Study of Calcium, Magnesium and Phosphorus Levels among Hypothyroid Patients in Trichy, Tamil Nadu

Rasheed Khan M.[1], Thivyah Prabha A.G.[2], Siva Kumar K.[3]

[1]Department of Biochemistry, Trichy SRM Medical College Hospital and Research Centre, Tiruchirapalli, Tamil Nadu, India. [2]Department of Biochemistry, St. Peter's Medical College Hospital and Research Institute, Hosur, Tamil Nadu, India. [3]Department of General Medicine, Trichy SRM Medical College Hospital and Research Centre, Tiruchirapalli, Tamil Nadu, India.

ABSTRACT

BACKGROUND

Mineral metabolism is frequently disturbed in thyroid dysfunctions. Among thyroid dysfunctions, hypothyroidism is one of the most common form resulting from the deficiency of thyroid hormones. Studies done on serum calcium, phosphorus and magnesium in hypothyroid patients earlier have conflicting results. Hence the present study has been undertaken to study the levels of serum calcium, phosphorus, and magnesium among hypothyroid patients and analyse their correlation with thyroid stimulating hormone (TSH).

METHODS

The case control study was conducted in the Department of Biochemistry in Trichy SRM Medical College Hospital and Research Centre for a period of 6 months from 2017 January to July 2017. The study was undertaken involving 50 hypothyroid cases and 50 healthy volunteers as controls after proper ethical clearance and informed consent of all the study subjects. Serum calcium, phosphorus and magnesium were measured along with tri-iodothyronine (FT3), tetra-iodothyronine (FT4) and TSH among all study subjects. Statistical analysis of data was done using statistical package for social sciences (SPSS) software.

RESULTS

The mean value of serum total calcium and total magnesium was lower among hypothyroid cases and phosphorus value was increased as compared to controls. ($P < 0.001$) Statistically significant negative correlation was observed between serum calcium, magnesium and TSH among hypothyroid cases. Statistically significant positive correlation was observed between serum phosphorus and TSH among hypothyroid cases.

CONCLUSIONS

Among hypothyroid patients the values of serum calcium, magnesium and phosphorus is significantly altered. Thyroid disorders have an important role in bone and mineral metabolism. Thus, monitoring of these minerals among hypothyroid patients in regular follow up may effectively improve the clinical manifestations in them. Hence, monitoring of mineral status of the hypothyroid patients on follow-up will be of benefit to the patients.

KEYWORDS

Hypothyroidism, Calcium, Phosphorus, Magnesium, Minerals

Corresponding Author:
Dr. Thivyah Prabha A.G.,
No. 101, Doctor's Quarters,
(Teaching Staff Quarters),
St. Peter's Medical College,
Hospital and Research Institute,
Opp. SIPCOT-II, Hosur-635130,
Tamilnadu, India.
E-mail: drthivyahprabha@gmail.com

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BACKGROUND

Optimal health maintenance requires adequate and balanced amount of macronutrients and micronutrients. Macro-minerals have a definite role in various biological functions by influencing enzymatic activity, protein function and cell membrane permeability. Hormones influence mineral metabolism at several levels of action, including transport and excretion of minerals.[1] Thyroid gland produces tri-iodothyronine and tetra-iodothyronine which are commonly known as T3 and T4 respectively. T3 is biochemically more active form of thyroid hormone and is produced by deiodination of T4 by the enzyme 1,5' deiodinase in the peripheral tissues. These hormones are in turn regulated by thyroid stimulating hormone and thyroid releasing hormone (TRH) secreted by pituitary gland and hypothalamus respectively. Thyroid hormones play a major role in the cell differentiation, in fetal development and also to maintain thermogenic, metabolic and mineral homeostasis in adults. Hypothyroidism in the sub–normal activity of thyroid gland that leads to many metabolic processes to slow down causing clinical, psychological and biochemical alterations. According to the recent studies the prevalence of hypothyroidism in India varies from 4 – 11 %, more prevalent in women and elderly age group.[2]

