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Study Bioroles of Serum Meteorin-Like Protein Level in Patients Suffering from Thalassemia Major and its Correlation with Insulin Resistance

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Abstract

Beta-thalassemia major (β-TM) is a prevalent hereditary condition. Because they are highly prone to infection, the patients will have higher rates of infection-related death and morbidity. Meteorin-like protein (METRNL) a minor secreted protein and weighs about 28 kDa, which comprise 311 amino acids. This study aimed to evaluation immune inflammatory markers METRNL in sera patients with β-TM groups. Thalassemia Unit" at the "Al Zahra Teaching Hospital" in Najaf, Iraq, registered 60 patients with β-TM, including children and adolescents. They were 28 females and 32 males, ages 7 to 20. during the January–March 2022 timeframe. In the current study, it is found a significant increase in serum levels of FSG, insulin, and HOMA-IR, as well showed significantly lowered in BMI, HOMA-β, and METRNL in patients with β-TM as compared with control group. The linear regression analysis showed that the levels of FSG, insulin and HOMA-IR were significantly negative correlation with METRNL. ROC curve form METRNL that might be diagnosis of patients with β-TM with an AUC (0.748), the cut-off value was 29.0025 (ng/mL) for serum METRNL (95% CI: 0.585-0.911; p=0.003), a sensitivity of 73.3% and a specificity of 78% were acquired for METRNL in β-TM patients. The lower serum METRNL levels in β-TM patients than the healthy group, may be used potential risk indicator of the patients' worse prognosis, for induces endothelial dysfunction and lead to inflammation in most organs tissues could be later outcome to heme induce damage.

Keywords: Thalassemia, β thalassemia major, Meteorin-like protein.

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INTRODUCTION

Beta-thalassemia major (β-TM) is a prevalent hereditary condition. Because they are highly prone to infection, the patients will have higher rates of infection-related death and morbidity. Although iron chelation and frequent blood transfusions are the primary treatments for β-TM, some patients may remedy from bone marrow transplantation (Zafari *et al.,* 2021) (Kahnoji *et al.,* 2023). Severe haemolysis and markedly inefficient erythropoiesis are other characteristics of β-TM. Due mostly to anovulation following hemosiderin deposition,

these patients frequently suffer from delayed sexual development and decreased fertility (Ejaz *et al.,* 2023).

Meteorin-like protein a minor secreted protein and weighs about 28 kDa, which comprise 311 amino acids. The evolutionary connection between METRNL and a gene encoding Meteorin (Metrn), a recognized neurotrophic factor that exist in the central nervous system, is reflected in this nomenclature (Reboll *et al.,* 2022). It was reported that METRNL is an adipokine or hormone that has a role in metabolic reactions. Activated macrophages generate METRNL, and that its production is connected with numerous human autoimmune diseases, like psoriasis (Khajebishak *et al.,* 2022). In *vitro*, METRNL levels rise in response to electrical pulse stimuli, while in *vivo*, METRNL is released amid muscular contractions.

Furthermore, METRNL enhances the uptake of glucose in skeletal muscle cells through the calcium-dependent adenosine monophosphate-activated protein kinase-alpha2 (AMPKα2) pathway in skeletal muscle cells as well as AMPKα2-dependently proliferations the phosphorylation of histone deacetylase-5 (HDAC5), a transcriptional repressor of GLUT4 (J. O. Lee *et al.,* 2020)(Zhang *et al.,* 2020).

METRNL can be useful in inhibiting cancer because it raises thermogenesis, improves glucose tolerance, and lowers insulin resistance (Chung *et al.,* 2018) (Kocaman & Artaş, 2020). METRNL's functions include reducing adipose inflammation, improving lipid metabolism, promoting energy expenditure and the expression of genes linked to thermogenesis in brown people, and reducing obesity-mediated insulin resistance, as well as an anti-inflammatory effect (Zuo *et al.,* 2019) (Gholamrezayi *et al.,* 2020), It plays significant roles in both innate and acquired immunity (Ushach *et al.,* 2018). Moreover, the adipocyte-specific deletion of METRNL worsens insulin resistance induced by a high-fat diet. However, an adipocyte-specific transgenic accumulation of METRNL prevents insulin resistance caused by either a high-fat diet or leptin deletion, suggesting that METRNL in adipocytes reduces overall insulin resistance through its effects on local adipose tissue in an autocrine-paracrine manner. (Z.-Y. Li *et al.,* 2015)(Jiang *et al.,* 2022).

When the pancreatic islet cells secrete insulin but the hormone is no longer able to efficiently trigger glucose uptake in metabolic tissues, this condition is known as insulin resistance syndrome. The two main signs of insulin resistance, hyperglycemia and hyperinsulinemia, are caused by the metabolic tissues' incapacity to absorb glucose (Archer *et al.,* 2017) (Mulyani *et al.,* 2020).

