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RESEARCH ARTICLE
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A potential biomarker of the association between hypothyroidism and reduced Meteorin-like levels: a case- control study

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ABSTRACT

Background: Hypothyroidism occurs when the thyroid gland doesn't generate enough thyroid hormone. Meteorin like protein (Metrnl) a tiny secreted protein, regulates cell differentiation, survival, and migration in several organs.

Aim of study: The purpose of this research was to see whether serum Metrnl levels might be used as a biomarker for hypothyroidism complication.

Materials and Methods: This case-control study comprised 90 individuals ranging in age from 20 to 50 years. These people were separated into three groups: those with overt hypothyroidism (OH), those with subclinical hypothyroidism (SCH), and those who were healthy. sex, age, weight, height, body mass index (BMI), and hormonal indicators were all assessed and recorded for each participant.

Results: serum Metrnl levels were considerably lower in hypothyroid patients compared to those with normal thyroid function (p 0.001). Furthermore, Metrnl levels were negatively connected with TSH levels (r =- 0.32, p 0.041) and favorably correlated with T4 levels (r =0.303, p 0.040)..

Conclusion: Serum Metrnl levels may be a biomarker for hypothyroidism detection and monitoring. The research excluded systemic disorders and pharmaceutical usage to ensure accuracy. Thus serum Metrnl levels may be useful clinical tools for hypothyroidism identification and monitoring.

Keywords: *Hypothyroidism, subclinical hypothyroidism, overt hypothyroidism, Meteorin-like protein*

INTRODUCTION

Hypothyroidism is characterized by low amounts of thyroid hormone and is related to a sluggish metabolic rate. This syndrome results in a decrease in the amount of energy that is expended when at rest, weight gain, increased levels of cholesterol, a decrease in the breakdown of lipids (lipolysis), and a reduction in the creation of glucose (gluconeogenesis) [1]. Through its interaction with either the or thyroid hormone receptor, thyroid hormone (TH) may exert an impact on metabolism. The brain, white adipose tissue (WAT), and brown adipose tissue (BAT), as well as skeletal muscle and the liver, are among the primary organs and tissues that this hormone affects in the body. Interactions between these tissues and their receptors are the mechanism through which TH exerts its influence on metabolic processes [1]. Problems with the thyroid may have an effect on the amounts of many cytokines that are circulating throughout the body, including irisin, fibroblast growth factor 21 (FGF21),

and neuregulin 4 (Nrg4). Cytokines are proteins that are produced by the cells of the body. These proteins play an important role in the signaling process as well as in the regulation of the immune system and inflammation. The function of the thyroid may have an effect on the amounts of these cytokines, which can have repercussions for both the body's general health and its metabolism. This leads one to believe that TH interacts with cytokines generated by adipose tissue, skeletal muscle, or the liver in order to influence the metabolism of the whole body[2]–[4] .

Both adipose tissue and skeletal muscle produce the recently discovered adipomyokine protein known as mtrnl. Metrnl is synthesized and secreted in response to two different stimuli, namely physical activity and exposure to cold. This suggests that Metrnl may have a role in how the body reacts to the aforementioned circumstances[5], [6]. Metrnl levels that are higher than normal in the circulation may cause browning of adipose tissue and an increase in the amount of energy that is burned by upregulating a number of genes involved in thermogenesis. These genes include UCP-1, DIO2, PGC-1, and others[5]. Metrnl has also been shown to minimize weight gain brought on by a high-fat diet as well as improve insulin resistance by activating AMP-activated protein kinase and PPAR-dependent pathways in skeletal muscle. These pathways are responsible for regulating insulin sensitivity[7]. The purpose of this research was to evaluate the possible link between TH and Metrnl, both of which play an important role in regulating the browning of adipose tissue and the amount of energy that is expended. In particular, the research looked at the levels of Metrnl in the blood of individuals who had hypothyroidism to evaluate whether or not there was a connection between hypothyroidism and Metrnl levels.