Mineral metabolism is frequently disturbed in thyroid dysfunctions. Among thyroid dysfunctions, hypothyroidism is one of the most common form resulting from the deficiency of thyroid hormones. Studies done on serum calcium, phosphorus and magnesium in hypothyroid patients earlier have conflicting results. Anatomical abnormalities and dysfunction of thyroid are the most common diseases of endocrine glands. Hypothyroidism and hyperthyroidism are two primary pathological conditions involving the thyroid glands.[3] Among thyroid dysfunctions, hypothyroidism is one of the most common form resulting from the deficiency of thyroid hormones or from their impaired activity.[4] Hypothyroidism is ten times more common in women than men and its prevalence increases with age.[5] Hyper secretion of pituitary TSH occurs by the decrease in T3 and T4 concentration and causes amplified increase in TSH levels. It plays a key laboratory finding in diagnosis of hypothyroidism.[6] Thyroid hormones play a role in the metabolic functions by regulating the lipid, carbohydrate, protein and mineral metabolism.[7]

Thyroid hormones are essential for normal growth and maturation of skeletal system. Calcium and phosphorus homeostasis is frequently altered in thyroid dysfunction. Hence thyroid disorders are important causes of secondary osteoporosis. Serum calcium levels can be fairly used as an index of bone resorption.[8] The depressed turnover due to impaired mobilization of calcium into the bone in hypothyroidism leads to decrease in blood calcium level. In hypothyroidism the increased production of calcitonin can promote tubular reabsorption of phosphate and tubular excretion of calcium.[9] The renal phosphate reabsorption is elevated by FT3 and hence elevates the serum phosphorus levels in rats. Animal studies propose thyroid hormones as long term regulators for phosphate metabolism.[10] Normal calcium and phosphorus have been shown in few studies[11,12] while other studies have shown decreased levels in hypothyroidism.[13,14] Even though the changes in calcium and phosphorus may be slight in thyroid disorders, these disturbances will be important for the patient in long run.[15] Studies show that metabolic disorders, hypertension and cardiovascular diseases are related to defects in metabolism of divalent cations such as calcium and magnesium.[16,17] Hence the present study was undertaken to study the levels of serum calcium, phosphorus and magnesium among hypothyroid patients and to analyse their correlation with TSH.

METHODS

The case control study was conducted in the Department of Biochemistry in Trichy SRM Medical College Hospital and Research Centre for a period of 6 months from 2017 January to July 2017. The study was conducted after approval from ethical committee [IEC NO: 47 24 / 11 / 2016] and informed consent was taken from all patients. Study participants of age group 20 - 50 years were selected from patients who have underwent thyroid profile. Among 100 participants, 50 were selected as cases and 50 as controls based on their thyroid profile report.[18] The reference range of thyroid profile according to Tietztextbook[19] was followed and patients were categorized as controls and hypothyroid cases based on the report. The reference ranges are Free T3: 2.1 - 4.4 (pg/ml), Free T4: 0.8 - 2.7 (ng/dl) and TSH: 0.4 - 4.2 (mcIU/ml).

Exclusion Criteria

Patients suffering from infectious diseases, renal diseases, hepatic diseases, pituitary diseases, bone diseases, diabetes mellitus, alcoholism and patients on mineral supplementation were excluded from the study.

Under aseptic precaution 5 ml venous blood was collected from the ante-cubital fossa for all the patients. Serum was separated by centrifugation and analysis was done. Routine IQC was run and after confirmation the samples were analysed for biochemical parameters. Serum was analysed for FT3, FT4 and TSH by eCLIA method in Cobas e411 auto-analyser followed by calcium (Arsenazo III method), phosphorus (phosphomolybdate UV method) and magnesium (xylidyl blue method) in MindrayBS420 auto-analyser in the biochemistry section of SRM college laboratory.

