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Biochemical effects in patients of pediatric nephrotic syndrome related Vitamin D and Calcium metabolism

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Abstract
Minimal Change Disease (MCD) is the leading cause of childhood Nephrotic Syndrome (NS). Therefore in pediatrics nephrotic syndrome, most children beyond the first year of life will be treated with corticosteroids without an initial biopsy. Children with NS often display a number of calcium homeostasis disturbances causing abnormal bone histology, including hypocalcemia, reduced serum vitamin D metabolites, impaired intestinal absorption of calcium, and elevated levels of immunoreactive parathyroid hormone (iPTH). These are mainly attributed to the loss of a variety of plasma proteins and minerals in the urine as well as steroid therapy. Early diagnosis and management of these abnormalities, could prevent the growth retardation and renal osteodystrophy that affects children with nephrotic syndrome. Here we reviewed the literature for changes of calcium and vitamin D metabolism in nephrotic syndrome and its consequences on bones, also the effect of corticosteroid and possible preventive strategies that could be done to avoid long term outcomes in children. Although the exact biochemical basis for Changes in levels of calcium and vitamin D metabolites in patients with NS remains speculative; Because of the potential adverse effects of these changes among growing children, widespread screening for vitamin D deficiency or routine vitamin D supplementation should be considered.

Keywords: pediatric nephrotic syndrome, calcium, vitamin D

Introduction
In children up to the age of 15-16 years, the most frequent glomerular disease is idiopathic nephrotic syndrome including minimal change disease, FSGS (Focal Segmantal Glumerulo Sclerosis), and diffuse mesangial proliferation, with MCD being the most common form. So the term minimal change disease has become synonymous with steroid-sensitive idiopathic nephrotic syndrome; therefore in pediatrics nephrotic syndrome, considering MCD as the most probable diagnosis, most children beyond the first year of life will be treated with corticosteroids without an initial biopsy [1-3].
Children with NS often display a number of calcium homeostasis disturbances causing abnormal bone histology, including hypocalcemia, reduced serum vitamin D metabolites, impaired intestinal absorption of calcium, and elevated levels of immunoreactive parathyroid hormone (PTH). Serum phosphorus concentration is usually normal. These are mainly attributed to the loss of a variety of plasma proteins and minerals in the urine as well as steroid therapy [4-10]. Most patients with nephrotic syndrome also have renal failure, so it may play a role in the abnormalities of calcium metabolism in these patients, although these patients can show calcium and vitamin D abnormalities even with normal GFR (Glomerular Filtration Rate) [10-12]. As a result, children with idiopathic nephrotic syndrome are at risk for metabolic bone disease such as reduced Bone Mineral Density (BMD) and abnormal bone histology, including osteomalacia as well as excessive bone resorption resembling secondary hyperparathyroidism. Early diagnosis and management of these abnormalities, could prevent the growth retardation and renal osteodystrophy that affects children with nephrotic syndrome [8, 10, 12-16]. However, hypocalcemia may also lead to other neuromuscular (e.g. tetany), cardiovascular and mental disorders. Symptoms may range from mild (perioral numbness, paresthesias, and muscle cramps) to severe (carpopedal spasm, laryngospasm, and focal or generalized seizures) [9].
So we conducted a literature review to have a better perspective on the changes of calcium and vitamin D metabolism in nephrotic syndrome and its consequences on bones, along with the effect of corticosteroid therapy to provoke this phenomenon, and possible preventive strategies that could be done to avoid long term outcomes in children.

Aim and Objectives
Early diagnosis and management of these abnormalities, could prevent the growth retardation and renal osteodystrophy that affects children with nephrotic syndrome. Here we reviewed the literature for changes of calcium and vitamin D metabolism in nephrotic syndrome and its consequences on bones, also the effect of corticosteroid and possible preventive strategies that could be done to avoid long term outcomes in children.

