

Original Article

Thyrotoxicosis and osteomalacia: from symptom to pathogenesis

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Abstract: Thyroid hormones have a direct effect on bone mineral homeostasis, leading to increased bone mineral resorption and calcium loss through the kidneys. Osteomalacia is conceptualized as a disorder of bone tissue characterized by inadequate or delayed mineralization of osteoid in mature cortical and spongy bone, and is associated with thyrotoxicosis. This article assessed the impact of thyrotoxicosis on the occurrence and development of osteomalacia for better diagnosis and treatment of the disease. We searched databases such as Pubmed with “osteomalacia” and “thyrotoxicosis”, 15 papers were found; with “osteopenia” or “osteomalacia” or “osteoporosis” and “thyrotoxicosis”, 129 papers were found. The causes of osteomalacia include insufficient intake of calcium, phosphorus and vitamin D, impaired absorption and metabolism of vitamin D, kidney diseases (nephrotic syndrome, chronic renal failure, renal tubular acidosis, Fanconi syndrome, etc.), hereditary and neoplastic hypophosphatemia, and other diseases such as heavy metal poisoning, high fluoride intake. At present, the pathogenesis of osteomalacia caused by thyrotoxicosis are mainly attributed to catabolism of vitamin D, vitamin D deficiency and mechanisms underlying calcium metabolism disorder. Since thyrotoxicosis can cause osteopenia and may coexist with osteomalacia, attention should be given to the changes of alkaline phosphatase, liver function and clinical symptoms. If necessary, chest X-ray and pelvic X-ray should be carried out to find out potential osteomalacia for timely treatment to avoid the occurrence of fracture and even deformity.

Keywords: Thyrotoxicosis, osteomalacia, vitamin-D deficiency, osteopenia

Introduction

Von Recklinghausen described a case of osteomalacia in a thyrotoxic patient around a century ago. Since then, more cases of osteomalacia have been observed in patients with thyrotoxicosis [1, 2]. Thyrotoxicosis is a well-known cause of metabolic bone disease [3]. However, metabolic bone disease resulted from thyroid diseases are frequently misdiagnosed, or simply missed, and fewer cases of osteomalacia are reported in the context of thyroid disease. It is important that clinicians remain alerted to the dangers of osteomalacia, which remains prevalent in emigrant and native Asians [3, 4]. To assess the impact of thyrotoxicosis on the occurrence and development of osteomalacia for better diagnosis and treatment of the disease, we reviewed the related original articles in databases such as Web of Science, PubMed, Springer and Clinical Key published before June

6, 2020, with the following keywords: “osteopenia”, “osteomalacia” “osteoporosis” and “thyrotoxicosis”. Previous studies of osteomalacia and thyrotoxicosis are scattered as case analysis or case reports, and no review has been published on this topic recently. In the present review, we will address the common clinical manifestations and definitions of osteomalacia and thyrotoxicosis, the distinctions between thyrotoxic and osteomalacic myopathies and advance in the pathogenesis of thyrotoxicosis-related osteomalacia. We showed that successful treatment of such patients may be facilitated by proper identification of a related metabolic disorder.

Definition of thyrotoxicosis and osteomalacia

The clinical syndrome that arises from the exposure to excessive circulating free thyroid hormones-thyroxine (3, 5, 3', 5'-tetraiodo-L-thyro-

Table 1. Etiologies of hypophosphatemic bone disease

Etiologies
Renal hypophosphatemic osteomalacia
Tumour-associated osteomalacia
Malabsorption
Vitamin D dependent rickets
Vitamin D deficiency
Fanconi syndrome
Other hypophosphatemic tubular disease
Aluminum hydroxide adjuvant
Hyperparathyroidism

nine, T4) and/or triiodothyronine (3, 5, 3'-triiodo-L-thyronine, T3) is termed thyrotoxicosis. It affects approximately 1-1.5% of the world population [5], and is thus a prevalent presentation. It occurs 5-10 times more frequently in women than men. The overwhelming majority of cases (up to 80%) are the result of the Graves' disease (GD), although it may potentially stem from several other conditions, such as toxic adenoma (TA), toxic multinodular goitre (TMNG) and thyroiditis of any aetiology. In iodine-replete countries, thyrotoxicosis caused by GD is far more frequently than by other factors. GD is an autoimmune condition, where thyrotropin receptor antibodies (TRAbs) is stimulated to bind with the thyrotropin receptor (TSHR) gene, leading to hyperthyroidism. The resulting thyroid hypertrophy causes a diffuse goitre in approximately 80% of patients.