Statistical Analysis

Data was entered in Microsoft Excel and analysed using SPSS software. Descriptive statistics such as mean and standard deviation (SD) were computed for the data respectively. Pearson's correlation was done to correlate the relationship between FT3, FT4, TSH and minerals (calcium, phosphorus, and magnesium)

RESULTS

The results of the study are presented in the tables. There were a total number of 42 females and 8 males in controls and 33 females and 17 males in hypothyroid cases. The mean age of controls was 38.8 ± 12.45 (years) and the mean age of cases was 37.0 ± 10.06 (years). The mean TSH values were 2.15 ± 0.81 µIU/L among controls and 61.49 ± 34.82 µIU/L among hypothyroid cases. There was a statistically significant increase in TSH among cases as compared to the controls. The mean FT3 values were 2.84 ± 0.44 pg/ml among controls and 2.84 ± 0.44 pg/ml among hypothyroid cases. FT3 values were significantly decreased in cases as compared to the controls (2.52 ± 0.91 vs 2.84 ± 0.44 pg/ml). The mean FT4 values were 1.28 ±0.18 ng/ml among controls and 0.85 ± 0.36 ng/ml among hypothyroid cases. Similarly, FT4 values were also decreased among cases as compared to the controls (0.85 ± 0.36 vs 1.28 ± 0.18 ng ml).

The study observed a significant decrease level of calcium among cases 8.01 ±0.17 (mg/dl) as compared to the controls 10.16 ± 1.47 (mg/dl) and also magnesium of 2.25 ± 0.20 (mg/dl) among cases as compared to controls of 2.49 ± 0.07 (mg/dl). But the serum phosphorus values were increased among cases as compared to the controls (4.81 ± 0.88 vs 3.83 ± 0.40 mg/dl). The mean calcium values were 10.16 ± 1.47 mg/dl among controls and 8.01 ± 0.17 mg/dl among hypothyroid cases. The mean phosphorus values were 3.83 ± 0.40 mg/dl among controls and 4.81 ± 0.88 mg/dl among hypothyroid cases. The mean magnesium values were 2.49 ± 0.07 mg/dl among controls and 2.25 ± 0.20 mg/dl among hypothyroid cases. The mean calcium, and magnesium levels were significantly lower in hypothyroidism cases compared to healthy controls. (P < 0.001). Similarly, significant increase in serum phosphorus concentration was found among hypothyroidism patients (P < 0.001) when compared to controls. Table 1 shows the mean & SD values of parameters.

Parameters	Cases	Controls	P Value
Age [Years]	37.0 ± 10.06	38.8 ± 12.45	--
Sex [M / F]	17/33	8/42	--
FT3 [pg/ml]	2.52 ± 0.91	2.84 ± 0.44	< 0.0001*
FT4 [ng/dl]	0.85 ± 0.36	1.28 ±0.18	< 0.0001*
TSH [µIU/L]	61.49 ±34.82	2.15 ± 0.81	< 0.0001*
Calcium [mg/dl]	8.01 ±0.17	10.16 ± 1.47	< 0.0001*
Phosphorus [mg/dl]	4.81 ± 0.88	3.83 ± 0.40	< 0.0001*
Magnesium [mg/dl]	2.25 ± 0.20	2.49 ± 0.07	< 0.0001*

Table 1. Mean & SD Values of Parameters

P value < 0.05 is statistically significant (* is highly significant)

The correlation coefficient between TSH and calcium was r = [-0.566] and correlation coefficient between TSH and phosphorus was r = [0.376]. The correlation coefficient between TSH and magnesium was r = [-0.479]. The serum TSH values of hypothyroid patients were studied in relation to serum calcium phosphorus and magnesium levels. On statistically analysing the values, a significant negative correlation was observed between serum TSH with serum total calcium and total magnesium. Also, a statistically significant positive correlation was observed between serum phosphorus levels and TSH. Table 2 shows correlation between TSH and other parameters. Figure 1, 2 and 3 represent the correlation between serum TSH and calcium, phosphorus and magnesium respectively.

