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Research Article

The Correlation between Serum Inositol 1,4,5 Triphosphate Level and Primary Hypothyroidism

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ABSTRACT

Background: Most primary hypothyroidism patients also experience inefficiency and irregularity. It is possible to understand the significance of myo-inositol in treating the thyroid gland by relating it to the synthesis of thyroid hormones. Study aimed to estimate serum of inositol 1,4,5-triphosphate (IP3) in primary hypothyroidism disorder and through that level it can shed light on whether it is accused of inactivity of the thyroid gland and at the same time open the doors for the use as a treatment.

Subject and Methods: The study was taken from the analytical cross-sectional design.120 subjects were divided into three groups, the first group included 40 healthy subjects, the second group included 25 patients with subclinical hypothyroidism, and the last group had 55 patients with primary hypothyroidism. with the subjects chosen from a teaching laboratory in the medical city. thyroid hormones and serum TSH was determined using Enzyme Immunoassay by Tosoh instrument assay, while serum inositol 1,4,5-triphosphate (IP3) using (ELISA) system.

Results: primary hypothyroidism patients showed a significant ($p \leq 0.05$) decrease level of serum IP3 when compared with healthy subjects. There is significant positive correlation with serum inositol 1,4,5 triphosphate (IP3) and each triiodothyronine S.T3 ($r = 0.581$, $p \leq 0.05$), thyroxine S.T4 ($r = 0.597$, $p \leq 0.05$), and significant negative correlation thyroid-stimulating hormone S.TSH ($r=-0.820$, $p \leq 0.05$), in primary hypothyroidism Patients.

Conclusions: inositol 1,4,5 triphosphate (IP3) deficiency in primary hypothyroidism disorder may be a cause of it happening, at the same time may be useful in its treatment even if it was not studied adequately in the study, but through its effect on a thyroid hormone.

Introduction

Primary Hypothyroidism is a condition in which the thyroid gland does not produce enough thyroid hormone to meet the body's needs for regulating metabolism and energy utilization. It affects practically every organ in the body. (1)

A rise in blood TSH with normal thyroxine (T4) and triiodothyronine (T3) concentrations in the first biochemical anomaly in primary hypothyroidism (i.e., subclinical hypothyroidism). (2)

Phosphoinositide is part of the phosphatidylinositol signal transduction channel across the plasma membrane via the second

messenger 1,4,5-triphosphate, which modulates intracellular Ca+2 release, according to several studies (3).

Inositol triphosphate is a group of somewhat distinct molecules generated from the C6 sugar alcohol. It is composed of an inositol ring with three phosphate groups bound at the 1, 4, and 5 carbon positions, and three hydroxyl groups bound at positions 2, 3, and 6. it is the nine types of isomers, Other inositols (epi-, allo-, muco-, cis, l-chiro-, d-chiro-, scyllo-and neo) are less well known, except d-chiro-inositol, which plays an important insulin resistance and insulin signal transduction (4).

Inositol derivatives are important components of the cell's structural lipids, and they regulate cell proliferation, morphogenesis, glucose metabolism, and cytoskeleton reorganization, among other things. (5).

MYO Inositol-containing phospholipids serve as precursors for the manufacture of several signaling intermediates, including inositol1,4,5 triphosphate (IP3), phosphatidylinositol (PI), inositol phosphates (IP), phosphatidylinositol-phosphates (PIPs), inositol-phosphoglycans (IPGs), glycosyl Phosphoinositides are made up of myo-I, which are mediators in the phosphatidylinositol (PIP2) signal transduction pathway. (6,7)

Phosphatidylinositol 4,5biphosphate (PIP2), the precursor of diacylglycerol (DAG) and inositol 1,4,5 triphosphate (IP3), modulates intracellular Ca+2 released by hydrolysis, which is involved in the (phospholipase C) PLC dependent inositol phosphate Ca+2 / DAG, acting as second messengers of many hormones such as FSH, TSH, insulin and LH (3)

Inositol plays a role in the signaling of various hormones, including, thyroid-stimulating hormone (TSH), gonadotropins, and insulin. In specific, inositol metabolism impairment can negatively affect secretion in mammalian thyroid, hormone storage, and biosynthesis. (8)

MYO Inositol derivates and dietary MYO Inositol are absorbed in the gut via sodium-dependent transporters called sodium-myoinositol channels type 2 (SMIT2) and type 1 (SMIT1), which are found in the jejunum and duodenum, respectively. (9).