MATERIALS AND METHODS

Acase-contral study design for a total of 90 subjects included in the study: 60 samples from over and subclinically diagnosed hypothyroidism and 30 healthy controls. The participants' ages ranged from 20 to 50 years. The first group consisted of 30 individuals who had been diagnosed with overt hypothyroidism (OH), (20 female: 10 male). The patients in the second group, who had been diagnosed with subclinical hypothyroidism (SCH), included a 30 patients (19 females: 11 males). As the control group, the third group consisted of 30 individuals who were apparently healthy. (17 females and 13 males) in this group. Patients with overt hypothyroidism had both elevated TSH levels >10 µIU/mL and low blood T4 and T3 levels, but subclinical patients had higher serum TSH levels >4.5 µIU/mL along with normal serum T4 and T3 levels. The Al-Hakim Teaching Hospital, located in the Al-Najaf Governorate of Iraq, was admitted to choose the participants for this study. During the period of October 2022 to February 2023, samples were collected, and all patients were evaluated using biochemical analytical techniques. A questionnaire was used to gather information about the participants, including their weight, height, age, and any other pertinent data.

Excluded from the study patients who were younger than 20 years old or who suffered from a variety of medical conditions, such as diabetes, hyperthyroidism, acute infections, chronic liver or renal diseases, rheumatic diseases, cancer, recent surgeries, cardiac diseases, hypertension, smokers, pregnant or breastfeeding women, or those with anemia.

The participants' age, sex, height, and weight were recorded, and their BMI was calculated by dividing their weight in kilograms by their height in meters squared: BMI = (weight in kg) / (height in meters2)[8] . Blood samples were obtained from participants following a 12hour, fast venipuncture to acquire serum. The serum was extracted by centrifuging the blood serum for 15 minutes at 3000 Xg. Serum levels of thyroid-stimulating hormone (TSH), total triiodothyronine (T3), total tetraiodothyronine (T4), insulin(FIN), and METRNL were measured using an enzyme-linked immune sorbent assay (ELISA) kits from Melsin Medical Co. China. The colorimetric method was used to get quantitative data. Using kits from (BIOLABO, France), we measured high density lipoprotein cholesterol (HDL), total cholesterol (TC), fasting

serum glucose (FSG), and triglyceride (TG). Homeostatic model assessment-insulin resistance (HOMA-IR) index was calculated as: HOMA /IR = [(glucose (mg/dl) * insulin (U/ml)) / 405] HOMA/β =[360 insulin/(Glucose - 63)-1 [9].

Low density lipoprotein cholesterol (LDL-C) was measured by the indirect method using Friedewald equation [10]

Statistical analysis

In order to determine whether or not there were differences between the research variables, the Kruskal-Wallis test was run with the SPSS v27 software program (SPSS Inc., Chicago, Illinois, United States). In the situations in which the p-values were less than 0.05 or less than 0.01. The link between analyte levels within each research group was analyzed using Pearson's correlation coefficient, which was utilized to assess the association between the two variables. In addition, receiver operating characteristic (ROC) curves were created using the MedCalc program in order to evaluate the efficacy of biomarkers in the diagnosis and prognosis of hypothyroidism. As a means of evaluating the reliability of the test, the area under the curve (AUC) was computed. The threshold for statistical significance was established at P less than 0.05 and P less than 0.01, which indicates that differences with a probability of less than 5% or 1% were deemed to be statistically significant.

RESULTS

Hypothyroid individuals' serum levels of Metrnl were evaluated. The baseline characteristics of participants with overt (OH), subclinical (SCH), and healthy control (HC) hypothyroidism are shown in Table(1) and figure (1,2). Parameter values, separated by sex and health status, are shown below for both the control and patient groups. There were no discernible age or sex differences between the groups. There were statistically significant differences (P 0.05 or P 0.01) in TT3, TT4, TSH, T-CHO, TG, HDL-C, VLDL-C, LDL-C, FSG, insulin, and HOMA/IR between SCH and OH patients and the control group.The study found a significant difference in the levels of circulating Metrnl between hypothyroid patients and controls, with lower levels observed in the former group (P < 0.001).