Thyroid hormones have receptors present in almost all human tissues, and impact both synthesis and metabolism rate of proteins. Hence, the fact that the clinical symptoms and indications of thyrotoxicosis are pleiotropic is unsurprising. Inadequately treated or untreated thyrotoxicosis would therefore result in severely impaired quality of life, as we expect for cardiovascular mortality, osteoporosis, atrial fibrillation, thromboembolic events and neuropsychiatric states [6].

Osteomalacia, conceptualised as a bone-tissue disorder, is characterized by retarded or insufficient mineralisation of osteoid in mature cortical bone. Osteomalacia is linked to further growth-plate abnormalities or rickets (i.e. disruption of normal growth-plate mineralisation and development) in children [7]. Osteomalacia may be broadly classified into three categories

of disorder, namely phosphate deficiency, calcium deficiency or vitamin D deficiency. The aetiologies of hypophosphatemic bone disease include tumour-associated osteomalacia, vitamin-D deficiency, aluminium hydroxide adjuvant, renal hypophosphatemic osteomalacia, malabsorption, vitamin-D-dependent rickets, Fanconi syndrome and other hypophosphatemic tubular diseases as well as hyperparathyroidism (**Table 1**).

As a result of their disparate impacts on the parathyroid hormone, presentations that cause hypophosphatemia should be addressed separately, rather than with conditions that cause vitamin-D- or calcium deficiency. Parathyroid levels increase when vitamin-D or calcium levels are low. When phosphate is elevated, it would generate the typical imaging feature of bone resorption. In contrast, low phosphate levels do not increase parathyroid hormone levels nor generated the classic imaging features of hyperparathyroidism [8]. An inherited X-linked abnormality, where phosphate is ineffectively reabsorbed by the renal tubes, is the most widespread cause of hypophosphatemic osteomalacia. Up to a third of the patients occur as sporadic cases, which probably result from mutation. In children, the condition has been termed "refractory rickets" or "vitamin-D-resistant rickets", since vitamin D supplements do not produce a good response [9]. Oncogenic hypophosphatemic osteomalacia (a tumour-associated condition) and Fanconi syndrome (a collection of conditions with renal tubular dysfunction and loss of amino acids through urination) are additional potential causes of hypophosphatemic osteomalacia.

Common clinical manifestations and related examinations of osteomalacia and thyrotoxicosis

Proximal myopathy

Both Graves [10] and von Basedow [11] reported weakness as a symptom of thyrotoxicosis. Up to 50% of thyrotoxicosis patients show clinically detectable chronic muscle weakness [12]. The extent of weakness is variable, with only a small minority of patients being bedridden. The known causes of myopathy include hypokalemic periodic paralysis (up to 24% of glucose-induced degradation-deficiency (GID)), myasthenia gravis (1% of Graves' disease (GD)), and

Thyrotoxicosis and osteomalacia

chronic thyrotoxic myopathy (50% of GD). Osteomalacia is linked to thyrotoxicosis [1, 2]. Osteomalacia myopathy evinces a typical proximal distribution. Proximal muscle weakness may independently be caused by osteomalacia and thyrotoxicosis in 50% and 61% of cases, respectively [13]. Hypophosphatemic osteomalacia presents diverse clinical features, depending on the causes of the condition. With the exception of X-linked hypophosphatemic osteomalacia [9], muscle weakness has been reported with other causes of osteomalacia. Gait is a further significant indicator of hypophosphatemic osteomalacia, and is frequently described as “waddling”. Another simple indicator of myopathy is an inability to rise unaided from a seated position with one’s arms folded in front. However, if there is pain, myopathy may be difficult to diagnosis clinically. Even when myopathy is known to be present, it may not show specific electromyographic abnormalities or simply absent. Furthermore, misdiagnosis of myopathy can occur as a result of the vagueness of muscle weakness and pain in osteomalacia patients [14].