Parameters	Correlation Coefficient [r Value]	P Value
TSH VS Calcium	r = [-0.566]	0.001
TSH VS Phosphorus	r = [0.376]	0.01
TSH VS Magnesium	r = [-0.479]	0.003

Table 2. Correlation between TSH and Other Parameters

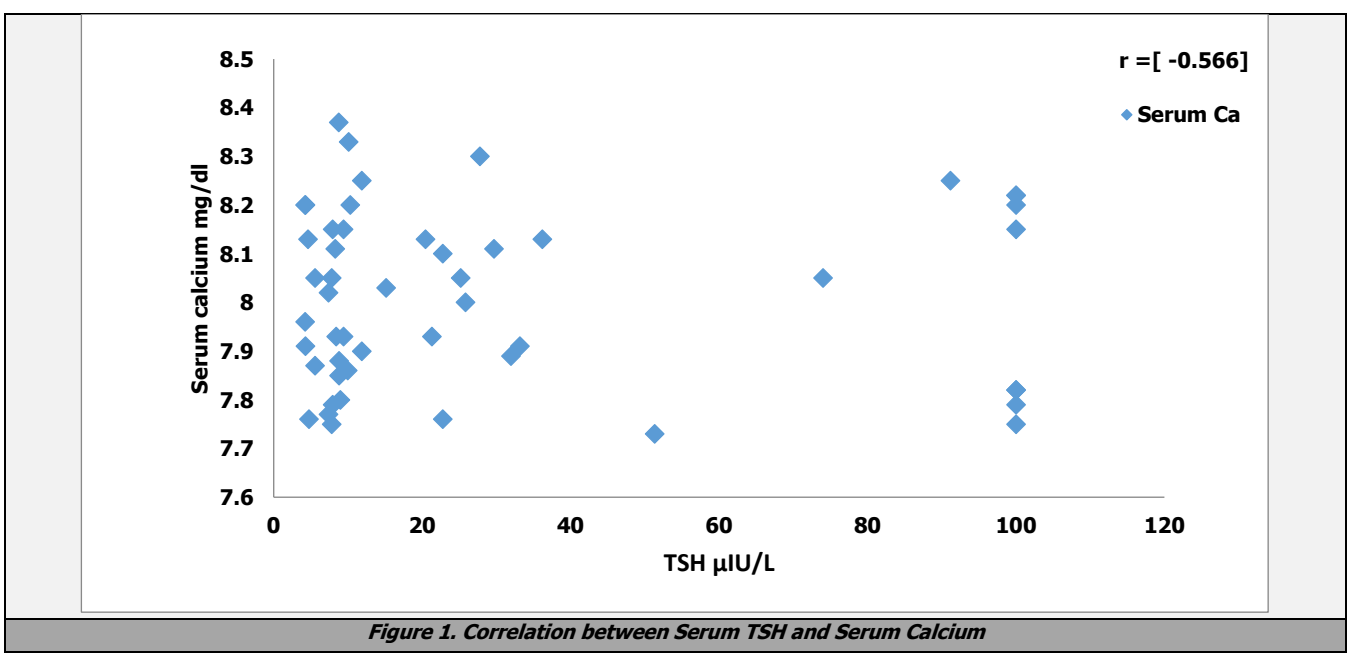

Figure 1. Correlation between Serum TSH and Serum Calcium

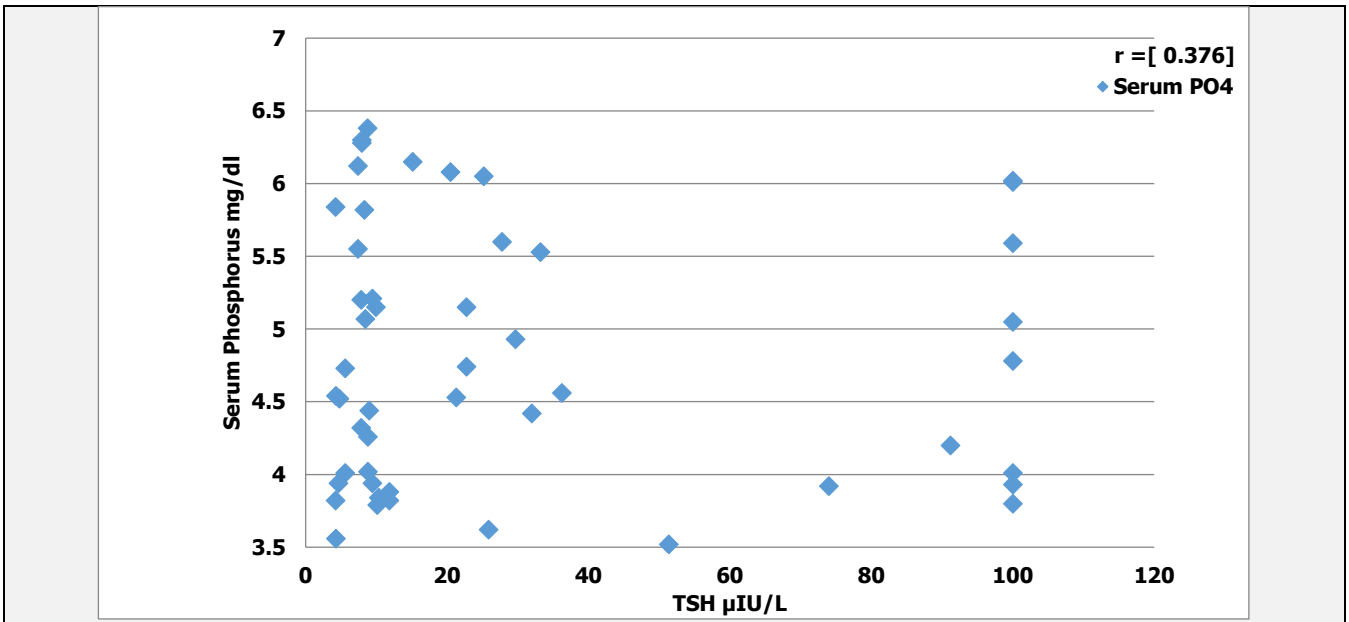

Figure 2. Correlation between Serum TSH and Serum Phosphorus

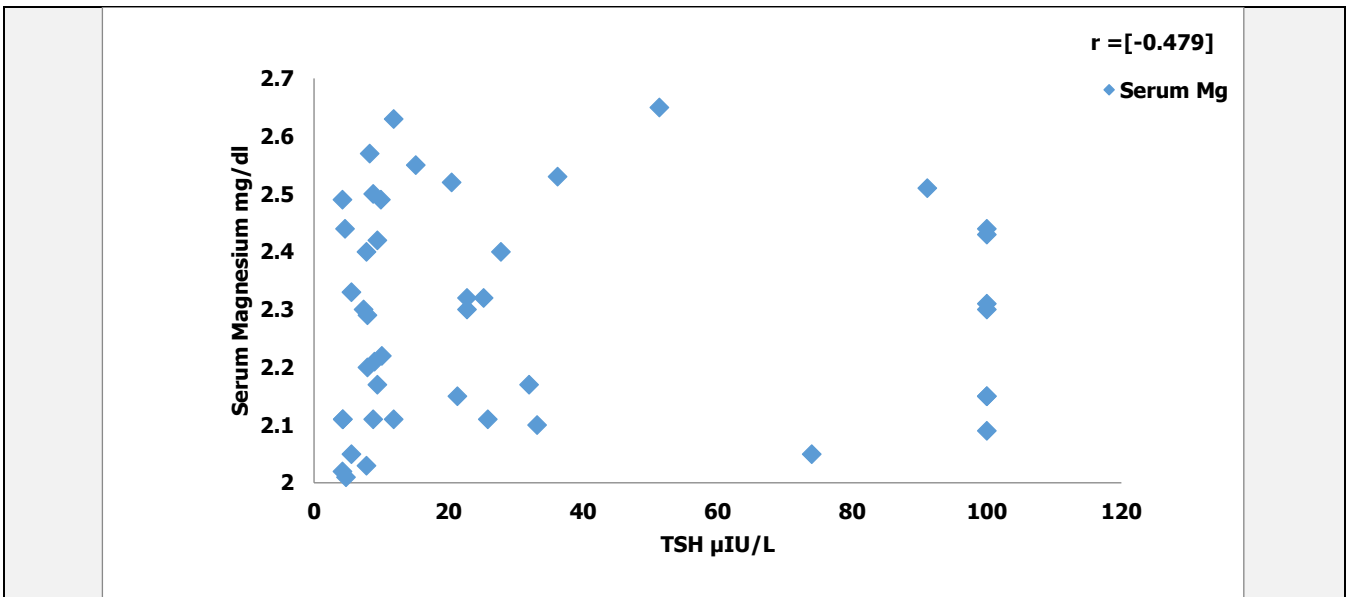

Figure 3. Correlation between Serum TSH and Serum Magnesium

DISCUSSION

Normal growth and maturation of skeletal system needs the thyroid hormones. In thyroid dysfunction, calcium and phosphorus homeostasis is frequently altered. Hence secondary osteoporosis is commonly seen in thyroid disorders. Serum calcium levels can be fairly used as an index of bone resorption. The depressed turnover due to impaired mobilization of calcium into the bone in hypothyroidism leads to decrease in blood calcium level. The increased production of calcitonin in hypothyroidism can promote tubular reabsorption of phosphate and tubular excretion of calcium. The renal phosphate reabsorption is elevated by FT3 and hence elevates the serum phosphorus levels in rats. Animal studies propose thyroid hormones as long-term regulators for phosphate metabolism. Normal calcium and phosphorus levels have been shown in few studies while other studies have shown decreased levels in hypothyroidism. Even though the changes in calcium and phosphorus may be slight in thyroid disorders, these disturbances will be important for the patient in long run.

