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Osteopontin as a Marker in Thyroid Diseases and Its Relation to Vascular Affection in These Patients.

Heba Kamal Sedrak[1], Olfat Gamil Shaker[2], Mohamed Mady Mohamed Saied[1], Mai Galal Elshenoufy[1], Ahmed Ashraf Twakol Mansour[1], Marwa Sayed Eissa[1,3].

1-Internal Medicine and Endocrinology Department, Faculty of Medicine, Cairo University, Egypt.
2-Medical Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University.
3-Endocrinology Department, Faculty of Armed Forces of Medical College (AFMC), Cairo, Egypt.
Corresponding author drheba_sedrak@yahoo.com

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Abstract

Background: *Thyroid disorders are the most common endocrine problems worldwide. With a prevalence rate of 5%-10%. Osteopontin (OPN) is a plasma marker that implicated in many diseases and has been found to be involved in numerous pathological conditions, such as inflammation, angiogenesis, fibrogenesis, biomineralization, cell viability and wound healing.*

Aim: *To measure the osteopontin level in patients with hypothyroidism and hyperthyroidism and assess its relationship with plasma lipid levels and carotid intima-medial thickness (IMT).*

Methodology: *Ninety subjects from Kasr - Aainy Endocrinology Outpatient Clinic were divided into 3 groups. Group (1) included 30 hypothyroid patients. Group (2) included 30 hyperthyroid patients and group (3) included 30 healthy controls. Lipid profiles, thyroid profile (TSH, FT4, FT3) and OPN level were analyzed, and carotid IMT was assessed.*

Results: *The mean OPN level was significantly lower in the hypothyroid group (P< 0.001) and greater in the hyperthyroid group (P < 0.001). There was a negative correlation between OPN and thyroid stimulating hormone (TSH) and a positive correlation between FT3 and FT4 levels. A negative correlation was found between OPN and low-density lipoprotein (LDL), cholesterol and TGs levels (P <0.001), and positive correlation between OPN and high-density lipoprotein (HDL) in the hypothyroid group (P value <0.001). Moreover, there was no significant correlation between the OPN level and the IMT.*

Conclusions: *Alterations in thyroid function and lipid profile cause changes in serum OPN level with no effect on IMT.*

Key words: *Thyroid dysfunction, Osteopontin, IMT.*

Background

Thyroid dysfunctions involve subclinical and overt disease have significant adverse health outcomes if left undiagnosed or untreated (1).

Hypothyroidism can be complicated by hypertension, neurological diseases, hematological problems, cardiovascular diseases, fertility, dyslipidemia, and liver problems. Subclinical and overt hyperthyroidism can also result in many conditions such as heart failure, arrhythmias, osteoporosis, osteopenia, neurological problems, and frequent abortions (2). Therefore, timely investigations and proper management are obligatory.

Human Osteopontin (OPN) is a multicellular phosphoprotein known as secreted phosphoprotein-1 (SPP1) and sialoprotein-1 that was discovered in 1986 in osteoblasts. OPN consists of 314 amino acids and acts as a proinflammatory cytokine. Previous data have indicated that an increased concentration of OPN contributes to inflammatory processes and atherosclerosis (3, 4).

OPN is expressed in bone (osteoblasts and osteoclasts), activated macrophages and T cells, smooth muscle, hepatocytes, endothelial, and epithelial cells, the inner ear, the placenta, and the brain (5). It has also been implicated in many autoimmune diseases, such as SLE, RA, IBD and MS (6).

OPN was implicated not only in pathogenesis of some tumors but also in the prognosis, as OPN expression

positively correlated with unfavorable prognosis (7). as malignant thyroid tumors (8).

The relationship between thyroid status and bone metabolism has been intensively studied and explained by the wide expression of thyroid receptors on bone, which leads to increased bone turnover in patients with hyperthyroidism and decreased bone metabolism in patients with hypothyroidism (9).

However, the real role of OPN in thyroid dysfunction, dyslipidemia and vascular effect is still vague. Therefore, we conducted this study to assess OPN levels in cases of thyroid dysfunctionship with dyslipidemia and vascular affection.

Patients and methodology:

Study design

The study included 90 subjects from the endocrine outpatient's clinic, at Kasr Al-Aini Hospital from May 2021 to August 2022, Patients were divided equally into 3 groups hypothyroid group, hyperthyroid group and euthyroid (control) group.

