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Research Article

Selenium and Selenium-Dependent Enzymes in Hypothyroidism

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A B S T R A C T

Introduction and Aim: Hypothyroidism is a prevalent endocrine disorder characterised by an underactive thyroid gland and reduced production of thyroid hormones. Selenium, an essential trace mineral, plays a critical role in thyroid function and the synthesis of thyroid hormones. Selenium-dependent enzymes, including glutathione peroxidase (GPx) and iodothyronine deiodinases (DIOs) type II, thioredoxin reductase and superoxide dismutase (SOD) are involved in regulating thyroid hormone metabolism and maintaining thyroid gland health. Understanding the significance of selenium and selenium-dependent enzymes in hypothyroidism can provide valuable insights into the disease mechanisms and potential therapeutic interventions.

Materials and Methods: 100 healthy individuals and 100 age-matched hypothyroid subjects were included in this study after getting informed consent. Thyroid profile, selenium and selenium-dependent enzymes were measured in all subjects.

Results: The TSH level in hypothyroid subjects was 9.54 ± 7.03 when compared with healthy subjects and it was statistically significant (p = 0.000). Selenium level was 53.32 ± 15.80 in hypothyroid subjects which was very much reduced as compared to that of healthy subjects (p = 0.000). Selenium-dependent enzymes such as GPx, deiodinases type II and SOD were greatly reduced in subjects with hypothyroidism, and it was found to be highly statistically significant.

Conclusion: The present study concludes that in hypothyroidism, both selenium levels and selenium-dependent enzymes are reduced. This reduction may contribute to the increased formation of free radicals and the development of oxidative stress. These findings highlight the significance of selenium in thyroid metabolism. Further research should extensively investigate the role of selenium supplementation in thyroid metabolism.

Keywords: Selenium, Selenium-Dependent Enzymes, Hypothyroidism, Glutathione Peroxidase, Iodothyronine Deiodinases Type II, Oxidative Stress, Supplementation

Introduction

Hypothyroidism is characterised by reduced production and secretion of triiodothyronine (T3) and thyroxine (T4), the two primary thyroid hormones. Autoimmune thyroiditis (AIT) is an autoimmune disorder characterised by the autoimmune destruction of thyroid cells, the production of autoantibodies against thyroglobulin and thyroid peroxidase enzyme, and the excessive formation of reactive oxygen species. There is an increased incidence of thyroiditis in regions where selenium deficiency is prevalent.[1] This is attributed to the reduced activity of selenium-dependent enzymes in the thyroid gland cells.[1] Due to decreased glutathione peroxidase (GPx) activity, the breakdown of peroxide in thyroid cells is impaired.[2] Severe selenium deficiency has been observed to result in increased necrosis of thyroid cells and invasion by macrophages.[3,4] Decreased selenium levels lead to a decline in selenium-dependent antioxidant enzymes such as GPx and thioredoxin reductase, which subsequently increases the production of reactive oxygen species.[5] Consequently, selenium deficiency affects thyroid hormone synthesis in two ways: by disrupting the antioxidant capacity of thyrocytes and by interfering with the metabolism of thyroid hormones both locally and systemically.[6,7] The relationship between selenium status, selenium-dependent enzymes, and hypothyroidism is not well-established.[8] Therefore, we conducted this cross-sectional study to examine serum levels of selenium and selenium-dependent enzymes in individuals with hypothyroidism.

Materials and Methods

The present study was conducted at Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals. After obtaining ethical committee clearance and informed consent, 100 healthy individuals (Group 1) and 100 age-matched hypothyroid subjects (Group 2) aged between 20 years and 50 years were recruited. The study was conducted for a period of two years (December 2019 to December 2021). Along with T3, T4, TSH, selenium and selenium-dependent enzymes were estimated in all the subjects. Selenium levels were determined using dynamic reaction cell inductively coupled plasma mass spectrometry (DRC-ICP-MS). Enzyme-linked immunosorbent assay (ELISA) was employed to assess the activity of selenium-dependent enzymes and measure the levels of thyroid hormones.