Material and Methods
Relevant articles in English with specific interest in Calcium and vitamin D status in Nephrotic Syndrome were reviewed. References of such articles generated also enabled widening the reference pool.

Results and Discussion
Data regarding alteration in calcium and vitamin D metabolism in patients with steroid sensitive NS are conflicting and scarce. Although the onset of renal insufficiency may contribute, these abnormalities in calcium and vitamin D levels may be found in patients with NS and normal renal function [6, 7, 10, 12, 16-18].

Hypocalcemia seems to be a common feature in NS patients [9, 10, 18, 19] although some studies reported normal serum calcium levels [7, 11, 12]. In a study conducted by Thomas *et al*. in 1998 nephrotic syndrome, was among significant univariate predictors of hypovitaminosis D [20]. The Plasma concentration of 25-hydroxyvitamin D [25(OH) D] is low in patients with NS because of a loss of vitamin D-binding protein in the urine [7, 8, 11, 12, 16, 18]. 1,25(OH)2D levels, which shares the same plasma binding protein, have been found to have decreased [6, 7, 21, 22] or to have been unchanged [8, 11, 12, 18] in patients with nephrotic syndrome. Majority of the previous studied showed that despite low ionized serum calcium and histological evidence of secondary hyperparathyroidism hyperparathyroidism in some patients, PTH levels are not consistently elevated in NS patients [6-8, 11, 12, 16-19]. Increased blood immunoreactive parathyroid hormone (iPTH) levels were reported in rare number of studies [6, 17, 18]. The apparent conflicting results in iPTH and serum ionized calcium values may be related to differences in patient populations or differing conditions under which the measurements were made. Serum phosphorus concentration was normal in most of the studies conducted on these patients [10-12, 17, 19].

Histological bone alterations in these patients has also been reported, although in the presence of normal or low calcium levels [10, 13, 19, 23]. In contrast, some patients with elevated PTH and reduced calcium and vitamin D metabolites may display normal or near-normal bone histology on bone biopsy [11, 16, 24]. Although these changes may occur as a result of the prolonged proteinuric state or reduced vitamin D levels as the major determinants, it is likely that additional unknown factors may be operating in this group of patients. Furthermore, the frequent use of corticosteroid therapy may be associated with osteoporosis in children with NS [11].

Osteoporosis is a well-known serious side effect of long-term treatment with glucocorticoids. GCs (GlucoCorticoids) are associated with decreased gastrointestinal calcium absorption and increased urinary Ca excretion by decreasing its reabsorption in the renal tubule, resulting in a negative calcium balance. Furthermore, GCs stimulate bone resorption directly by enhancing osteoclast activity and indirectly via increasing parathormon (PTH) production. Glucocorticoids also inhibit osteoblasts through reduction of osteoblast differentiation and increasing apoptosis of the mature osteoblasts resulting in reduce in reduce the total number of osteoblasts, and an inhibition of the synthesis of osteoid by these cells, which results in significant reductions in bone formation [2, 4, 13, 14, 24, 25]. Reduced Bone mineral content (BMC) also has been reported in short term, high dose applications of GCs [26, 27].

Osteoporosis is of particular concern in growing children who underwent long term steroid therapy. During childhood andadolescence, skeletal changes result in increases in bone dimensions and density. Children therefore seem to be vulnerable to adverse glucocorticoid effects on bone formation, leading to possible compromises in peakbone mass [24, 28]. Steroid-dependent minimal-change nephrotic syndrome thatoriginates in childhood can persist after puberty in >20% of patients. These patients require immunosuppressive treatment during several decades of their life. Also 30% of these children develop a frequently relapsing course [3]. However, children may display preserved bone mineral mass even shortly after the cessation of intermittent high dose glucocorticoid therapy, suggesting the capability of the young skeleton to rapidly regain previous steroid-induced bone losses [29].