The patients were aged between 20 and 50 years. Patients with hypertension, smoking status, obesity (body mass index (BMI) greater than 30 kg/m2), drug-induced thyroid dysfunction, diabetes mellitus (per the ADA criteria 2021) (10) autoimmune, hematological, bone, liver, renal, malignant, or chronic inflammatory conditions were excluded.

A thorough history and examination were conducted to rule out any prior problems. The patients´ height in meters was divided by their weight in kilograms to determine their BMI.

The following laboratory test results were obtained for every patient: complete blood count (CBC), fasting blood glucose (FBS), glycosylated hemoglobin (HbA1C), lipid profile, liver function (AST, ALT), kidney function (creatinine, urea), and thyroid profile (TSH, FT4, FT3).

Color Doppler imaging of the neck: Was performed by an experienced sonographer. C-IMT was measured by recording ultrasonographic images of both the right and left common carotid arteries with a 7- MHz linear array transducer (11).

Quantitation of Human OPN (Osteopontin)

The serum levels of human (OPN) in both the control and patient groups were measured using an ELISA kit supplied by ELK Biotechnology (China) with Cat. No. ELK1047. No specific precautions were taken when taking the sample.

Statistical analysis.

All the gathered information was updated. On the computer, Precoded data were input into the computer using Microsoft Office Excel 2017. -After that, pre-coded data was moved and loaded into SPSS, version 26 of the Statistical Package of Social Science Software, for statistical analysis. -The mean, standard deviation, median, and IQR were used to summarize the quantitative data. To compare the groups, the Kruskal Wallis test was used. P value less than 0.05, was considered to indicate statistical significance. -For quantitative variables, Spearman correlation was performed; the results can be interpreted as follows: 0-0.2 is considered mild or no correlation, 0.25-0.75 is considered moderate correlation and 0.75-1 is considered strong correlation - Data were presented in tables and graphs.

Results:

The study included 90 patients, 30 hypothyroid, 30 hyperthyroid and 30 euthyroid control subjects with a mean age of 40±7 years in the hypothyroid group, 35±10 SD in the hyperthyroid group and 33 ± 9 SD in the control group, for a significant P value of 0.02 (Table 1).

There was a significant difference in sex distribution across the groups, female sex was significantly greater than male sex in all the groups (P value = 0.042) (Table 1).

Table (1) Distribution of patients in the study

Gender	Male n (%)	Female (%)	Total	P value
Control	10 (33.4)	20 (66.6)	30 (100%)	0.042
Hypothyroid	12 (40)	18 (60)	30 (100%)	
Hyperthyroid	9 (30)	21(70)	30 (100%)	

The mean BMI the control participants was 23.3 ± 2.2 (SD), that of hypothyroid patients was 27 ± 1.9 (SD) and that of hyperthyroid patients was 19.7 ± 2.7 (SD). The mean BMI significantly different among the groups (P value <0.001) (Table 1).

The mean cholesterol level in the control group was 165 ±15 SD, that in the hypothyroid group was 204.4 ± 45.7 (SD) that in hyperthyroid group was 193.9 ± 44 (SD). The mean cholesterol level was significantly different between the control and hypothyroid groups (P value <0.001). The mean TG levels were 154 ± 20 SD, 225.4 ± 98.6 SD and 163.1 ± 76.9 SD for the control, hypothyroid and hyperthyroid groups respectively. The mean TG levels were significantly different between the control and hypothyroid patients (P value <0.001).

The mean LDL cholesterol levels were 109 ± 39 (SD), 208.9± 37.4 (SD) and 113 ± 69.5 (SD). In the control hypothyroid and hyperthyroid groups, respectively and these differences were statistically significant (P value <0.001). The mean HDL cholesterol levels were 52.5 ± 13.7 (SD), 46.8 ± 26.1 SD and 42.4 ± 26.7 SD in the control hypothyroid and hyperthyroid groups respectively and were not significantly different between the groups (P value=0.051).

The mean OPN level was 8.9 ± 2.1 (SD) in the control group, 4.2 ± 1.2 (SD) in the hypothyroid group and 22 ± 12.1 (SD) in the hyperthyroid group. The mean OPN concentration was significantly different among the groups (P value <0.001) (Table 1).

The mean IMT was 0.58 ± 0.12(SD) in the control group, 0.8 ± 0.1(SD) in the hypothyroid group and 0.7 ± 0.1(SD) in the hyperthyroid group. The mean IMT was significantly different among the groups (P value <0.001) (Table 1).