Inclusion criteria: Hypothyroidism patients without selenium and antioxidant supplementation

Exclusion criteria: Other metabolic diseases

Statistical Analysis

All statistical analysis was performed using the SPSS software version 20. Quantitative variables were demonstrated as mean ± standard deviation. Statistical analysis was done using the student t test. The association between the factors was analysed by using Pearson correlation.

Results

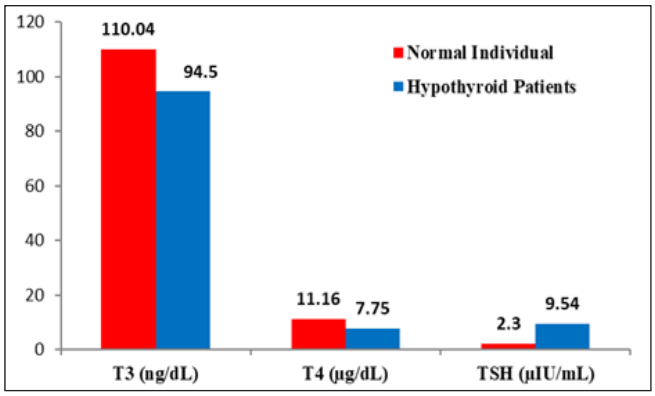

Figure 1.Comparison of Thyroid Profile Between Healthy Individuals and Hypothyroidism Patients

Table 1.Comparison of Selenium and Selenium-Dependent Enzyme Between Healthy Individuals and Hypothyroidism Patients by Student's t Test

Parameter	Healthy Individuals (Mean ± SD) (n = 100)	Hypothyroid Patients (Mean ± SD) (n = 100)	t Value	p Value
Selenium (µg/L)	147.94 ± 14.17	53.32 ± 15.80	44.57	< 0.0001***
GPx (U/mL)	62.91 ± 10.45	45.76 ± 11.85	10.62	< 0.0001***
SOD (U/mL)	21.12 ± 6.06	14.23 ± 5.45	8.391	< 0.0001***
Thioredoxin reductase (IU/L)	62.50 ± 14.68	33.03 ± 7.77	17.86	< 0.0001***
Deiodinases type II (IU/L)	50.14 ± 17.68	23.59 ± 5.68	14.41	< 0.0001***

***Correlation is significant at $p < 0.05$ level (2-tailed)

SD: Standard deviation; GPx: Glutathione peroxidase; SOD: Superoxide dismutase

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Figure 1 demonstrates the comparison of thyroid profiles and Table 1 demonstrate the comparison of selenium and selenium-dependent enzymes between healthy individuals and hypothyroidism subjects. Along with selenium, selenium-dependent enzymes (GPX, thioredoxin reductase, SOD, and deiodinases type II) were reduced, and they are found to be statistically significant.

Table 2.Correlation of TSH, Selenium and Selenium-Dependent Enzyme by Pearson Correlation Test

Parameter	TSH	p Value
Selenium	-0.764	0.000**
GPx	0.574	0.000**
SOD	0.676	0.000**
Thioredoxin Reductase	0.693	0.000**
Deiodinases type II	-0.581	0.000**

**Correlation is significant at p < 0.05 level (2-tailed)
GPx: Glutathione peroxidase; SOD: Superoxide dismutase

Discussion

Thyroid hormones are crucial for proper bodily functions. It mainly depends on two microelements, iodine, and selenium. Even though the role of iodine in the thyroid gland has been well appreciated, the importance of selenium for the thyroid hormone axis is least considered. So, this study is undertaken to find out the role of selenium and selenium-dependent enzymes on thyroid hormones.[8]

Our study demonstrates significant disparities in thyroid profiles between individuals with normal thyroid function and those diagnosed with hypothyroidism, where T3 and T4 levels were found to be decreased in hypothyroid patients compared to healthy individuals, and the differences were statistically significant. Healthy subjects exhibited lower levels of T3 (110.04 ± 32.77 ng/dL), whereas hypothyroidism patients displayed even lower levels (94.5 ± 26.84 ng/dL), with the statistical analysis yielding a significant t-value of 3.668. Similarly, healthy subjects had higher levels of T4 (11.16 ± 5.27 µg/dL) compared to hypothyroidism patients (7.75 ± 4.55 µg/dL), with a calculated t value of 4.903. Conversely, the TSH levels were elevated in hypothyroidism patients (9.54 ± 7.03 µIU/mL) compared to the normal range (2.30 ± 1.31 µIU/mL), resulting in a highly significant t value of -10.104. These findings are consistent with previous literature regarding hypothyroidism and provide strong evidence ($p \leq 0.0001$) of impaired thyroid gland function indicated by reduced T3 and T4 levels, as well as a compensatory elevation in TSH levels.[9]