Elevated alkaline phosphatase (ALP)

In 1952, marginally increased serum ALP levels in 10 of 14 cases of thyrotoxicosis were reported. Subsequently, in 1968, significant increases in mean serum ALP (SALP) levels in thyrotoxic patients were found [15]. In a large study, between 42% and 89% of individuals presenting with thyrotoxicosis are shown to have increased total serum ALP [16]. Due to excess thyroid hormones, thyrotoxicosis is likely to generate metabolic impact that change the biochemical profiles of blood, including increased levels of aspartate aminotransferase, SALP and alanine aminotransferase [17].

Osteoblasts secrete ALP, which has a half-life of 40 hours. Osteoblasts are directly targeted by thyroxine through the thyroxine receptors on the cells. Once activated, osteoblasts will subsequently stimulate bone resorption through osteoclasts. Usually, intestine alkaline phosphatase (IALP) may be detected in serum after fatty meal and this is especially true for individuals with type O and B blood [16]. High concentrations of ALP may also be found in the kidney. Nonetheless, kidney ALP (KALP) is believed typically to be excreted into the urinary tract and has a short half-life. Therefore, it is

generally not present in the serum. So far, thyroidally-derived ALP has not been detected in human sera. Hence, an increase in one or several serum ALP isoenzymes may lead to increased total SALP. Total ALP may increase due to various conditions. In animal, total ALP was observed to increase during osteogenesis.

These results suggest that pathological changes could occur in both liver and bone in the majority cases of feline thyrotoxicosis [16]. In normal peoples, total (T)-ALP or bone-derived alkaline phosphatase (B-ALP) will increase at least a month after treatment with exogenous thyroxine or triiodothyronine [18]. Moreover, in thyrotoxic GD patients, B-ALP is elevated, especially following treatment with anti-thyroid agents [19]. Bone ALP isoenzyme is the principal composition that causes the increase of serum ALP following treatment of hyperthyroidism [20].

The bone isoenzyme may be determined in order to define bone involvement. Liver-function tests can be undertaken to exclude the possibility of liver-function abnormality, if the bone isoenzyme cannot be detected. This is because ALP is elevated in biliary obstruction. In conditions such as secondary calcium deposit, fracture healing and growth, the bone isoenzyme level is also elevated. For hyperthyroid patients without liver-function abnormality, ALP may be used as a predictor for bone involvement [21]. In hyperthyroid cats with elevated SALP, BALP is also elevated in all the cats but only 44% of the cats evinced elevated serum osteocalcin [22]. Hence, serum osteocalcin is a less sensitive parameter to predict bone turnover in thyrotoxic cats than serum BALP. Not only treated patients with GD, as well as patients with painless thyroiditis evinced an increase in serum ALP. After the commencement of antithyroid drugs (ATD) for GD, ALP increases gradually and reaches the peak in 3-5 months. In parallel, compared with GD patients, patients with painless thyroiditis have similar but more moderate changes in ALP after ATD [23]. These data suggest that bone metabolism may be affected even by thyrotoxicosis of relatively brief duration.