Parameter	Control	Hypothyroid	Hyperthyroid	P value	Significance between groups
	Mean ± SD	Mean ± SD	Mean ± SD		
Age	33 ±9	40 ± 7	35 ± 10	0.022	Control& hypothyroid
BMI (kg/m2)	23.3 ± 2.2	27.0 ± 1.9	19.7 ± 2.7	<0.001	Control & hypothyroid Control & hyperthyroid hypothyroid &hyperthyroid
TSH	2.17(± 0.89)	28.0 (± 22)	0.3 (± 0.1)	<0.001	Control & hypothyroid Control & hyperthyroid hypothyroid &hyperthyroid
IMT millimeters	0.58 ± (0.12)	0.8 ± (0.1)	0.7 ± (0.1)	<0.001	Control & hypothyroid Control & hyperthyroid Hypothyroid &hyperthyroid
LDL mg/dL	109 (± 39)	208.9 (± 37.4)	113 (± 69.5)	<0.001	Control & hypothyroid Hypothyroid &hyperthyroid
HDL mg/dL	52.5 (± 13.7)	46.8 (± 26.1)	42.4 (± 26.7).	0.051	
Cholesterol. mg/dL	165 (±15)	204.4 (± 45.7)	193.9 (± 44)	<0.001	Control & hypothyroid
TG mg/dL	154 (± 20)	225.4 (± 98.6)	163.1 (± 76.9)	<0.001	Control & hypothyroid
Osteopontin ng/ml	8.9 (± 2.1)	) 4.2 (± 1.2)	22 (± 12.1)	<0.001	Control& hypothyroid Control & hyperthyroid hypothyroid & hyperthyroid

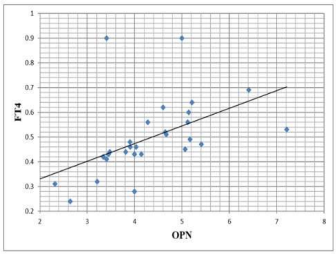
Correlations between all variables and OPN in hypo and hyperthyroid patients: There were significant negative correlations between OPN and TSH (graph 1-b), LDL (graph 2-a), cholesterol (graph 2-c) and TG levels (graph 2- b). In contrast there were significant positive correlations between OPN and FT4 (graph 1-a), and between FT3 and both hypo- and hyperthyroid patients, but there were no significant correlations between OPN and age,

BMI or IMT (Table 3).

There was a significant positive correlation between OPN level and HDL in the hypothyroid group only (figure 2-d).

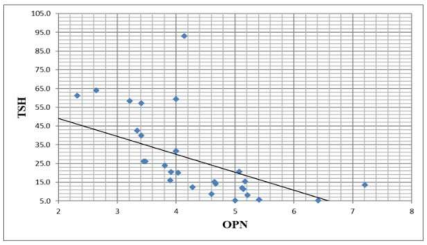
Table (3): Correlations between all variables and OPN in hypo and hyperthyroid patients

		Osteopontin in hypothyroid patients	Osteopontin in hyperthyroid patients
Age	r	-0.02	0.08
	P	0.92	0.68
BMI	r	-0.15	-0.33
	P	0.42	0.07
TSH	r	-0.76	-0.35
	p	<0.001	0.05
FT4	r	0.71	0.54
	P	<0.001	<0.001
FT3	r	0.75	0.38
	P	<0.001	0.04
LDL	r	-0.69	-0.26
	P	<0.001	0.17
HDL	r	0.65	0.22
	P	<0.001	0.25
Cholesterol	r	-0.50	-0.38
	P	0.01	0.04
TG	r	-0.42	-0.57
	P	0.02	<0.001
IMT	r	-0.40	-0.11
	P	0.98	0.58



Graph (1-a)

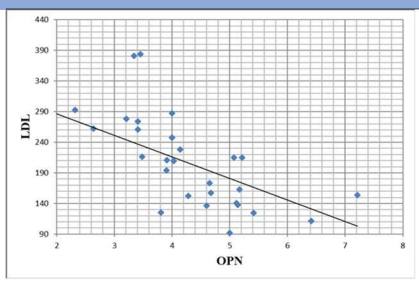
Positive correlation graph between FT4 and OPN