Thyroid hormones have a direct effect on the calcium and phosphorus resorption by altering the blood flow and glomerular filtration rate (GFR).[20] Thyroid hormones play a role as the central regulator of body haemodynamics, thermoregulation and metabolism. It has an influence on renal haemodynamics, glomerular filtration and electrolyte handling.[21] Mineral pool in the blood is determined by the thyroid hormones by influencing their mobilization into the blood, and also their clearance through effect on glomerular filtration rate. There is an increased renal blood flow leading to increased clearance of calcium as well as decreased extracellular release of calcium in hypothyroidism.[22] Our

study has shown significant low levels of serum calcium in cases than controls. The serum phosphorus levels were markedly increased among hypothyroid patients in the present study compared to the controls. Serum magnesium levels were found to be significantly lower in hypothyroid cases. There was a significant positive correlation between serum phosphorus and TSH and negative correlation between serum calcium, magnesium and TSH.

Normal growth and maturation of the skeleton needs thyroid hormones. In hypothyroidism there is a decreased turnover due to impaired mobilization of calcium into the bones, which leads to the decrease in blood calcium. In hypothyroidism there is also an increased production of calcitonin which promotes the tubular reabsorption of phosphate and favours the tubular excretion of calcium which leads to hypocalcaemia and hyperphosphatemia. Thyroxin regulates blood calcium level by releasing calcium from cells, but in hypothyroidism less thyroxin enters the cells and hence less calcium is released leading to hypocalciemia.