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Association of Serum Gelsolin with Thyroid Dysfunction in Hypothyroidism Patients: A case-control study

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ABSTRACT

Background: The thyroid hormone, also known as TH, plays a role in a wide variety of metabolic processes, including the promotion of the oxidation of carbohydrates, lipids, and proteins in a variety of tissues. There is a correlation between thyroid dysfunction and metabolic disorders. Gelsolin) GSN) a protein that under the control of Ca2+ sever, caps, and nucleates actin filaments, is a universal, a regulator of multiple cellular processes, including structure and metabolism.

Aims: The purpose of this investigation was to analyze the different levels of gelsolin in patients' serum hypothyroidism has correlate with insulin resistance and thyroid hormones as potential predictor marker for prognosis and complications in this group of patients.

Materials and Methods: A case-control investigation was carried out with a sample size of 120 patients and a control group (HC) of 60 individuals aged 20-50. Two groups of sixty patients, those with overt hypothyroidism (OH) and those with subclinical hypothyroidism (SCH), were created. Enzyme-linked immunosorbent assays (ELISAs) were used to measure serum levels of GSN, FIN, TT3, TT4, and TSH. Methods involving enzymes and colorimetry were used to quantify lipid profiles.

Results: Serum levels of GSN were decrease in hypothyroidism patient groups. However, as compared to the subclinical patients, significantly higher levels of GSN were reduced in overt groups. Overt hypothyroidism Patients (0.08 ± 0.04) had significantly lower serum GSN levels than subclinical hypothyroidism patients (0.13 ± 0.03). While, Healthy control group (0.17 ± 0.03), (P 0.001). This factor appears to be a significant predictor of hypothyroid-related complications. In the OH group, serum GSN levels correlated negatively with both age and TT3 concentrations. whereas a significantly negativity correlated with TT3 and TG levels in SCH group.

Conclusion: in this study concluded, serum GSN concentration was lower in hypothyroidism patients especially in OH group compared to the SCH group and HC group. Serum GSN, a naturally abundant circulating protein, is quickly depleted and consumed after extensive tissue injury, which may explain the decline in GSN levels. Thyroid and other organ damage can be avoided if people realize that severe depletion is associated with poor outcomes in a wide range of clinical situations involving severe inflammatory diseases.

Keywords: *Gelsolin, hypothyroidism, overt hypothyroidism, subclinical hypothyroidism, insulin resistance*

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INTRODUCTION

Hypothyroidism is caused by inadequate thyroid hormone synthesis or activity in target tissues Deficits in thyrotropin-releasing hormone (TRH) or thyroid-stimulating hormone (TSH) are also common causes of hypothyroidism, though primary hypothyroidism is more common, as well as excessive thyroid hormone inactivation, which leads to consumptive hypothyroidism. These disorders have the potential to cause catastrophic health emergencies[1, 2]. Approximately 50% of clinical hypothyroidism cases are caused by autoimmune causes [3]. Thyroid hormone is important in many metabolic processes because it promotes the oxidation of sugar, fat, and protein in numerous tissues. As a result, it regulates metabolism, energy balance, and effects growth, body weight, and thermogenesis[4, 5]. Hypothyroidism has been associated with metabolic disorders [4, 6, 7], Changes in the levels of metabolic regulators originating from adipocytes and hepatocytes, such as leptin, fibroblast growth factor 21 (FGF21), adiponectin, retinol-binding protein-4, and resist in have also been seen in thyroid dysfunction patients[8, 9]. Gelsolin (GSN) is a protein found in the blood of healthy persons; its cytoplasmic isoform promotes inflammatory homeostasis[10] ,but these two forms of the protein have distinct functions. This protein exists in two different isoforms. Cytoplasmic GSN is an isoform of GSN that circulates in the blood and is structurally similar to intracellular GSN but performs different biological functions. Gelsolin induces the DE polymerization of actin filaments[11, 12]. As a result, actin filaments wouldn't be able to set off any further inflammatory responses. Gelsolin levels tend to drop in the aftermath of serious injury or inflammation. Gelsolin is an anti-inflammatory modulator involved in the immune response[13]. Decreased gelsolin levels have also been associated with increased production of inflammatory mediators. Using a wide range of mechanisms[11], GSN aids the immune system in flushing out toxins, both microbial and host-derived, from the body. GSN consumes the debris released by injured cells by severing actin filaments, thereby suppressing the immune response. It also helps macrophages engulf pathogens so they can be destroyed. Conditions as varied as bacterial sepsis, severe trauma, burns, oxygen toxicity, and malaria all contribute to the depletion of circulating GSN, which leads to widespread tissue damage[12]. Levels of gelsolin tend to drop in situations where there is extensive damage or inflammation[14]. The severity of the initial insult, the magnitude of the subsequent decline in GSN, and the risk of death or organ failure have all been studied in patients who had suffered from a wide variety of common injuries, and a consistent correlation has been discovered between the three variables. Patients who presented with the most severe cases of community-acquired pneumonia (CAP) and had the lowest GSN levels had a poorer prognosis [15, 16] . GSN is a Ca2+-regulated actin filament severing and capping protein that can be found in a variety of tissues. These tissues include the heart, brain, immune cells, and cancer. Gelsolin is able to cap the barbed ends of actin filaments, which leads to a reduction in actin polymerization. Actin severing is another mechanism that Gelsolin uses to promote actin depolymerization [17]. An inflammatory response is brought on by cellular injury, such as that brought on by a severe infection, which releases actin from the intracellular compartment into the surrounding tissue[18]. GSN has recently been linked to atherosclerosis in a variety of ways, including lipid metabolism, inflammation, cell proliferation, migration, and thrombosis[19]. Recent studies have shown that plasma gelsolin (pGSN) is also involved in immunomodulation, revealing the multifunctional roles of pGSN in inflammation and wound healing, cancers, and tumor microenvironment[20].