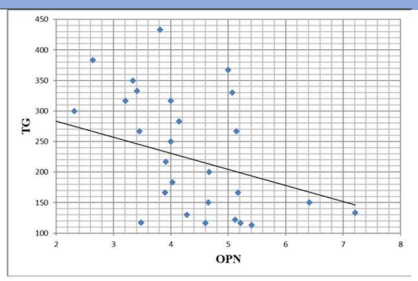
Graph (1-b)

Negative correlation graph between TSH and OPN

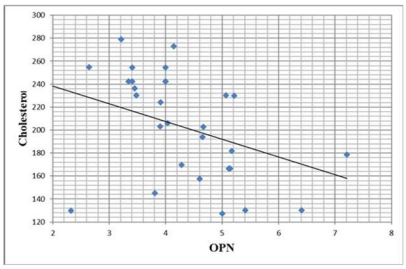
Graph (1): Correlation between OPN with TSH &FT4



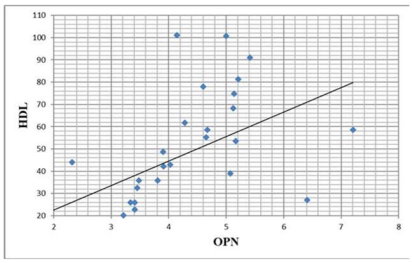
Graph (2a) Negative correlation between LDL & OPN



Graph (2b) Negative correlation between TGs & OPN



Graph (2c) Negative correlation between Cholesterol & OPN



Graph (2d) Positive correlation between HDL & OPN

Graph (2) : Correlations between OPN level and lipid profile parameters

The correlations between lipid fractions and IMT in hypothyroid patients: There were significant positive correlations between IMT and LDL and cholesterol. and a significant negative correlation between IMT and HDL. However, There was no significant correlation between IMT and TG (Table 4).

The correlations between lipid fractions and IMT in hyperthyroid patients revealed that There were no significant correlations between IMT and LDL, HDL or TG. There was a significant positive correlation between IMT and cholesterol (P = 0.02) (Table 4).

Table (4) Correlations between lipid fractions and IMT in hypothyroid and hyperthyroid patients.

		IMT in hypothyroid patients	IMT in hyperthyroid patients
LDL	r	0.51	0.08
	P	<0.001	0.66
HDL	r	-0.37	-0.30
	P	0.04	0.11
Cholesterol	r	0.62	0.43
	P	<0.001	0.02
TG	r	0.32	0.12
	P	0.08	0.51

Correlations between lipid fractions and TSH, FT4 in hypothyroid patients: There were significant positive correlations between TSH and LDL, and between cholesterol and TG and negative correlation between TSH and HDL in both hypo and hyperthyroid patients. There were significant negative correlations between FT4 and LDL, total cholesterol and TG, a positive correlation between FT4 and HDL in the hypothyroid group, and negative correlations between FT4 and LDL and TG but no significant correlations between FT4 and HDL and cholesterol in hyperthyroid patients (Table 5).

(5): Correlations between lipid parameters with TSH and FT4 in hypothyroid and hyperthyroid patients.

		TSH in hypothyroid patients	TSH in hyperthyroid patients	FT4 in hypothyroid patients	FT4 in hyperthyroid patients
LDL	r	0.86	0.40	-0.70	0.40-
	p	<0.001	0.03	<0.001	0.03
HDL	r	-0.62	-0.36	0.64	0.30
	p	<0.001	0.05	<0.001	0.12
Cholesterol	r	0.73	0.43	-0.57	-0.34
	p	<0.001	0.02	<0.001	0.08
TG	r	0.53	0.61	-0.58	-0.73
	p	<0.001	<0.001	<0.001	<0.001

Discussion

This study evaluated the relationship between OPN levels and thyroid dysfunction in the form of hypo and hyperthyroidism and whether IMT and lipid profile levels can affect OPN level or not.

The study showed that the mean value of serum OPN concentration in patients with hyperthyroidism was significantly greater than the mean serum OPN concentration in patients with hypothyroidism and the control group (P value <0.001). These findings are in line with those of Xu et al, who studied 76 hyperthyroid patients in comparison with 65 healthy controls and demonstrated that the serum OPN concentration is greater in serum of hyperthyroid patients (12). El-Zawawy et al. conducted a recent study with 75 participants who were evenly split into three groups. Twenty five patients had hyperthyroidism, 25 had hypothyroidism, and 25 had normal thyroid function. The serum OPN level in hyperthyroid group was substantially greater than that in the control group, whereas the serum OPN level was significantly lower (13). Reza et al. found that there was a substantial increase in blood OPN levels in hyperthyroid patients compared to hypothyroid patients after studying 50 hypothyroid patients and 50 hyperthyroid patients (14). The impact of thyroid hormones on bone turnover and metabolism can be used to explain these findings. Hyperthyroidism leads to considerable bone loss and an increase in the levels of biochemical indicators of bone turnover, while hypothyroidism has the opposite effect (15).