MATERIALS AND METHODS

"Thalassemia Unit" at the "Al Zahra Teaching Hospital" in Najaf, Iraq, registered 60 patients with β-TM, including children and adolescents. They were 28 females and 32 males, ages 7 to 20. during the January–March 2022 timeframe.

Exclusion Criteria: Patients above 20 years of age and those with a history of chronic sickness or other forms of thalassemia were not included.

The control group consisted of thirty people who appeared healthy and whose ages and sexes were analogous to those of the patients who had no immunological or chronic illnesses or anemia.

A serum separator tube was utilized to hold the collected blood samples. After letting the samples clot for 15 minutes at room temperature, they were centrifuged at 3000 X g for approximately 15 minutes. At 20 °C, serum samples were then stored. The amount of FSG was obtained using a set of standard enzymatic methods. Serum insulin and METRNL levels were measured using an enzyme-linked immunosorbent assay (kit). The Body Mass Index (BMI), calculated using a specific formula, is the ratio of weight in kilograms to height in meters squared. The homeostasis model assessment (HOMA-IR) is used to measure insulin resistance, employing the formula fasting insulin concentration (IU/L) glucose (mmol/L)/22.5. Individuals with a HOMA-IR value greater than 2.7 were recognized as having insulin resistance, and the calculation of HOMA-β was performed using the formula HOMA -β = 360× Insulin /(Glucose-63)%.

Statistics Analysis:

The statistical data were examined using SPSS 26. All data are presented with means and standard deviations. The differences among groups were analyzed using one-way ANOVA and Fisher's least significant difference (LSD), with a p-value threshold of ≤0.05. Pearson's correlation coefficient assessed the relationship between METRNL and biochemical measures, The METRNL marker serves to diagnose β-TM by means of the receiver operating characteristic (ROC)-area under the curve.

RESULTS

It is established in the current study that serum levels of FSG, insulin, and HOMA-IR have significantly increased, as well showed significantly lowered in BMI, HOMA-β, and METRNL in patients with β-TM as compared with control group. table (1).

Table 1: Comparing Patients with Control Groups in Terms of Glycemic Indices, Insulin Resistance, and METRNL

Parameters	Control Mean±SD (n=30)	Patients Mean±SD (n=60)	p-value
Age (year)	16.27±4.118	16.33±4.34	NS
BMI (Kg/m^2)	23.85±4.059	18.57±4.7	0.001
Metrnl (mg/dL)	35.794±3.523	32.9±7.2	0.001
FSG (mg/dL)	88.35±11.33	121.2± 23.57	0.000
Insulin	6.12±3.03	12.31±5.43	0.000
HOMA-IR	1.33±1.12	2.177±1.9	0.01
HOMA-β	94.11±11.12	67.17±12.97	0.01

Data represented as Mean ±SD, SD: Standard deviation, METRNL: Meteorin-like Protein, NS=non-significant at >5% level.

The linear regression analysis showed that Age, BMI, and HOMA-β levels which shows a non-significant correlation with METRNL level in patients with β-TM group, but positively correlated between BMI and HOMA-β when correlated with METRNL.

Table (2) showed in group of β-TM the levels of FSG, insulin and HOMA-IR were significantly negative correlation with METRNL.

Table 2: Univariate Analysis of Serum METRNL Level in relation to the Investigated Parameters among β-TM Patients

Parameters	r	p-value
Age (years)	-0.042	0.774
BMI (kg/m^2)	0.069	0.633
FSG (mg/dL)	-0.342	0.015
Insulin (µU/mL)	-0.343	0.015
HOMA-IR	-0.344	0.014
HOMA-β	0.197	0.170

r: pearson correlation cofficient, BMI: Body mass index, FSG: Fasting serum glucose, IR: Insulin Resistance, HOMA: Homeostatic Model Assessment

ROC curve form METRNL that might be diagnosis of patients with β-TM with an AUC (0.748), the cut-off value was 29.0025 (ng/mL) for serum METRNL (95% CI: 0.585-0.911; p=0.003, Figure 1), a sensitivity of 73.3% and a specificity of 78% were acquired for METRNL in β-TM patients.