Studies have demonstrated defective bone mineralization and an inverse correlation between the administered dose of corticosteroid therapy and bone formation rates in bone biopsies of children with NS [3, 14, 15, 30, 31]. Although others found no difference in bone mineral content in children receiving corticosteroids compared with those who were off steroids [29]. These discrepancies may be attributed to variations in the number and age of the studied patients, duration of the disease, steroid dose and the methodology used to assess the laboratory markers of bone metabolism. These findings indicate the need for further studies regarding the prevention of steroid-induced osteoporosis in children.

Although long duration of steroid therapy in children with Nephrotic syndrome may increase the risk for osteoporosis, the long-term outcome of this chronic disease is favorable [2, 3].

Some of the detrimental bone effects which seems to be because of glucocorticoids, may be caused by the underlying inflammatory disease. For example, inflammatory cytokines that are elevated in chronic disease, such as tumor necrosis factor, suppress bone formation and promote bone resorption through mechanisms similar to glucocorticoid-induced osteoporosis [24]. The accurate characterization of glucocorticoid and disease effects on skeletal development is necessary to identify and evaluate targeted therapies to optimize skeletal architecture and peak bone mass [24]. Mohamed *et al*. reported that, the significant decrease of markers of bone formation and the increase of the marker of bone resorption in newly diagnosed patients with NS, prior to GC therapy, as compared with controls, may point to the significant role of the renal disease itself in the abnormality of bone metabolism in NS [4]. Gulati *et al*. also mentioned that biochemical derangements caused by the renal disease itself is one of the important leading causes of metabolic bone disease in NS and GC is not the only factor responsible for osteopenia [32]. According to review done by Mohamed *et al*., other factors that may contribute to resorption include nutritional deficiency, hypoproteinemia, immobilization, and proinflammatory cytokines excessively produced in active inflammation, which triggers excessive osteoclastic activity [4].

There are few studies to date which has evaluated the role of vitamin D and calcium supplements in NS patients. It is likely that these children will fail to achieve their peak bone mass, which is a key determinant of the lifetime risk of osteoporosis and are at risk for fractures later on during their lifetime. Osteoporosis prevention is best achieved by optimizing gains in bone mineral throughout childhood and adolescence [13]. Because replacement therapy is simple and reduces the risk of fractures, an understanding of the importance of supplement therapy in childhood NS is of particular importance [20]. some studies has been reported that supplementation with calcium and vitamin D is beneficial in preventing bone loss [10, 13, 26]. The treatment with a high dose of vitamin D3 may correct the abnormalities, which suggests vitamin D3 should be used in children with protracted active NS [18]. Sedman et al suggested that Children with [33, 34]. despite all these evidence, some studies studies have been suggested that increase in serum calcium levels cannot be affected by calcium and vitamin D supplementation [35] and it's primarily due to disease remission

after steroid therapy and Good management of NS patients leads to improved serum calcium levels, with or without supplementation [9, 36]. On the other hand supplementation may increase serum levels of calcium or vitamin D, but it won't necessarily reduce the risk for low BMD [10, 13].

Steroid induced osteoporosis could be prevented by administration of a bisphosphonate, such as risedronate. So in patients with NS receiving steroids, administration of a bisphosphonate might be advisable [25, 37]. although evidence concerning these issue are not quite concluding.

Conclusion

In summary changes in levels of calcium and vitamin D metabolites in patients with NS are considered to be following urinary losses of these metabolites or their carrier proteins or secondary to corticosteroid therapy, especially in long term therapeutic courses; but the exact biochemical basis for these changes remains speculative. Because of the potential adverse effects of calcium and vitamin D deficiency on the skeleton and other organ Systems of NS patients, especially among growing children, widespread screening for vitamin D deficiency or routine vitamin D supplementation should be considered.

Future Scope

Supplementation with calcium and vitamin D is beneficial in preventing bone loss. The treatment with a high dose of vitamin D3 may correct the abnormalities, which suggests vitamin D3 should be used in children with protracted active NS.Routine vitamin D supplementation should be considered.

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