Some patients with thyrotoxicosis have increased ALP, stemming from mild, nonspecific abnormalities of liver function and liver histolo-

Thyrotoxicosis and osteomalacia

Table 2. Common clinical manifestations and related examinations of osteomalacia and thyrotoxicosis

Common clinical manifestations and related examinations
Proximal myopathy
Clinically detectable chronic muscle weakness thyrotoxicosis
the known causes of such myopathy
myasthenia gravis [1% of Graves disease (GD)]
hypokalemic periodic paralysis (up to 24% of GD)
chronic thyrotoxic myopathy (50% of GD)
Osteomalacia myopathy
other causes of osteomalacia except for X-linked hypophosphatemic osteomalacia
Elevated alkaline phosphatase (ALP)
the cause in human thyrotoxicosis
malnutrition
congestive heart failure
hepatic hypoxia
infections
associations of intrinsic liver disease with intrinsic thyroid disease through autoimmune mechanisms
direct toxic effect of thyroid hormones on hepatocytes
subclinical hepatitis
the cause in patients with rickets or osteomalacia
the disorder of bone mineralization
Decreased Bone Mineral Density
the cause in thyrotoxicosis
malabsorption of calcium due to increased motility of the gut
steatorrhoea
effects of thyroid hormones on osteoblasts
increased serum ionised calcium concentrations
reduced renal tubular resorption of calcium
the cause in osteomalacia
retarded or insufficient mineralisation of osteoid

lished that infectious mononucleosis may give rise to subclinical hepatitis as a complication. Alternatively, the causes of abnormal liver-function tests in patients with thyrotoxicosis and subacute thyroiditis may be similar. Hepatobiliary diseases, e.g. chronic cholecystitis with gallbladder and cystic duct stones [25], may cause elevated ALP in patients with thyrotoxicosis, and clinicians must take note of this possibility. In virtually all patients with osteomalacia or rickets, serum ALP activity is elevated except for patients with hypophosphatasia, which features hypophosphatemia [14]. Due to the disorder of bone mineralization, bone formation is enhanced through coupling, and the level of ALP, an indicator of bone formation, is increased. The common clinical manifestations and related examinations of osteomalacia and thyrotoxicosis are summarized in **Table 2**.

Decreased bone mineral

density

In patients with either subclinical thyrotoxicosis associated with over-supplementation of L-thyroxine, or spontaneous hyperthyroidism, osteopenia has been observed [16]. A variety of mechanisms that directly impact bone, or cumulatively generate negative calcium balance, may lead to reduced bone density in the context of thyrotoxicosis. These mechanisms may include steatorrhoea, effects of thyroid hormones on osteoblasts both directly by increasing cAMP level in these cells facilitating bone resorption and indirectly by elevating the sensitivity of β -adrenergic receptors to catecholamines. Further possible mechanisms are

gy. In the context of thyrotoxicosis in humans, these changes may be attributed to a variety of possible causes, including infections, congestive heart failure, malnutrition, associations of intrinsic liver disease with intrinsic thyroid diseases through autoimmune mechanisms and hepatic hypoxia. It is very likely that thyroid hormones have a direct toxic effect on hepatocytes [16]. The cause of thyrotoxicosis derived from subacute thyroiditis is, as yet, unknown. Nonetheless, one current theory holds that the same virus that causes subacute thyroiditis may also give rise to subclinical hepatitis. Two reported instances of subacute thyroiditis and increased ALP have been associated with infectious mononucleosis [23, 24]. It is well estab-

reduced renal tubular resorption of calcium, or increased serum level of ionised calcium that reduces the secretion of parathyroid hormones that in turn decreases the formation of 1,25-dihydroxy vitamin D from vitamin-D. Moreover, malabsorption of calcium due to increased motility of the gut may also be significant here. In patients with thyrotoxicosis, the pathophysiology of demineralisation of bone does not imply necessarily increased parathyroid hormone secretion. In fact, this secretion is generally reduced in this cohort. Loss of bone mass stemming from thyrotoxicosis tends to be recovered readily after the administration of ATDs. In addition, for osteomalacia patients, retarded or insufficient mineralisation of osteoid in spongy and mature cortical bone also leads to reduced bone density.