MATERIALS AND METHODS

The study was designed as a case-control for 180 samples consisted of 120 patients with hypothyroidism divided in to two groups: 60 overt hypothyroidism patients (OH) and 60 subclinical hypothyroidism patients (SUB) the hypothyroidism was divided in two subgroups as diagnosis of hypothyroidism is based primarily upon laboratory testing .60 Overt hypothyroidism (OH)patient's clear hypothyroidism by a high serum TSH concentration and low serum T4 and T3 concentration. Sixty subclinical hypothyroidism Patients by a high serum TSH concentration > 4.5 μIU/ml and a normal serum T4 and T3 concentration may have a mild hypothyroidism . Between October 2022 and February 2023, at Al Hakeem hospital in the Al-Najaf province of Iraq, the subjects' medical histories were

gathered, their anthropometric measurements were recorded (including their age, sex, weight, height, and body mass index), and their thyroid hormonal parameters were tested. Sixty healthy adults served as a control group (HC), matching the patients in age (20_55) and sex. Patients who were anemic, had a history of thyroidectomy for cancer, or had any other serious or chronic illness were not included. By dividing a person's weight in kilograms by their height in meters squared, researchers were able to determine their body mass index (BMI)[21] .Venipuncture was used to collect samples into gel tubes after a 12-hour fast. Serum was separated by centrifugation at 3000 Xg for 15 minutes, then frozen at -20 °C for later use. Serum Thyroid Stimulating Hormone (TSH), Total Triiodothyronine (T3), Total Tetraiodothyronine (T4), Gelsolin, and Fasting Insulin (FIN) were measured using ELISA KITs (Melsin Medical Co Company, China). Serum glucose, high-density lipoprotein cholesterol, total cholesterol, and triglycerides were all measured enzymatically (kits BIOLABO, France).

The insulin resistance index (HOMA-IR, Homeostatic model assessment-insulin resistance) was estimated as follows:

HOMA IR = [glucose (mg/dl) * insulin (U/ml) / 405

HOMA B percentage =360 insulin/ (Glucose - 63) [22]

Low density lipoprotein cholesterol (LDL-C) was measured by the indirect method using Friedewald equation [23]

LDL-C= total cholesterol – (HDL-cholesterol + VLDL cholesterol).

LDL-C = total cholesterol - (HDL-cholesterol + TG/5)

Statistical Analysis

Data was analyzed using the Kruskal-Wallis test in SPSS v27 (created by SPSS Inc. and headquartered in Chicago, Illinois, United States) to check for statistically significant differences between independent variables. If the p-value was less than 0.05 or less than 0.01, then the hypothesis is significant. Within each study group, we analyzed the relationship between analyte levels using Pearson's coefficient of correlation to see if there was any statistically significant connection between the two variables. To see if there was a connection between the two factors, this was done. In addition, the diagnostic and prognostic value of biomarkers for hypothyroidism were assessed with the aid of ROC curves generated with the help of MedCalc software. Calculating the area under the curve (AUC) was done so that we could evaluate the test's accuracy. Differences with probabilities of less than 5% or 1%, respectively, were deemed to be statistically significant at the P 0.05 and P 0.01 significance levels. At Berkeley, a cutoff point for statistical significance was determined.