TABLE 1: Clinical characteristics of participants with and without Hypothyroidism

Parameters	Control (n=30)	Patients (n= 60)		P value
		SCH (n=30)	OH (n=30)	
Sex (Fe/M)	17/13	19/11	20/10	--
Age (Years)	36.50 ± 7.09	39.50 ± 9.41	39.75 ± 10.57	0.207a 0.172b 0.9916c
BMI(Kg/m2)	24.08 ± 4.46	30.86 ± 5.39	33.31 ± 7.81	0.018a 0.001b 0.120c
TT3(ng/mL)	2.13 ± 0.56	1.85 ± 0.39	1.43 ± 0.74	0.068a 0.001b 0.007c
TT4(ng/mL)	101.78 ± 9.58	92.91 ± 19.99	69.79 ± 26.59	0.089a 0.001b 0.001c
TSH(µIU/mL)	2.95 ± 0.90	8.47 ± 3.62	19.19 ± 15.69	0.024a 0.001b 0.001c
T-CHO (mg/dL)	171.90 ± 14.32	183.30 ± 23.31	195.87 ± 24.79	0.041a 0.001b 0.025c

TG (mg/dL)	101.90 ± 12.06	156.80 ± 40.48	180.60 ± 54.27	0.001a 0.001b 0.023c
HDL-C (mg/dL)	38.37 ± 3.00	21.17 ± 4.34	21.07 ± 4.78	0.001a 0.001b 0.925c
VLDL-C(mg/dL)	20.38 ± 2.41	31.36 ± 8.10	36.12 ± 10.85	0.001a 0.001b 0.023c
LDL-C(mg/dL)	113.15 ± 13.90	130.77 ± 21.70	138.68 ±19.98	0.001a 0.001b 0.107c
FSG (mg/dL)	87.85 ± 2.70	104.91 ± 9.30	110.10 ± 9.71	0.001a 0.001b 0.129c
FIN (µU/mL)	7.15 ± 0.90	12.00 ±1.95	13.30 ± 1.64	0.001a 0.001b 0.060c
HOMA-IR	1.53 ± 0.23	3.13 ± 0.69	3.63 ± 0.67	0.001a 0.001b 0.046c
HOMAβ	66.18 ± 8.33	61.99 ± 6.64	49.75 ± 6.50	0.188a 0.001b 0.001c
Metrnl (ng/ml)	0.28 ± 0.05	0.26 ± 0.0.05	0.16 ± 0.04	0.105a 0.001b 0.001c