Differential diagnosis between osteomalacic and thyrotoxic myopathy

Ultrastructural study, muscle enzymes and electromyography are unable to distinguish thyrotoxic and osteomalacic myopathy [13]. Unless it is clinically suspected and biochemically confirmed, osteomalacia may coexist with thyrotoxicosis but not be diagnosed. The metabolic disorder is, nonetheless, highly responsive to treatment. Therefore, it is recommended that thyrotoxicosis patients presenting with unusually severe myopathy should be examined for signs of vitamin-D deficiency. This is especially important for patients originating in regions where osteomalacia is known to be prevalent.

Pathogenesis of osteomalacia with thyrotoxicosis

Direct catabolic effect

Skeletal development and the establishment of peak bone mass both require thyroid hormones. In adults, bone mineral density (BMD) and bone turnover are regulated by 3,5,3'-triiodo-L-tyronine (T3). Moreover, to maintain optimal bone strength, euthyroid is essential [26]. Both in vivo and in vitro, thyroid hormones impact bone cells by increasing skeletal remodelling and stimulating osteoclastic bone resorption [27].

As a bone disease, thyrotoxicosis seems to be a high-turnover osteoporosis where bone resorption is increased to a degree greater than

bone formation. Bone mineral homeostasis is directly affected catabolically by thyroid hormones. As a result, there is an increased calcium loss via the kidneys and heightened bone mineral resorption [28, 29]. Bone resorption is stimulated by thyroid hormones, perhaps via the activation of bone cells by a triiodothyronine receptor [1].

Decreased BMD in thyrotoxicosis patients was demonstrated in an Indian study [27]. A further study showed the decreases in BMD in the osteoporotic patients were 22%, 36% and 20% at the lumbar spine, forearm and hip, respectively [30]. It was found that 92% of participants from an Indian village presenting with hyperthyroidism evinced bone involvement, with 60% showing osteoporosis. Moreover, this condition has been shown to be reversible with ATDs [27]. In patients with GD, calcium and bone metabolism is generally characterised by enhanced bone turnover in the cortical and cancellous bone, high levels of bone metabolic markers and hypercalcemia. It is possible that the accumulation of osteoid tissue is additionally accelerated by the elevated bone turnover derived from thyrotoxicosis.

Vitamin D deficiency

For the maintenance of bone mineralisation and calcium homeostasis, vitamin D is indispensable [31]. Indian patients with active thyrotoxicosis were shown to be at increased risk of osteoporosis or osteomalacia, because of related vitamin-D deficiencies [32]. Research findings also suggested that bone loss in hyperthyroidism patients is worsened by vitamin-D deficiency.

A case of apparent osteomalacia in a 37-year-old woman with GD was reported [33]. For five years, she had been working in a darkened warehouse and had been a strict vegetarian since the age of 29. Severe vitamin-D deficiency was suggested by the fact that serum vitamin 25(OH)D level was less than 5 nmol/L (normal range: 25-137).

Subclinical vitamin-D deficiency may become symptomatic if hyperthyroidism is present. One study showed that eight of 30 subjects newly diagnosed with hyperthyroidism (26%) showed vitamin-D deficiency (less than 25 nmol/L), and it was also found that 30% of Indian patients

Thyrotoxicosis and osteomalacia

Table 3. Vitamin-D deficiency in thyrotoxicosis (vitamin-D <25 nmol/L)

Authors	Number of Subjects	Number of vitamin-D deficiency patients	% vitamin D deficiency patients
Dhanwal DK <i>et al.</i> [30]	F/M: 30	8	26% (8/30)
Yamashita <i>et al.</i> [34]	F/M: 146/62	F/M: 58/11	Female: 40% (58/146) Male: 18% (11/62)
Doi Y <i>et al.</i> [35]	(F/M): 343	120	35% (120/343)