RESULTS AND DISCUSSION

Results

Table1 and figure1 shows the study's baseline characteristics. This included data from study groups comparing patients with OH, SCH, and healthy controls(HC): Age and sex on significant study group. The mean levels of FSG, insulin, BMI, serum TSH, FSG, TG, cholesterol TC, VLDL-C, LDL-C, and HOMA-IR were significantly higher in all hypothyroidism patient groups, with the exception of the subclinical group, where the HOMA- index was non-significantly different when compared to the healthy control group. While when compared to the subclinical hypothyroidism group, the serum means levels of T3, T4, and gelsolin were significantly higher in the overt hypothyroidism group.

TABLE 1: Clinical parameters compared means between patients (overt and subclinical hypothyroidism groups) with control group

Parameters	Healthy Control group HC No=60 Mean±SD	Patients No =180		P_value
		SCH group No=60 Mean±SD	OH group No=60 Mean±SD	
Total Age (yrs.)	34.12±8.69 35.13±7.27 35.65±5.0	36.65±12.29 36.90±6.38 41.89±8.88	35.65±10.27 37.10±9.02 39.90±11.94	----------
Sex F/M	44/16	50/10	50/10	----------
BMI (Kg/m 2)	26.60±4.67	29.06±4.63	32.38±6.15	0.010a 0.001b 0.001c
TT3(ng/mL)	2.30±0.65	1.97±0.37	1.68±0.74	0.003a 0.001b 0.009c
TT4(ng/mL)	103.42±15.90	102.93±22.78	74.15±23.54	0.898a 0.001b 0.001c
TSH(µIU/mL)	3.70±2.90	8.28±3.79	21.53±19.24	0.003a 0.001b 0.001c
FSG (mg/dL)	90.15±6.75	99.48±9.46	111.25±10.51	0.001a 0.001b 0.001c
Insulin (µU/mL)	7.13±2.33	11.20 ±2.37	13.00±2.19	0.001a 0.001b 0.001c
HOMA IR	1.56±0.41	2.08±0.89	3.06±0.91	0.001a 0.001b 0.001c
HOMA-β	121.35±22.99	110.26±10.63	109.22±11.81	0.724a 0.001b 0.001c
T-CHO (mg/dL)	168.17±17.49	169.23 ±14.44	187.07±24.79	0.733a 0.001b 0.001c
TG (mg/dL)	105.72±22.72	144.58 ±36.56	161.82±47.07	0.001a 0.001b 0.011c
LDL-C (mg/dl)	111.57±16.97	117.30±12.99	132.42±16.32	0.045a 0.001b 0.001c
VLDL-C(mg/dL)	21.14±4.54	28.92±7.31	32.36±9.41	0.001a 0.001b 0.011c
HDL-C (mg/dl)	35.45±6.85	23.02±4.42	22.28±4.84	0.001a 0.001b 0.464c
GELSOLIN (ng/ml)	0.17±0.12	0.14 ±0.08	0.13±0.03	0.216a 0.001b 0.025c

Data are displayed as Mean SD, where SD stands for standard deviation, and NS stands for not significantly different at (P>0.05). *indicates a statistically significant difference at the P 0.05 threshold (OH: overt hypothyroidism; SCH: subclinical hypothyroidism). No: number of

patients a:p = significantly different values in the SCH group and the HC group. b:p = statistically significant difference between the values of the OH and HC groups. cp means that there is a statistically significant difference between the values of group OH and group SCH. BMI stands for body mass index; FBG stands for fasting blood glucose. Hemostasis model assessment of in's resistance (HOMA-IR) and hemostasis model assessment of beta cell percentage (HOMA-%). HDL-C stands for high-density lipoprotein cholesterol, while LDL-C refers to low-density lipoprotein cholesterol. TG stands for triglyceride.

The findings of the correlation analysis are as follows: bData are displayed as Mean SD, where SD stands for standard deviation, and NS stands for not significantly different at (P>0.05). *indicates a statistically significant difference at the P 0.05 threshold (OH: overt hypothyroidism; SCH: subclinical hypothyroidism). No: number of patients a:p = significantly different values in the SCH group and the HC group. b:p = statistically significant difference between the values of the OH and HC groups. cp means that there is a statistically significant difference between the values of group OH and group SCH. BMI stands for body mass index; FBG stands for fasting blood glucose. Hemostasis model assessment of in's resistance (HOMA-IR) and hemostasis model assessment of beta cell percentage (HOMA-%). HDL-C stands for high-density lipoprotein cholesterol, while LDL-C refers to low-density lipoprotein cholesterol. TG stands for triglyceride.