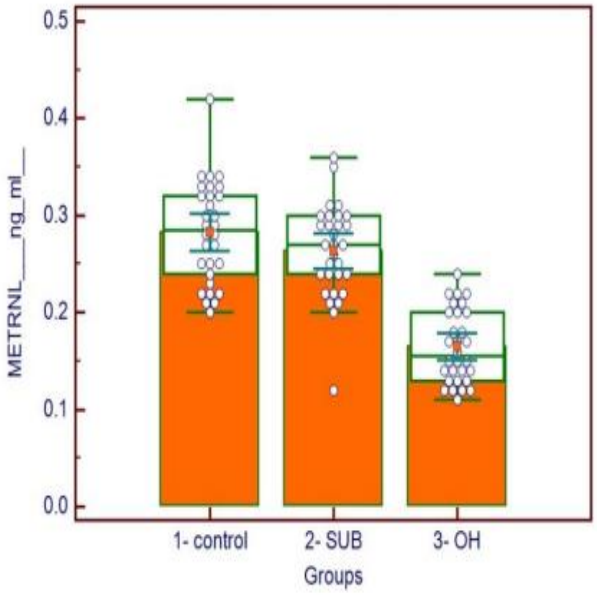

FIGURE 1: comparison of serum Metrnl in OH, SCH, CH groups

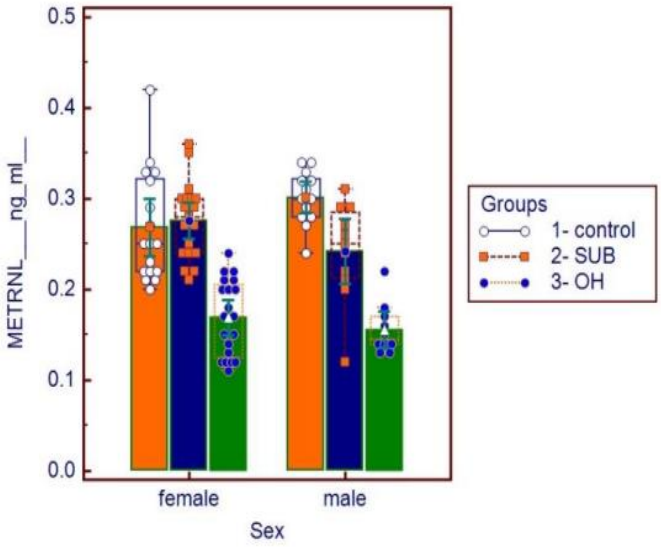

Figure 2: comparison of serum Metrnl in males and females Metrnl Levels in OH, SCH, and Control Groups

Table 2 displays the results of a correlation study showing a positive and statistically significant relationship between the blood level of Metrnl and TT4 among SCH patients. In contrast, TC serum levels have been shown to correlate negatively and significantly with Metrnl in this patient population.

TABLE 2: Correlation between serum Metrnl levels and biochemical parameters in patients with subclinical hypothyroidism

Parameters	Pearson's Correlation (r)	P value
Age (Years)	-0.154	0.416
BMI (Kg/m2)	0.054-	0.777
TSH(µIU/mL)	-0.076	0.689
TT3(ng/mL)	0.021	0.912
TT4(ng/mL)	0.303	0.104
T-CHO (mg/dL)	-0.218	0.246
TG (mg/dL)	-0.192	0.310
HDL-C (mg/dL)	-0.115	0.545
VLDL-C(mg/dL)	-0.192	0.310
LDL-C(mg/dL)	-0.139	0.463
FSG (mg/dL)	-0.045	0.815
Insulin (µU/mL)	-0.162	0.393
HOMA-IR	-0.138	0.466
HOMAβ	0.132	0.488

Table 3 shows a strong negative connection between blood levels of Metrnl OH patients and (BMI,TSH, TG, VLDL-C, FIN, and HOMA/IR). While there was a positive significant connection with levels in the TT3 and HDL-C with OH group.

TABLE 3: Exploring the Association between Serum Metrnl Level and Biochemical Parameters in Patients with OVERT Hypothyroidism: A Correlation Analysis

Parameters	Pearson's Correlation (r)	P value
Age (Years)	-0.074	0.697
BMI (Kg/m2)	-0.357	0.043
TSH(µIU/mL)	-0.295	0.021
TT3(ng/mL)	0.130	0.493
TT4(ng/mL)	0.033	0.863
T-CHO (mg/dL)	-0.131	0.489
TG (mg/dL)	-0.297	0.03
HDL-C (mg/dL)	0.321	0.02
VLDL-C(mg/dL)	-0.297	0.03
LDL-C(mg/dL)	-0.100	0.599
FSG (mg/dL)	-0.164	0.385
FIN (µU/mL)	-0.338	0.01
HOMA-IR	-0.325	0.01
HOMAβ	0.202	0.062

Table 4 and Figure 3 provide the statistical findings of the ROC analysis for the Metrnl biomarker. Cut-off value in SCH group (0.270), AUC (0.607), Sensitivity (60.0), Specificity (56.7), and P-value (0.156) are all shown on the ROC curve for Metrnl.