Table 3: Receiver Operating Characteristic-Area Under Curve Analysis of the Measured Biomarker in β-TM Patients

Variable	Cut-off concentration	Sensitivity %	Specificity %	AUC	95% CI of AUC	p-value
METRNL (ng/mL)	29.0025	73.3	78.0	0.748	0.585-0.911	0.003

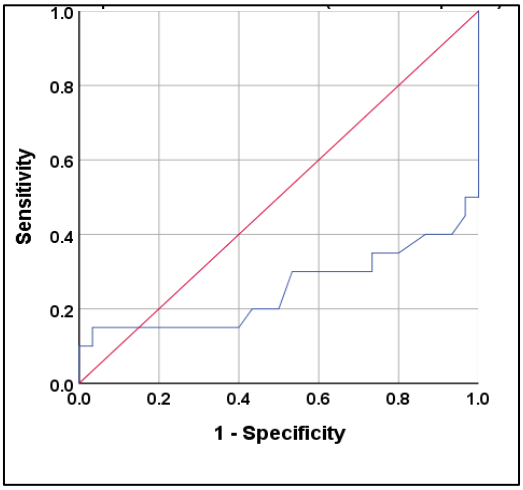

Figure 1: ROC Curve of METRNL Display Recognition of β-TM Patients Group

DISCUSSION

As the first study to assess serum METRNL levels to the best of our knowledge, the results showed a lower level of METRNL in Iraqi β-TM patients compared to healthy individual. METRNL is homeostatically expressed by barrier tissues and plays a

specialized role by activated macrophages. The primary cellular sources are skin fibroblasts and mucosal epithelial cells (Jia *et al.,* 2023) (Khajebishak *et al.,* 2022). It was previously demonstrated that cultured myotubes and entire muscle must secrete METRNL (Uzun *et al.,* 2023), which was discovered to promote an anti-inflammatory macrophage phenotype in adipose tissue, hence modifying the immunological milieu (Moradi *et al.,* 2023), As well, has expanded this mechanism in relation to the restoration of skeletal muscle (Zidong Li *et al.,* 2022). It has been identified that METRNL increases the expression of anti-inflammatory genes such TGF-β and IL-10 (Zhi-Yong Li *et al.,* 2014). Pro-inflammatory cytokine expression, including TNF-α, INF-γ, and IL-1β, was slightly reduced by METRNL (Qi *et al.,* 2020). According to earlier research, METRNL therapy reduces the expression of inflammatory cytokines like IL-6 as well as pro-inflammatory indicators like TNF-α and MCP-1 in skeletal muscle from a high-fat diet (C. Wang *et al.,* 2019). According to a study via Z-Y *et al.,* METRNL is both an adipokine and a myokine. Yet, studies regarding its effect on adipocytes has shown conflicting findings demonstrated that METRNL regulates adipocyte insulin sensitivity and stimulates adipogenesis (Z.-Y. Li *et al.,* 2015). The METRNL levels were significantly lowered in recently diagnosis T2D patients than in those with normal glucose tolerance or prediabetes, according to another study by Kara *et al.,* and Lee *et al.,* this finding is related to the fact that METRNL inhibits insulin resistance in adipose tissue (J. H. Lee *et al.,* 2018) (Kara *et al.,* 2022).

There have been some contradictory studies in the past about METRNL's function in adipose tissue. Rao et al. discovered that elevated levels of METRNL promote energy expenditure, enhance glucose tolerance and the expression of genes interrelated to anti-inflammatory cytokines and beige fat thermogenesis (Rao *et al.,* 2014). However, Löffler et al. demonstrated that METRNL suppressed human adipocyte differentiation by controlling the expression of the METRNL gene (Löffler *et al.,* 2017).

Dadmanesh *et al.,* discovered that people with T2D and coronary artery disease had lower serum METRNL concentrations than healthy individuals (Dadmanesh *et al.,* 2018). Chung et al. found that T2D patients had significantly greater levels of METRNL than healthy individuals (Chung *et al.,* 2018), Furthermore, Wanng *et al.,* showed that T2D patients had higher serum levels of METRNL than controls (K. Wang *et al.,* 2019).

Moreover, a prior study via Gholamrezayi *et al.,* revealed reduced serum levels of METRNL, indicating an inverse association between METRNL and inflammatory cytokines. Further, it was noted that METRNL might regulate inflammatory pathways (Gholamrezayi *et al.,* 2020).

Sun *et al.,* demonstrated that, in comparison to healthy controls, the serum METRNL concentrations were considerably lower in individuals with obstructive sleep apnea syndrome (Sun *et al.,* 2019), According to METRNL, skeletal muscles' expression of pro-inflammatory markers, IL-6, TNF-α, and MCP-1 is suppressed, preventing inflammation and preventing obstructive sleep apnea syndrome (Pellitero *et al.,* 2018)(AlKhairi *et al.,* 2019).

CONCLUSION

The lower serum METRNL levels in β-TM patients than the healthy group, may be used potential risk indicator of the patients' worse prognosis, for induces endothelial dysfunction and lead to inflammation in most organs tissues could be later outcome to heme induce damage.

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