Table 2 and figure 1 present a summary of the findings of an analysis done to determine whether or not there is a correlation between the levels of serum gelsolin in a group of patients with overt hypothyroidism and other parameters. There was an inverse relationship found between the use of Gelsolin and BMI, HOMA-IR, VLDL-C, TG HOMA B, and TSH levels. whereas, the correlation of gelsolin in the group of subclinical patients showed a significant positive correlation with HDL-C, TT3, and TT4

The relationships between serum gelsolin levels in patients with overt hypothyroidism and the other parameters are summarized in table 2 and figure 1 respectively. There was an inverse relationship found between the use of Gelsolin and BMI, HOMA-IR, VLDL-C, TG HOMA B, and TSH levels. whereas, the correlation of gelsolin in the group of subclinical patients showed a significant positive correlation with HDL-C, TT3, and TT4

TABLE 2: presents the results of the univariate analysis of the serum gelsolin level in relation to the parameters that were investigated in the patients who were enrolled who had either subclinical or overt hypothyroidism.

	SCH group		OH group	
Parameters	r	P-Value	r	P-Value
Age (years)	-0.296	0.022	-0.049	0.708
BMI (Kg/m2)	-0.159	0.224	-0.068	0.605
TT3(ng/mL)	0.252	0.033	0.321	0.012
TT4(ng/mL)	0.037	0.781	0.119	0.366
TSH(µIU/mL)	-0.116	0.377	-0.036	0.787
FSG (mg/dL)	-0.173	0.185	-0.123	0.347
Insulin (µU/mL)	-0.070	0.597	-0.163	0.212
HOMA IR	-0.038	0.776	-0.027	0.837
HOMA-β	0.135	0.303	0.090	0.492
TG (mg/dl)	-0.129	0.325	-0.230	0.077
TC (mg/dl)	-0.040	0.762	-0.158	0.227
LDL-C (mg/dl)	-0.112	0.395	-0.009	0.943
VLDL-C (mg/dl)	-0.129	0.325	-0.230	0.077
HDL-C(mg/dl)	0.016	0.904	0.147	0.262

p-vale=significantly different between values in group(OH), group(SUB), and group (CONTROL).1.Thyroxine (T4), tri-iodothyronine (T3), and TSH Subclinical

hypothyroidism, overt hypothyroidism, fasting serum glucose, HOMA-IR: hemostasis model assessment-insulin resistance, HOMA-.β%: beta cell percentage, TG: triglyceride HDL: high-density lipoprotein-cholesterol, LDL: low-density, VLDL.C: VLDL-Cholesterol Total cholesterol in Table 3 shows that serum gelsolin levels negatively correlate with FSG, TG, LDL-C, and VLDL-C.Gelsolin levels correlated positively with TSH HOMA-β and HDL serum levels.

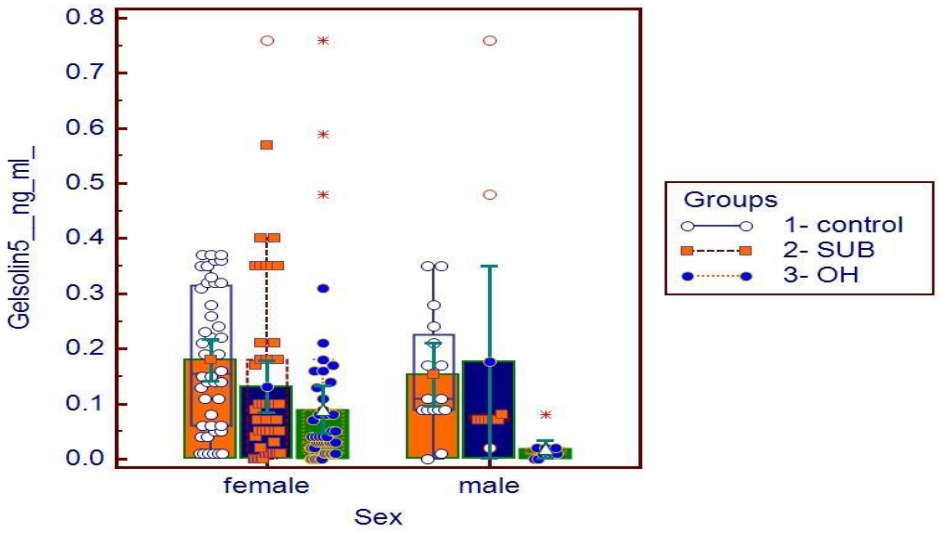

FIGURE 1: Comparison of serum gelsolin levels means between males and females of overt, subclinical hypothyroidism Patients group with males and females healthy Control Groups.