TABLE 4: Statistics output of ROC analysis of Metrnl between healthy and Sub clinical Hypothyroidism patients

variables	
	METRNL
Area Under Curve (AUC)	0.607
P-value	0.156
Cut-off value	<0.270
Sensitivity	60.0
Specificity	56.7
Accuracy (Youden Index)	0.2667
Positive Predictive Value (PPV)	58.3
Negative Predictive Value (NPV)	83.3

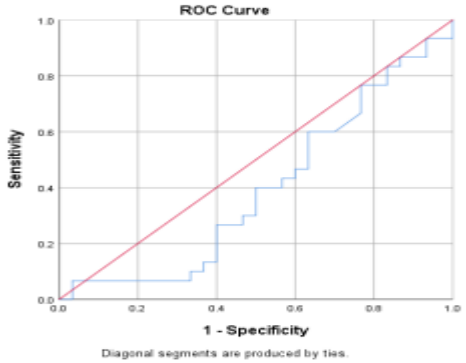

FIGURE 1: Statistical Analysis of Metrnl ROC Curve for Distinguishing Between Healthy and Subclinical Hypothyroidism Patients

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Table 5 and Figure 4 provide the statistical findings of the ROC analysis for the Metrnl biomarker. Cut-off value in OH group (<0.2), AUC (0.971), Sensitivity (80.0), Specificity (96.7), and P-value (0.001) are all shown on the ROC curve for Metrnl.

TABLE 5: Statistics output of ROC analysis of Metrnl between healthy and Overt Hypothyroidism patients

Statistics	Markers
	METRNL
Area Under Curve (AUC)	0.971
P-value	<0.001
Cut-off value	<0.2
Sensitivity	80.0
Specificity	96.7
Accuracy (Youden Index)	0.7667
Positive Predictive Value (PPV)	96.0
Negative Predictive Value (NPV)	82.9

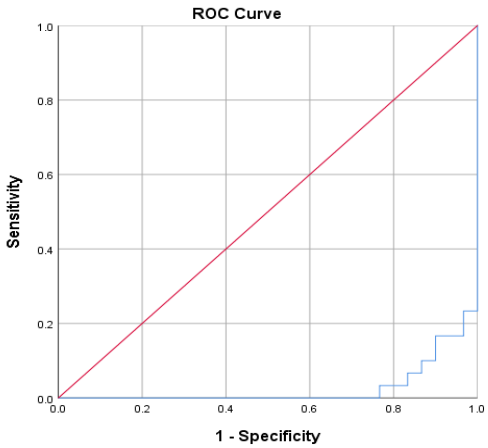

FIGURE 2: Statistics output of ROC analysis of Metrnl between healthy and Overt Hypothyroidism patients

The data provided here establishes a link between low levels of Metrnl in the serum and hypothyroidism. Serum Metrnl levels were shown to be decreased in those with hypothyroidism compared to the healthy controls. After taking into account factors such as sex, age, and body mass index, the study found that low blood Metrnl levels remained independently associated with hypothyroidism. These findings point to a possible involvement of Metrnl in hypothyroidism and may have therapeutic implications for the treatment of this ailment. Nonetheless, greater study into the processes involved and possible therapeutic implications of Metrnl in hypothyroidism is required. The recently identified adipomyokine "Metrnl" has been linked to several metabolic and thermogenic benefits. Overexpression of muscle-specific PGC-1 led to increased expression and secretion of Metrnl in mice, suggesting a potential function for Metrnl in regulating energy expenditure and glucose metabolism[5]. After exercise and acute exposure to cold, skeletal muscle and adipose