Inositol homeostasis involves three distinct processes: 1) absorption and excretion through the intestines; 2) transport from plasma to the interstitial fluid of cells via specific carriers; 3) endogenous synthesis and catabolism. Exogenous MYO is generally -well tolerated in daily doses ranging from 4 to 30 g for up to 12 months. Mild adverse effects such as nausea and diarrhea may occur only when daily dosages exceed 12 g.(10).

Myo Inositol is produced endogenously from glucose in two enzymatic steps. A hexokinase converts glucose to glucose-6-phosphate, which is ultimately converted to myoinositol-1-phosphate. In humans, this endogenous synthesis produces up to 2 g MYO per day in each kidney, totaling 4 g per day. (11).

Myo Inositol is found in fresh fruits, vegetables, cereals, legumes, and nuts, and is the most widely dispersed in nature. Myo-inositol is a crucial component of cell membrane structural lipids (12)

The Aim of this study is to estimate serum of inositol 1,4,5-triphosphate (IP3 in primary hypothyroidism disorder and through that level it can shed light on whether it is accused of inactivity of the thyroid gland and at the same time open the doors for the use as a treatment.

Subjects and Methods

The study was taken from the analytical cross-sectional design. The Scientific of Committee Biochemistry Department, College of Medicine, University of Baghdad, Iraq, provided ethical permission. Between December 2021 and January 2022, the research was conducted, and the individuals were picked from a teaching lab in the medical city. At the consultation at the Baghdad Teaching Hospital, a thyroid specialist made the clinical diagnosis. Participants were asked to complete questionnaires to indicate their consent for the study's data collection on both sick groups and healthy people. The study involves 72 females and 48 males. The study involved 120 subjects divided into three groups, First group: was 40 healthy individuals in age range (25 -69 years) 22 female, 18 male. were examined by laboratory tests for their serum TSH, Total T4, and Total T3) match the normal reference range of thyroid hormones. Second group: 25 patients with subclinical hypothyroidism have a serum TSH level of 4.6 to 10 mIU/L with age range (25 -69 years) 15 female, 10 male. Third group: 55 patients35 female, 20 males. who had the same specifications for the diagnosis of primary hypothyroidism with a TSH level higher than 10mIU/L. the clinical diagnosis by thyroid specialist and laboratory investigations. the Third group was divided into two sub-groups First newly diagnosis15 patients were 9 females, and 6 males in the age range (28 -63 years). the second group was diagnosed with hypothyroidism in the treatment of 40 patients 26 female, 14 male in age range (27 -68 years). Each serum sample was tested for TSH, Total T4, Total T3, and IP3.Inclusion criteria Hypothyroidism patient matching selection of study specification. Exclusion criteria Patient thyroidectomy. Patients with Radioactive Iodine (Radioiodine) Therapy for Thyroid Cancer (RAI). Patient with secondary hypothyroidism. thyroid hormones and serum TSH was determined using Enzyme Immunoassay, while serum inositol 1,4,5-triphosphate (IP3) using enzyme-linked immune sorbent assay (ELISA) system.

Results and Statistical Analysis

In the study, there are 48 men and 72 women. The successful matching of groups in terms of age and gender by matchings of subjects' ages and genders (non-significant difference with P> 0.05). Both results clarified in table 1.

Primary hypothyroidism patients showed a significant (with $p \leq 0.05$) decrease level of serum IP3 when compared with two other studied groups Subclinical and healthy subjects

Subclinical Subjects also show a significant (with $p \leq 0.05$) decrease level of serum IP3 when compared with the healthy subjects. Both results clarify in table 2 Figure (1).

There is significant positive correlation with serum inositol1,4,5 triphosphate (IP3) and each S.T3 (with $r=0.581$, $p \leq 0.05$), S.T4 (with $r=0.597$, $p \leq 0.05$), and significant negative correlation S.TSH (with $r=-0.820$, p 0.000, $p \leq 0.05$), in primary hypothyroidism Patient. In figure (2,3,4).

Table 1: Mean ± Standard deviation SD of Age and sex number in healthy, subclinical subjects and hypothyroidism patients

Studied parameter	Studied groups	Mean ±SD	P-Value	LSD P-Value
Age (years)	Healthy subject (A) NO.40	42.38 ±12.26	P>0.05 N.Sig.	AVS B P>0.05 N.Sig.
	Subclinical Subject(B) NO.25	45.36 ±12.41		A VS C P>0.05 N.Sig.
	Hypothyroidism Patient (C) NO.55	42.49 ±11.31		B VS C P>0.05 N.Sig.
Studied parameter	Studied groups	No.%	Chi-square test p-value	
Gender No%	female% in Healthy subject	55%	P >0.05 N.Sig	
	female% in Subclinical Subject	60%		
	female% in hypothyroidism Patient	65%		
	male % in Healthy subject	45%		
	male % in Subclinical Subject	40%		
	male % in Hypothyroidism Patient	35%	P >0.05 N.Sig	

sig. = significant, N.sig. = non-significant, LSD = fisher least significant difference.