[23] In hypothyroidism there is hypomagnesaemia because of urinary output and fractional excretion of magnesium through urine. Hypothyroidism is six times more common in women than in men has been suggested by earlier statistics. The higher prevalence of thyroid diseases in women shows that oestrogen might be involved in the pathophysiology of thyroid dysfunction. Estradiol has an antagonistic effect on thyroid hormones as estradiol competes with the thyroid hormone binding sites on the receptor proteins. Estradiol also limits the thermogenic action of thyroid hormones and promotes the storage of fat.[24] Gantus MA et al. studied the effects of oestrogen on a homogeneous stromal cell population of rat thyroid gland. Their results point to the cytokine transforming factor brta 1/transcription factors mad-2 signalling pathway as a putative target of oestrogen actions on a thyroid stromal cell.[25]

Roopa M et al. & Jaikiran K et al. studied the changes in electrolyte profile in patients with hypothyroidism and reported that calcium level is significantly reduced and magnesium and phosphorus level is increased in patients with hypothyroidism. It was also found that there was a significant negative correlation between serum calcium and TSH, positive correlation between serum TSH and magnesium and phosphorus. But in our study, we observed a negative correlation between magnesium and TSH.[23,26] The animal study done by Kumar and Prasad et al. have concluded that renal calcium excretion was increased in rats with high TSH levels.[27]