tissue are the primary sites of Metrnl production; this hormone is subsequently secreted into the circulation and distributed systemically[5]. The therapy with metrnl has been proven to have a variety of impacts on the development of tissues and metabolism. Studies have shown that therapy with metrnl may cause browning of white adipose tissue, which promotes the conversion of white adipose tissue into brown adipose tissue, which is more metabolically active and can burn more calories. In addition, it has been discovered that therapy with Metrnl encourages the development of muscle and improves muscular function by activating certain signaling pathways[5], [7], [11]; these findings have been published. The link between circulating Metrnl and metabolic variables in a variety of disorders has been the subject of a significant number of investigations. According to the findings of a number of studies [12], [13], circulating Metrnl levels have been reported to have a negative correlation with body weight, BMI, and the amount of visceral fat, as well as to rise after bariatric surgery. Research also discovered that there was a negative link between serum Metrnl levels and BMI. Furthermore, exercise-induced Metrnl in both muscle and plasma was shown to significantly decrease fat formation in obese mice fed a high-fat diet. This lends credence to the notion that Metrnl might be useful as a therapy for obesity[14]. Metrnl may have a role in regulating adipose tissue browning and energy balance, according to certain research; nevertheless, the mechanism by which acute exercise enhances Metrnl secretion and its entire physiological function in humans are still not fully understood. In the process of controlling both basal metabolism and thermogenesis, thyroid hormones (TH), and in particular T4 and T3, play a significant role. It is probable that thyroid function and Metrnl regulation are connected due to the similarities in the effects that TH and Metrnl have on metabolism. The fact that TH and Metrnl share a receptor is the reason for these similarities. On the other hand, there is a dearth of knowledge about the connection between thyroid dysfunction and Metrnl. It was shown in this research that individuals with hypothyroidism had lower blood levels of Metrnl, which is similar to the findings of an earlier study[15]. That reported reduced Metrnl levels in patients with Graves' illness. When comparing our findings to those of other research, it is essential to take into account a number of aspects, including the metabolic characteristics of the participants. These aspects may include glycemic parameters and lipid profiles, both of which may be different from ours. Previous research has shown a correlation between circulating levels of Metrnl and lipid profiles[16] , serum glucose [17], and insulin resistance [18]. Hypothyroidism is related to a drop in thyroid hormone levels, which may lead to reduced energy expenditure and weight gain. Additionally, high cholesterol levels are frequently present in hypothyroidism, which can increase the risk of cardiovascular disease. Metrnl may have a role in regulating thyroid function and energy metabolism based on the linear regression models' findings of a positive connection between serum Metrnl levels and FT3 and FT4, as well as a negative correlation with TSH. These results imply that Metrnl is involved in these processes. On the other hand, further research is required to have a complete comprehension of the processes behind this association as well as the therapeutic consequences of it [1]. Within brown adipose tissue (also known as BAT), TH is an essential component in the process of regulating energy metabolism and thermogenesis. TH may boost the expression of genes involved in adaptive thermogenesis in brown adipocytes, such as UCP-1 and PGC-1. This can lead to an increase in the generation of heat and an increase in `energy expenditure, both of which can assist in the regulation of body temperature and energy balance[18]. In the process of converting thyroxine (T4) to the more active form of thyroid hormone, triiodothyronine (T3), DIO2, which is expressed at high levels in BAT, plays a crucial role. This conversion results in an increase in the local concentration of T3 in BAT, which in turn contributes to the thermogenic impact that thyroid hormone has in this tissue [19]. According to the findings of our research, serum levels of Metrnl were positively associated with hypothyroidism as well as positively associated with FT3 and FT4 levels. This finding is not surprising given that TH plays a crucial role in

regulating the function of skeletal muscles, including muscle contraction, regeneration, and metabolism [20].

CONCLUSION

The results of the present study showed independent association of Metrnl hypothyrodism, and negative correlation with insulin resistance and yhyroid dysfunction. These results suggest a possible role for Metrnl in the pathogenic mechanisms of hyopthyrodism, which could be a possible explanation for the association of Metrnl with hypothyrodism and complications.

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Declaration of interest

The authors certify that they do not have any conflicting interests that they would want to reveal.

Ethical Clearance

All participants (both controls and patients) or their parents or legal guardians gave written informed permission in accordance with the most stringent ethical requirements. All local, national, and international ethical and privacy regulations were followed, and the research was approved by the institutional ethics board at the University of Kufa (1311/2023). The Declaration of Helsinki of the World Medical Association, the Belmont Report, the CIOMS Guideline, and the International Conference for Harmonization of Good Clinical Practice are all examples of such regulations. In addition, the ICH-GCP (International Council for Harmonization Good Clinical Practice) standards for human research safety are adhered to by our institutional review board.

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