doses were calculated from the patients' prescribed dialy calcium carbonate doses.
Figure 7: The Percentages of Black and White Patients with Daily Elemental Calcium Dose* Above 1 Gram

\[ p = 0.0230 \]

*The daily elemental calcium doses were calculated from the patients' prescribed daily doses of calcium carbonate.
IX. References


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