Table 4. Pathogenesis of osteomalacia with thyrotoxicosis

Pathogenesis of osteomalacia with thyrotoxicosis
Direct catabolic effect
increased bone mineral resorption
the activation of bone cells by a triiodothyronine receptor
increased calcium loss through the kidneys
Vitamin D deficiency
malabsorption
fat malabsorption
steatorrhea
negative nitrogen balance
hyperpigmentation of skin
poor exposure to sunlight
decreased intake of calcium and vitamin D
increased metabolic clearance of 25(OH)-vitamin D
inhibiting 1- α -hydroxylase activity
avoiding ultraviolet rays and using sunscreen
accelerated metabolism of 25(OH)D by calcium deficiency
Mechanisms of disturbed calcium metabolism
increased urinary, fecal, and, sweat loss of calcium
decreased production of 1,25 dihydroxy vitamin D
decreased production of calcium binding protein
negative calcium balance
Previous potential metabolic bone diseases

with hyperthyroidism have osteomalacia [30]. Using the same criteria for vitamin-D deficiency, Yamashita *et al.* found hypovitaminosis D in 18% and 40% male and female GD patients, respectively, in Japan [34]. A further Japanese study indicated vitamin-D deficiency in 35% of participants with thyrotoxicosis [35] (**Table 3**).

Findings from bone biopsy conducted in 34 hyperthyroidism patients showed increased surface coverage by osteoid in the trabecular bone, raised osteoblastic activity and porosity in the cortical bone, however, the mean width of osteoid seams remained consistent [36]. This study measured mean 25(OH)D levels and this could be an explanation of why the changes didn't occur.

There are a number of mechanisms underlying vitamin-D deficiency. Steatorrhea linked to decreased fat absorption coefficient (COFA) was reversed in 46% of GD patients [37]. Reversible steatorrhea is a recognized manifestation of thyrotoxicosis. Poor nitrogen balance (negative) may provoke a fall in the output of pancreatic enzyme output resulting in worse fat malabsorption and decreased weight. Fat malabsorption may be a factor in the significant weight loss in these patients. Moreover, the absorption of fat-soluble vitamins is probably impeded in such circumstances. Several new features of thyrotoxicosis in the later stages of GD have been reported, such as negative nitrogen balance and skin hyperpigmentation [37, 38]. Because of inadequate exposure to sunlight and skin pigmentation, vitamin-D deficiency is widespread in both urban and rural India [39]. The vegetarian diet, which implies a reduced intake of vitamin D and calcium, also probably contributes to vitamin-D deficiency. Indeed, the deficiency is likely exacerbated by the

increased metabolic clearance of 25(OH)-vitamin D. A further relevant mechanism is that 1- α -hydroxylase activity is inhibited by excess thyroid hormone, leading to sub-optimal levels of calcitriol [1].

It was found that female GD patients has lower serum 25(OH)D levels than their male equivalents. This may be due to the fact that women often use sunscreen to avoid direct ultraviolet light, because of cosmetic concerns. On other hand, men are more likely to be engaged in outdoor work and activities [33].

Clements *et al.* suggested new mechanisms for vitamin-D depletion, proposing that metabolism of 25(OH)D may be accelerated by calcium