Table 2: Mean ± Standard deviation SD of serum IP3 in primary hypothyroidism patients, Subclinical subjects, and healthy subjects

Studied marker	Studied groups	Mean ±SD	P-Value	LSD P-Value
S.IP3 (ng/ml)	Healthy subject (A) No.40	9.16 ±4.72	P ≤0.05 Sig	B VS A P ≤0.05 Sig
	Subclinical Subject (B) No.25	3.40 ±0.72		C VS A P ≤0.05 Sig
	hypothyroidism Patient (C) No.55	2.02 ±0.57		C VS B P ≤0.05 Sig

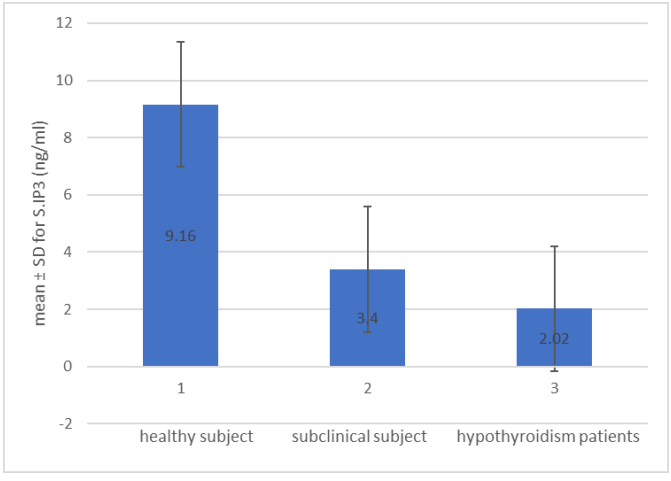

Figure 1: Mean ± Standard deviation (SD) of S. IP3 in healthy subjects, Subclinical subjects, and primary hypothyroidism patients

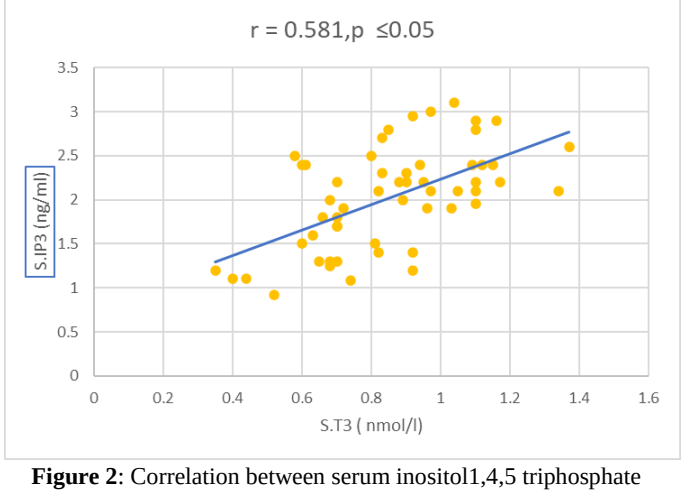

Figure 2: Correlation between serum inositol1,4,5 triphosphate (IP3) and S.T3 in primary Hypothyroidism Patients

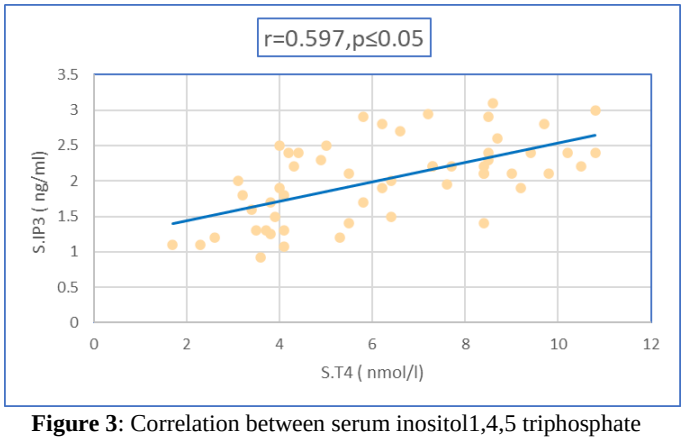

Figure 3: Correlation between serum inositol1,4,5 triphosphate (IP3) and S.T4 in primary Hypothyroidism Patients