The decreased T3 and T4 levels in hypothyroidism can be attributed to the impaired thyroid gland function, resulting in reduced synthesis and secretion of these hormones.[10] These findings align with the clinical manifestations observed in hypothyroidism, such as fatigue, weight gain, and cognitive impairment.[10]

Studies have consistently reported elevated TSH levels in hypothyroidism patients compared to healthy individuals. The elevated TSH levels indicate the compensatory mechanism of the body to stimulate the thyroid gland and restore normal thyroid hormone production. Monitoring TSH levels is essential for diagnosing and managing hypothyroidism.[11]

Previous studies have investigated the role of selenium and selenium-dependent enzymes in hypothyroidism, providing valuable insights into their significance in thyroid function and the pathophysiology of the disease.[12] By comparing our findings with previous studies, we can gain a better understanding of the relationship between selenium, selenium-dependent enzymes, and hypothyroidism.[12]

The reduced selenium levels in hypothyroidism may contribute to the disruption of thyroid hormone synthesis and metabolism.[13] Selenium is an essential trace mineral involved in the functioning of selenoproteins, including glutathione peroxidase (GPx) and iodothyronine deiodinases type II, which are important for thyroid hormone production and metabolism.[14]

Our study reveals a significant decrease in selenium levels among individuals diagnosed with hypothyroidism when compared to those with normal thyroid function. In healthy individuals, the mean selenium level was measured at 147.94 ± 14.17 µg/L, whereas hypothyroidism patients exhibited a markedly lower level of 53.32 ± 15.80 µg/L. The resulting t value was calculated as 44.57, indicating a highly significant difference. Similarly, healthy individuals showed a mean GPX level of 62.91 ± 10.45 U/mL, while hypothyroidism patients displayed a lower level of 45.76 ± 11.85 U/mL, with a corresponding t value of 10.62. Additionally, the mean SOD level in healthy individuals was 21.12 ± 6.06 U/mL, compared to 14.23 ± 5.45 U/mL in hypothyroidism patients, resulting in a t-value of 8.391. Furthermore, the mean thioredoxin reductase level in healthy individuals was 62.50 ± 14.68 IU/L, whereas hypothyroidism patients demonstrated a reduced level of 33.03 ± 7.77 IU/L, yielding a t value of 17.86. Lastly, the mean deiodinases type II level in healthy individuals was 50.14 ± 17.68 IU/L, whereas in hypothyroidism patients, it was 23.59 ± 5.68 IU/L, resulting in a t value of 14.41. These findings align with previous research conducted which also observed decreased selenium levels in individuals with hypothyroidism.[14]

A study by Kelly investigated the interplay between selenium-dependent enzymes and thyroid hormone metabolism. The findings revealed that selenium deficiency led to decreased activity of GPx and DIOs, resulting in

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impaired thyroid hormone metabolism. This disruption in enzyme activity affected the conversion of thyroxine (T4) to triiodothyronine (T3), the active form of thyroid hormone, and subsequently led to alterations in thyroid hormone levels.[15]

Additionally, a study by Rua et al. focused on the role of GPx in maintaining thyroid hormone homeostasis. The research demonstrated that GPx activity was crucial for protecting the thyroid gland from oxidative damage and for regulating the availability of selenium for the synthesis of selenoproteins, including DIOs.[16] The decrease in GPx activity due to selenium deficiency was associated with reduced DIO activity and altered thyroid hormone metabolism.[16]

The results of the present study showed a decrease in selenium level which may contribute to oxidative stress and impaired thyroid hormone metabolism. Gpx plays a crucial role in protecting the thyroid gland from oxidative damage, while DIO enzymes are involved in the conversion of T4 to the active form T3. The reduction in these enzymes may further exacerbate the hormonal imbalance in hypothyroidism.