Thyrotoxicosis and osteomalacia

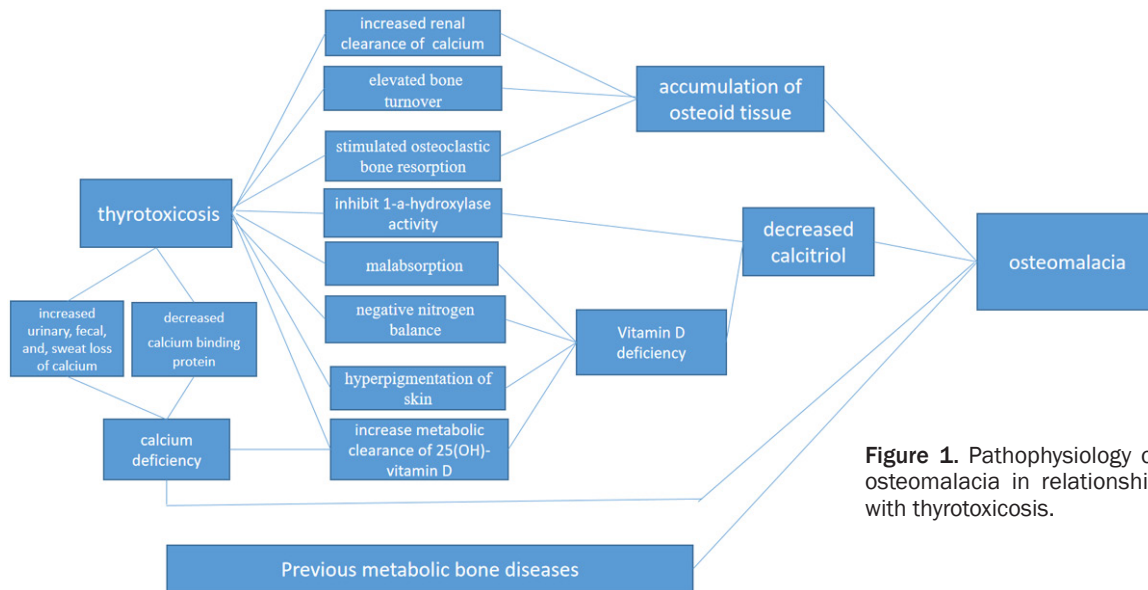


Figure 1. Pathophysiology of osteomalacia in relationship with thyrotoxicosis.

deficiency [40]. Gascon-Barre *et al.* [41] mentioned that urolithiasis patients on diets low in calcium (300 mg per day) would have notably decreased 25(OH)D and elevated 1, 25(OH)2D than those eating high calcium diet (1000 mg daily) [41]. The vitamin D deficiency may be explained by heightened clearance of 25(OH)D in GD patients, particularly for those whose supply of the vitamin is restricted. In the hyperthyroid state, steatorrhea may reduce the intestinal reabsorption of vitamin-D metabolites in the enterohepatic circulation. This in turn may cause additional loss of vitamin-D metabolites [42].

Mechanisms of disturbed calcium metabolism

Assorted mechanisms of disturbed calcium metabolism in hyperthyroidism have been proposed, including reduced production of 1, 25 dihydroxy vitamin D and calcium binding protein, and heightened urinary, faecal and sweat loss of calcium [43]. Taken together, these factors would lead to a negative calcium balance and, subsequently, a fall in 24-hour urinary calcium. Plausible causes for significant abnormalities in bone mineral homeostasis among thyrotoxic patients include increased skin pigmentation, malabsorption and also deficiency in vitamin D and lower calcium due to urinary loss.

Previous metabolic bone diseases

The effect of elevated thyroid hormone on bone appears to be relatively mild: thyrotoxic patients

who develop fractures are typically post-menopausal women [44], implying that thyrotoxic bone disease may become symptomatic only if there is another metabolic bone disease. If thyrotoxicosis had not developed, these patients may have continued to be asymptomatic. The Pathogenesis of osteomalacia with thyrotoxicosis is summarized in **Table 4** and **Figure 1**.

Taken together, direct catabolic effect, vitamin D deficiency, mechanisms of disturbed calcium metabolism contribute to pathogenesis of thyrotoxicosis, which is partially responsible for osteomalacia. In addition, previous metabolic bone diseases can accelerate the process of osteomalacia in patients with thyrotoxicosis, and at the same time thyrotoxicosis can aggravate the potential metabolic osteopathy.

Conclusion

Thyrotoxicosis affects vitamin D and bone metabolism. A better understanding of thyrotoxicosis would reveal the mechanism underlying metabolic bone disease. In clinical practice, even subtle clinical and biochemical parameters in unrecognized metabolic bone disease should be altered.

For thyroid patients with abnormal myopathy, osteomalacia may be diagnosed via vitamin D deficiency, calcium metabolism disorder and bone mineral density decrease. Meanwhile, diagnosis of related metabolic disorders would help effectively treat these patients.

Disclosure of conflict of interest

None.

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Thyrotoxicosis and osteomalacia

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