Suneel B et al. studied mineral status in patients of thyroid disorders and found decreased calcium and increased phosphorus in hypothyroidism mainly due to influence of parathyroid hormone (PTH) and calcitonin. Magnesium level is decreased due to influence on GFR and decreased clearance. In hypothyroidism, the renal blood flow is increased leading to high clearance of magnesium from kidneys. So it will be causing hypomagnesemia which is matching our study findings of decreased magnesium in hypothyroid patients.[28] Khadem H had also shown reduced total and ionized magnesium in patients with hypothyroidism along with study of lipid profile.[29] Few studies have shown decreased levels of serum magnesium levels in hypothyroid patients as compared to the controls and show a negative correlation with thyroid hormones which is matching with our study finding of decreased magnesium in cases of hypothyroid as compared to the controls.[30] Abbas MM et al. study also indicated elevated phosphate and decreased calcium levels in hypothyroid patients which are in accordance with our study. But the magnesium levels increased in hypothyroid patients is not matching with our study finding as we have found decreased levels of magnesium among cases as compared to the controls of healthy volunteers.[31]

Asamaik AS et al. have observed that phosphorus levels are significantly increased in subclinical hypothyroid cases (SCH) and overt hypothyroid cases (OH) which is in accordance with our study finding of increased phosphate among hypothyroid cases.[32] In another study by AlTonsi, found altered phosphate concentrations in hypothyroid patients. The increased serum phosphate levels in hypothyroid cases is in accordance with our study.[33] Schwars C et al. study of 9012 patients found a significant positive correlation between TSH and phosphate levels. Phosphate levels are higher in cases with elevated TSH than in controls which is also matching with our present study.[34] Magnesium, on the other hand, is an important cation that ameliorates atherosclerosis and hypertension, promotes coronary vasodilatation and uploading of the heart causing an increase in its efficiency. Low serum magnesium is often associated with arrhythmias, coronary vasospasm and high blood pressure.[35] A significant decrease of serum magnesium in hypothyroid patients was observed which is in congruence with the results reported in humans[36] and in experimental animals.[37] A study done by Mamatah et al. have shown a statistically significant increase in serum magnesium levels and a positive correlation between serum magnesium and TSH which are not in accordance with our study, but we had a decrease in serum magnesium levels in hypothyroid cases and a negative correlation between serum magnesium and TSH levels.[38] As per the study conducted by McCaffrey and Quamme, magnesium retention increased by 15 – 30 % from kidneys due to increased reabsorption in renal tubules as the thyroid hormones have direct effect on renal tubules as well.[39] Sussanna et al. showed decrease in serum magnesium in hypothyroid patients with negative correlation with TSH which is correlating to our study findings.[40] But in a study by Frizel et al. they have observed increased plasma ionized and total magnesium levels among hypothyroid patients which is not in accordance with our study.[41] Thyroid hormones determine the mineral pool in the blood by influencing the mobilization of minerals like calcium and phosphorus, in the blood by influencing their clearance through urinary excretion by its effect on GFR or renal plasma flow. Low levels of calcium in hypothyroid cases reflect poor metabolism of calcium. Low levels of magnesium reflect poor influence of thyroid hormones on GFR and thereby clearance of these minerals by filtration. The treatment modalities can also be framed while treating the hypothyroid patients keeping in view of altered mineral metabolism. The decreased magnesium levels will be influencing the action of thyrotrophic hormone on the

thyroid gland through the formation of cyclic amp involved in the activation of adenylyl cyclases and stimulates cyclic 3, 5 nucleotide phosphodiesterase disturbing various metabolism in the body that has been shown in the in vitro studies.[42]

CONCLUSIONS

Our study demonstrated that hypothyroid patients show low serum total calcium, total magnesium and increased serum phosphorus levels compared to the healthy controls. Hence monitoring of mineral status of the hypothyroid patients on follow-up will be of benefit to the patients. Supplements can be initiated based on these values to avoid the effects resulting from changes in the mineral levels mainly related to bone metabolism.

Limitations of Our Study

Our study is limited by the limited number of patients. In addition, the list of confounders for the mineral metabolism disturbances is long which needs to be studied in details. The other markers related to mineral metabolism like vitamin D, PTH and calcitonin can also be studied for better understanding. Prospective study can also be planned to study the improvement on the clinical manifestations on initiating the supplements for these minerals among hypothyroid cases.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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