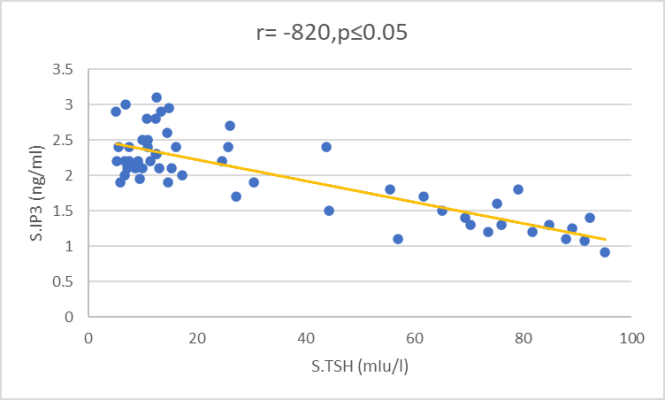

Figure 4: Correlation between serum inositol1,4,5 triphosphate (IP3) and S.TSH in primary Hypothyroidism Patients

Using receiver operator characteristic analysis (ROC) curve, to examine the diagnostic efficiency of serum IP3 level about primary hypothyroidism Patients. ROC curve is a graphical representation of the relationship/tradeoff between clinical Specificity and Sensitivity for each cut-off test. The results are tabulated in table (3) and figures (5) according to primary hypothyroidism Patients.

Table 3: Sensitivity and Specificity, the area under the curve and Cut-off value of serum IP3 in primary Hypothyroidism Patients

parameter	Sensitivity	Specificity	AUC	Cut-off value
S.IP3	82.5%	100%	0.95	5.25(ng/ml)

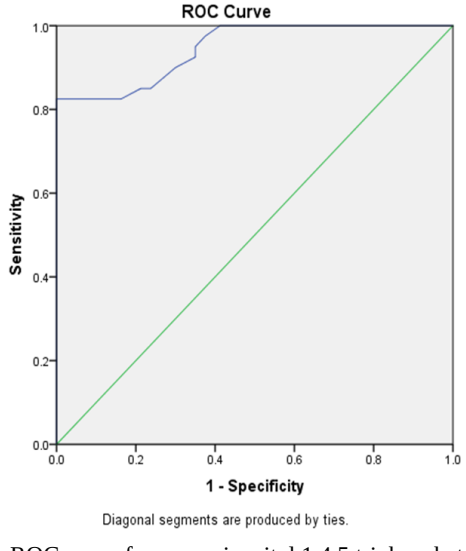

Figure 5: ROC curve for serum inositol 1,4,5 triphosphate (IP3) in primary Hypothyroidism Patients

Discussion

This study was conducted to match the age and gender No (male, female) and that was documented through (a non-significant difference with P ≥0.05) in table1.

Primary hypothyroidism individuals had the lowest levels of inositol 1,4,5 triphosphate (IP3) Once TSH attaches to its receptor on the thyroid cell surface, it stimulates cell proliferation and differentiation as well as thyroid hormone production. When TSH receptors bind, two post-receptor cascades are activated: one involves adenylyl cyclase, which results in increased intracellular cyclic AMP and protein kinase A phosphorylation, as well as activation of cytosolic and nuclear target proteins; the other is inositol-dependent and involves the phospholipase C-dependent inositol phosphate Ca+2/diacyl In addition, the inositol-dependent system controls H2O2-mediated thyroglobulin iodination, whereas the cAMP pathway is more involved in cell proliferation, differentiation, and thyroid hormone (T4, T3) release.(3,5,13).

Thyroid Peroxidase (TPO) is an enzyme that uses hydrogen peroxide H2O2 to oxidize and integrate iodide in the tyrosyl groups of Thyroglobulin Tg. (14).

It has recently been found to be a very effective and safe treatment of IP3 and selenium for those who have subclinical hypothyroidism due to Autoimmune Thyroiditis. (15). In a study published in 2013, researchers discovered that providing myo-inositol + selenium to patients with subclinical hypothyroidism for six months reduced TSH levels by 31% compared to a control group given only selenium. These findings were then verified in a different clinical investigation by the same authors. Another study looked at TSH levels in Hashimoto patients with subclinical hypothyroidism who were given myo-inositol + selenium for six months and found that they dropped significantly after three months and even more after six months. TSH levels did not alter appreciably in the control group, which got only selenium. (16).

In a study in 1993 a year. The tissue levels of inositol 1,4,5-trisphosphate isoform were found to be significantly higher in hyperthyroid Rats' hearts and lower in hypothyroid Rats' hearts than in euthyroid ones (17). Where the results are identical to our results, but our study was on humans. where the results were to the levels of inositol 1,4,5-trisphosphate in Subclinical subjects were lower than in healthy subjects while primary hypothyroidism Patients very lower than in the healthy subject.