DISCUSSION

Hypothyroidism, which results from inadequate production of thyroid hormone, leads to low blood levels of the hormone. About 6% of people over the age of 60 have it, and it affects women more frequently[24]. Hypothyroidism can occur when the hypothalamus or pituitary gland are not stimulating the thyroid gland enough, or when the primary gland fails, in most cases, hypothyroidism is brought on by autoimmune thyroid disease. Hypothyroidism has vague and often unnoticeable clinical symptoms, especially in the elderly[25, 26]. Biochemical testing is used to diagnose hypothyroidism, However, the consequences of not treating hypothyroidism or treating it insufficiently include an increased risk of cardiovascular disease as well as mortality [27, 28]. Carbohydrate metabolic abnormalities have been shown to be present in thyroid disease. The severity of the disease correlates with that of these conditions. Insulin resistance and glucose metabolism are both profoundly influenced by thyroid hormones. According to the literature, hypothyroidism is characterized by a predominance of insulin resistance in peripheral tissues[29]. Gelsolin (GSN) is a multifunctional protein that can cut, cap, and nucleate actin filaments. Its primary function is to participate in the remodeling of the cytoskeletal structure, which in turn has an effect on chemotaxis, secretion, and cell shape [30].Insulin resistance has multiple underlying pathophysiological mechanisms, including inflammation, mitochondrial dysfunction, and hormonal dysregulation. plasma proteins like gelsolin that have been linked to inflammatory processes could help us better understand risk profiles for this age-related metabolic disorder[31].

T3 and T4 hormones are known to have an impact on the development and the rate of function of a great deal of the body's other systems the neuromuscular, digestive, and cardiovascular systems are all included, in addition to regulating the rate of metabolism, which is one of their most well-known functions. Patients who have hypothyroidism typically have elevated levels of total cholesterol, low-density lipoproteins (LDL), triglycerides, and other lipid molecules that are linked to cardiovascular disease[32]. SCH and CVD, the leading global killers responsible for a third of all deaths each year. Understanding the interplay of various

cardiovascular disease risk factors is crucial, such as blood pressure, glucose levels, and cholesterol levels, and SCH as well as serum TSH levels[33]. Pressure overload, dilated and ischemic cardiomyopathy, myocardial infarction (MI), and end-stage heart failure are all conditions that increase gelsolin production in human heart tissues. Acute myocardial infarction patients, however, may have temporarily lower plasma gelsolin levels [34]. Heart disease, blood clots, and platelet activation all have a close relationship with one another. Blood stasis syndrome in coronary heart disease was discovered by comparing patients with and without the condition, and the results suggest that the platelet cytoskeleton may play a significant role in the development of BSS in CHD[35].

CONCLUSION

Patients diagnosed with hypothyroidism, particularly those with overt hypothyroidism, were found to have significantly lower levels of gelsolin in their bloodstreams compared to the healthy control group. Gelsolin was positively correlated with TT3, TT4, and HDL-C, which also has a negative correlation with insulin resistance in hypothyroid patients. The antioxidant gelsolin may play a role in reducing oxidative stress, which has been linked to thyroid dysfunction. These findings need to be confirmed in larger studies of hypothyroid patients.

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Declaration of interest

There are no potential biases or other competing interests that need to be disclosed by the authors.

Ethical Clearance

Everyone who took part in the study, whether they were a control subject or a patient, as well as their parents or legal guardians, gave their informed written consent. It has been determined by the institutional ethics board (8298/2022) of the University of Kufa that the research can move forward without further interference. The study followed all national and international guidelines for protecting participant privacy and adhering to ethical research practices. The World Medical Association has produced numerous sets of guidelines, including the International Conference for Harmonization of Good Clinical Practice, the Belmont Report, the CIOMS Guideline, and the Declaration of Helsinki. In addition, the standards established by our committee of experts served as the basis for the International Guideline for the Conduct, Reporting, and Review of Research Involving Human Subjects (ICH-GCP).

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