Table 2 shows the correlation of thyroid hormone with selenium and selenium-dependent enzymes. In the present study, TSH showed a significant negative correlation with selenium and selenium-dependent enzymes indicating the hormonal imbalance due to the reduced activity of selenium-dependent enzymes. TSH showed a significant positive correlation with SOD suggesting the compensatory mechanism in response to oxidative stress.

A study by Bhuyan et al. explored the relationship between selenium-dependent enzymes and thyroid hormone metabolism in individuals with thyroid dysfunction. The findings indicated that selenium deficiency was associated with decreased GPX and DIO activity, resulting in altered thyroid hormone levels and impaired metabolic function. The study emphasised the importance of selenium-dependent enzymes in maintaining thyroid hormone balance and highlighted the potential consequences of selenium deficiency on thyroid function. The correlation result observed in this study supports the existing literature on the relationships between thyroid hormones, selenium, and selenium-dependent enzymes in individuals with thyroid dysfunction.[17]

The results of our study clearly show that selenium-dependent enzymes, including GPx and DIOs, play a significant role in thyroid hormone metabolism and help in reducing free radicals and oxidative stress. Selenium deficiency can lead to decreased activity of these enzymes, resulting in altered thyroid hormone levels and impaired metabolic function. The findings of our study support the results from previous studies that emphasise the importance of maintaining optimal selenium levels for maintaining thyroid health and highlight the potential consequences of selenium deficiency on thyroid hormone metabolism.

Future Scope

The discussion of our study raises important considerations for future research directions. Firstly, there is an opportunity to enhance the comprehensiveness of the present investigation by incorporating age and gender as crucial variables in the context of hypothyroidism. Notably, with a sample size of 200, systematic exploration of age and gender-related variations can provide potential outcomes. Future studies can address this by stratifying the sample based on age and gender, offering a more nuanced understanding of the relationship between selenium deficiency and thyroid function across diverse demographic groups. Moreover, a notable future research direction involves delving into gene expression patterns associated with hypothyroidism. By exploring the molecular mechanisms underlying thyroid dysfunction through gene expression analysis, valuable insights can be gained. Future endeavours should integrate this aspect to unravel the genetic factors contributing to selenium-dependent hypothyroidism.

Additionally, the present study opens the door to further investigations by exploring protein expression related to hypothyroidism. Evaluating the protein expression of selenium-dependent enzymes like GPx and DIOs can provide a more comprehensive understanding of the molecular pathways involved in thyroid hormone metabolism. Future research should consider incorporating protein expression analysis to complement our findings on selenium deficiency and its impact on thyroid function. This forward-looking approach positions our study as a foundation for future endeavours, emphasising the potential for expansion and deeper exploration in the field.

Practical Strategies for Clinicians

Selenium deficiency can lead to various health issues, including thyroid dysfunction, emphasising its crucial role in maintaining proper thyroid function and overall health. Practical strategies for clinicians addressing selenium deficiency in individuals with hypothyroidism encompass dietary modifications, incorporating selenium-rich foods like Brazil nuts, shrimp, tuna, beef, liver, and eggs, though caution is advised for those with thyroid issues to avoid certain foods high in iodine or goitrogens.[18] Supplementation, with a daily dosage ranging from 60 mcg for women to 75 mcg for men, may be recommended, and higher doses can be considered for optimal levels.[19] Regular monitoring of thyroid function, and examining hormone levels and selenium levels in the blood, facilitates timely

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intervention. Recognising the individualised impact of selenium deficiency on immune function, cardiovascular health, and fertility, clinicians should tailor treatment plans to address specific needs.[20] Promoting awareness among patients about the importance of selenium for thyroid health and advocating for a balanced diet rich in selenium is crucial for prevention.

Conclusion

In conclusion, the present study highlights that both selenium levels and selenium-dependent enzymes are reduced in hypothyroidism. This reduction may contribute to the production of free radicals and oxidative stress. Our findings emphasise the significance of selenium in thyroid metabolism. Further investigation into selenium supplementation in hypothyroidism can provide valuable insights into its potential role in managing the condition.

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Conflict of Interest: None

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