The results showed a substantial correlation between inositol 1,4,5-trisphosphate and negative TSH and positive T3, and T4 in primary hypothyroidism patients, and the effect has been previously explained.

serum IP3 showed high Sensitivity of 82.5% and 100% Specificity in diagnosis patients with primary hypothyroidism, this result is withdrawn the serum IP3 as a diagnostic tool for hypothyroidism by (ROC) analysis the reference range of serum IP3 was determined represented by the Cut-off value of 5.25 (ng/ml).

Conclusion

A decrease in the level of serum inositol 1,4,5 triphosphate (IP3) may be one of the reasons for the occurrence of the primary hypothyroidism disorder. Through its effect on thyroid hormone, it can suggest its use in the treatment of the thyroid gland.

Funding

This research did not receive any specific fund.

Conflict of Interest

No conflict of interest

References

[1] Naji RI, Turki KM, Al-Osami MH. Frequency of Hypothyroidism in Patients with Fibromyalgia Syndrome. Journal of the Faculty of Medicine Baghdad. 2013 Apr 1;55(1):56-9.

[2] Alnidawi BF, Jabar MA. Evaluation of Etiological Causes of Hypothyroidism among Patients Visiting Specialized Center for Diabetes and Endocrinology. AL-Kindy College Medical Journal. 2013 Jun 30;9(2):32-4.
[3] Kutateladze TG. Translation of the phosphoinositide code by PI effectors. Nature chemical biology. 2010 Jul;6(7):507-13.
[4] Thomas MP, Mills SJ, Potter BV. The "other" inositols and their phosphates: synthesis, biology, and medicine (with recent advances in myo- inositol chemistry). Angewandte Chemie International Edition. 2016 Jan 26;55(5):1614-50.
[5] Papaleo E, Unfer V, Baillargeon JP, Chiu TT. Contribution of myo-inositol to reproduction. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2009 Dec 1;147(2):120-3.
[6] Croze ML, Soulage CO. Potential role and therapeutic interests of myo-inositol in metabolic diseases. Biochimie. 2013 Oct 1;95(10):1811-27.
[7] Bizzarri M, Fuso A, Dinicola S, Cucina A, Bevilacqua A. Pharmacodynamics and pharmacokinetics of inositol (s) in health and disease. Expert opinion on drug metabolism & toxicology. 2016 Oct 2;12(10):1181-96.
[8] Benvenga S, Antonelli A. Inositol (s) in thyroid function, growth and autoimmunity. Reviews in Endocrine and Metabolic Disorders. 2016 Dec;17(4):471-84.
[9] Schneider S. Inositol transport proteins. FEBS letters. 2015 Apr 28;589(10):1049-58.
[10] Papaleo E, Unfer V, Baillargeon JP, Fusi F, Occhi F, De Santis L. Myo-inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial. Fertility and sterility. 2009 May 1;91(5):1750-4.
[11] Croze ML, Soulage CO. Potential role and therapeutic interests of myo-inositol in metabolic diseases. Biochimie. 2013 Oct 1;95(10):1811-27.
[12] Dinicola S, Minini M, Unfer V, Verna R, Cucina A, Bizzarri M. Nutritional and acquired deficiencies in inositol bioavailability. Correlations with metabolic disorders. International journal of molecular sciences. 2017 Oct 20;18(10):2187.
[13] Ohye H, Sugawara M. Dual oxidase, hydrogen peroxide and thyroid diseases. Experimental biology and medicine. 2010 Apr;235(4):424-33.
[14] Luongo C, Trivisano L, Alfano F, Salvatore D. Type 3 deiodinase and consumptive hypothyroidism: a common mechanism for a rare disease. Frontiers in Endocrinology. 2013 Sep 4;4:115.
[15] Ferrari SM, Elia G, Ragusa F, Ruffilli I, Paparo SR, Caruso C, Gugliemi G, Fallahi P, Antonelli A. Myo-inositol and selenium in subclinical hypothyroidism. Int J Med Device Adjuv Treat. 2018;1:e166.
[16] Briguglia G. Time-dependent efficacy of myo-inositol plus selenium in subclinical hypothyroidism. Int J Med Device Adjuv Treat. 2018;1(1):e108.
[17] Jakab G, Kiss E, Kranias EG, Edes I. Effect of thyroid status on phosphatidylinositols in rat heart. Cardioscience. 1993 Dec 1;4(4):257-62.

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