According to Rosenbaum et al (16), the thyroid gland and its hormones are essential for metabolism, thermogenesis, food intake, and fat oxidation. This causes patients with hypothyroidism to have higher BMIs (17). People with hyperthyroidism who lost weight. Thus, this investigation provided evidence for this phenomenon. Patients with hypothyroidism had a significantly greater mean BMI than did the hyperthyroid patients and controls, while patients with hyperthyroidism had a significantly lower mean BMI than did both groups (P value <0.001).

The present study revealed no significant correlation between OPN and BMI in either the hypothyroid or hyperthyroid groups, in agreement with the findings of Catalán et al., who did not find any significant correlation between OPN and BMI (18).

The results of the present study demonstrated that, in the hypothyroid and hyperthyroid groups, there was a significant positive correlation (P value <0.001) between OPN and FT4 and between OPN and FT3, and a significant negative correlation (P values <0.001 and 0.05, respectively) between OPN and TSH. This was consistent with the findings of Alwakeel et al. and Xu et al. (12, 19). reported that TSH was favorably connected with FT3 and FT4 and negatively correlated with OPN.

Since clinical hypothyroidism is often accompanied by low LDL receptor activity, hypothyroidism affects the metabolism of LDL and intermediate density lipoprotein cholesterol, which increases the serum levels of TC and LDL. Additionally, hypothyroidism is associated with the downregulation of lipoprotein lipase, which increases the serum TG concentration (20). Dyslipidemia is a common finding in patients with clinical hypothyroidism, and is characterized by high levels of total cholesterol, LDL, and TG. These data corroborate our findings that hypothyroid patients had significantly greater cholesterol, LDL, and TG levels than controls

did (P value <0.001), although there was no discernible change in HDL cholesterol levels. Additionally, a substantial moderate negative correlation was found between OPN and cholesterol in the hypothyroid and hyperthyroid groups (P values 0.01 and 0.04, respectively), and a strong negative correlation was found between OPN and LDL in the hypothyroid group (P value <0.001).

Takemoto et al., assessed the relationship between plasma OPN levels and lipid parameters and age, and a noteworthy inverse relationship was observed between the concentration of total blood cholesterol and the plasma OPN level (21). found a strong negative correlation between the plasma OPN concentration and the serum LDL cholesterol concentration. The specific mechanism underlying this association is yet unknown ; however, it is likely due to the inhibition of OPN production by hyperlipidemia (21). Additionally, there was a substantial moderate positive association (P value <0.001) between OPN and HDL in the hypothyroid group and a strong negative correlation (P value <0.001) between OPN and TG in the hyperthyroid and hypothyroid groups. Additional research is required to validate these results.

Since LDL transfers cholesterol from the liver to peripheral tissues and causes atherosclerosis in the artery endothelium, hypothyroidism also promotes macrophage foaming through artery wall absorption. On the other hand, HDL promotes the liver's removal of extracellular cholesterol by stimulating its export. By preventing the expression of endothelial cell adhesion molecules caused by cytokines, high-density lipoprotein also prevents atherosclerosis (22).

Given these established pathways, it should come as no surprise that our research revealed a substantial negative association between IMT and HDL cholesterol and a significant positive correlation between IMT and LDL, TG, and total cholesterol. In a similar vein, Yang et al.'s cross-sectional study, which measured the IMT in 402 individuals free of apparent diseases, demonstrated a positive correlation between IMT and LDL and cholesterol levels but not between IMT and TG or HDL levels (23). Furthermore, after studying 116 Japanese men who appeared to be in good condition, Takahashi et al. reported that LDL and cholesterol were independent predictors of carotid IMT (24).

The IMT is a widely used marker for atherosclerosis worldwide. The carotid IMT is also a strong predictor of future cerebral and cardiovascular events. The carotid IMT is an indicator of subclinical atherosclerosis (25). Furthermore, the current study revealed that the mean carotid IMT was significantly greater in the hypothyroid group than in the control group (P value <0.001), which is in agreement with previous findings (26, 27, 28). The increased risk of atherosclerosis may be caused by a reversible condition of endothelial dysfunction, which is likely the etiology of clinical hypothyroidism. Flow-mediated vasodilation decreases with increasing TSH, indicating endothelial dysfunction. Insulin resistance is the primary cause of the increased risk of atherosclerosis associated with hypothyroidism. This inflammation is linked to a low-grade chronic state and is accelerated by the large amounts of adipokines secreted by adipose tissue, such as interleukin-6 and tumor necrosis factor alpha, which also accelerate atherosclerosis (29). showed that levothyroxine medication can reverse carotid IMT in patients with clinical thyroid hypofunction. Additionally, the current study demonstrated that the mean carotid IMT was significantly greater in the hyperthyroid group than in the control group (P value <0.001), which is consistent with the findings of Bilir et al., who examined 26 patients with Graves' hyperthyroidism and 33 healthy controls, and measured carotid IMT in each patient in both groups. Carotid IMT was assessed in patients with Graves' hyperthyroidism both before and after PTU therapy. There was a significant difference in the carotid IMT between the Graves' hyperthyroid patient group and the control group at baseline. After 18 months of treatment, there was a significant decrease in the carotid IMT compared to the baseline level (30). Similar results were confirmed by (31, 32); therefore, Graves' disease-related antibodies against thyroid tissues are a potential cause of elevated carotid IMT. These antibodies may result in endothelial dysfunction and inflammation, which in turn may promote atherosclerosis and increase carotid IMT (33).

Furthermore, contrary to the majority of studies (34, 35, 36, 37, 38) that concluded that there was a positive correlation between IMT and OPN, which plays a crucial role in the development of vascular calcification and atherosclerosis, the present study found no significant correlation between OPN and IMT. The limited sample size in our study is most likely the reason for the disparity. For the best correlation results, additional research on a broader patient population should be performed.

Conclusions: OPN may be a novel biomarker for dyslipidemia and thyroid dysfunction. In patients with

hyperthyroidism, plasma OPN levels were greater than those in patients with hypothyroidism. OPN was negatively correlated with TSH but positively correlated with thyroid hormones (FT3, and FT4). Carotid IMT increased in patients with both hypo- and hyperthyroidism. Furthermore, no discernible association was observed between the carotid IMT and the OPN level.

Limitations: The limitations of the current study are as follows. First, the patient sample size. was small. Second, we did not measure OPN levels in patients with various thyroid dysfunction etiologies. Third, the impact of managing thyroid dysfunction on OPN levels was not investigated.

Recommendations

However, additional studies are needed on a large number of patients to provide more definitive evidence for the role of OPN in patients with thyroid dysfunction, and to compare OPN levels among patients with diverse etiologies of thyroid dysfunction, including subclinical cases. Moreover, future studies are needed to determine whether restoring euthyroid status leads to a decrease in the serum OPN concentration. Additionally, future studies will be needed to determine the relationship between carotid IMT and OPN levels.

List of abbreviations: Osteopontin (OPN), carotid intima-medial thickness (IMT), thyroid stimulating hormone (TSH), low-density lipoprotein (LDL), triglyceride (TG), high-density lipoprotein (HDL), secreted phosphoprotein-1 (SPP1), systemic lupus erythromatosis (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), multiple sclerosis (MS), body mass index (BMI), American Diabetes Association (ADA), complete blood count (CBC), fasting blood glucose (FBS), and glycosylated hemoglobin (HbA1C),

Declarations

- **Ethics approval and consent to participate.**

The study was approved by the kasr Alainy (Cairo University) ethical committee in April 2021) (md-165-2021), and the study was in line with the Declaration of Helsinki. Informed consent was obtained from all study participants or their legal representatives after proper explanation, and they were informed that they were free to withdraw from the study at any stage.

- **Availability of data and materials:** original data and any secondary data are available upon request.
- **Competing interests:** no competing interests.
- **Funding:** no source for funding
- **Authors' contributions:** Prof. Heba Kamal Sedrak, and Prof. Olfat Gamil Shaker, formulated the main idea. Dr. Marwa Sayed Eissa, Dr. Mai Galal ElShenoufy, and Dr. Ahmed Ashraf Tawakol Mansour wrote the main manuscript, and Prof. Olfat Gamil Shaker was responsible for the laboratory work. Dr. Mohamed Mady Mohamed Saied analyzled the data statistically, and all the authors reviewed the manuscript.

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