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RESEARCH ARTICLE

CORRELATION OF SERUM OSTEOCALCIN LEVEL WITH THE INDICES OF OBESITY AND LIPID PROFILE IN TYPE II DIABETIC SUDANESE PATIENTS

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Abstract

Objectives: Osteocalcin, an osteoblast-specific protein, has recently been reported to affect energy metabolism, this study aimed to assess the relationship between serum total osteocalcin and measurements of adiposity and lipid profile in type II diabetic Sudanese patients.

Methods: In this cross-sectional study, 115 people with type II diabetes (34 men, 81 women) aged 18 to 94 years were enrolled in the study. Total osteocalcin and insulin were measured using ELISA (enzyme-linked immunosorbent assay) technique. Fasting blood glucose and lipid profile were measured by a spectrophotometer.

Results: Mean serum osteocalcin concentration in diabetic patients was significantly lower than those in control subjects ($p \leq 0.001$). When the test was done between TOC and lipid profile, there was a moderate negative correlation between TOC and TCHOL. Which was statistically significant (P = 0.003). There was a moderate negative correlation between TOC and TG. Which was statistically non-significant (P = 0.057). There was a strong positive correlation between TOC and HDL. Which was statistically significant (P = 0.000). There was a weak positive correlation between TOC and LDL. That is statistically non-significant P = 0.105.

Conclusion: Our findings showed a statistically highly significant negative correlation between TOC and fasting blood glucose concentration. Similarly, the correlation between FBG and ucOC, age, BMI, TCHOL, and HDL showed a negative correlation that was not significant.

Introduction:-

Over the last decades, a sheer increase in the prevalence of obesity in children and adolescents has been observed globally (1). Obesity is believed to be one of the key factors contributing to the development of type 2 Diabetes mellitus (DM). In fact, studies from different corners of the world have shown that obesity accounts for 80-85% of

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the risk of developing type 2 diabetes (2), and obese people with a body mass index of (BMI) more than 22are up to 80 times more prone to develop type 2 diabetes (3). The consequences of obesity in childhood are reflected in the earlier studies which state that it includes type 2 DM, obesity in adulthood, and increased incidences of metabolic syndrome and cardiovascular disease as adults (4). In current studies, the bone has been identified as an endocrine organ associated with the body's energy metabolism (5). It is also evident that bone health is affected by an increase or decrease in BMI (6). Therefore, a connection was established between the osteoblast-derived hormone osteocalcin (OC) and the mass and lipid parameters. This connection was first demonstrated by Kindblom et al. in a study performed on osteoporotic fractures in the Swedish male population (7). Several other studies on other populations, such as the Korean (8), the Chinese (9), and the American populations (11). subsequently followed the study and proved that osteocalcin level is associated with obesity and fat mass. The serum contains both Carboxylated as well as uncarboxylated OC (ucOC) forms, among which the ucOC is known to be the key element of the total OC (TOC). In fact, OC is known to be an indicator of both osteoblast activity and bone formation. In a recent study, Dawod et al. explained that OC can modulate the functions of adipocytes and insulin-producing β-cells as well. It is responsible for the proliferation of the β-cells of the pancreas, insulin secretion, insulin sensitivity, adiponectin expression, and energy expenditure by upregulation of the genetic expression of adiponectin in adipocytes (5). OC is responsible for metabolic regulation and its endocrine action involves the regulation of glucose metabolism and fat mass as well (5, 11). Nowadays, adults developing DM due to insulin resistance (IR) and insulin deficiency, is a common problem encountered globally (12). Besides, a number of clinical studies measured low osteocalcin levels in obese people (7,13) and explored the possible correlation between OC and glucose or lipid metabolism (14) where the uOC was found to be significantly and positively correlated with HDL-cholesterol and it was also evident that a low uOC is associated to an atherogenic, dyslipidemic profile (15)

Though most of the studies showed Osteocalcin is capable of modulating glucose and fat metabolism they fail to establish a correlation between the indices of obesity and lipid profile and the results were contradictory, possibly owing to the diversity of the ethnic origin of a particular population involved in different studies.

Thus, the present study aims to signify the link between osteocalcin and the indices of obesity and the lipid profile in type II diabetic Sudanese patients.

Methods: -

This hospital-based case-control cross-sectional study was carried out on one hundred fifteen adults who were referred for diagnosis of diabetes mellitus for the first time in Khartoum. The patient visited Khartoum diabetic centers during the period of March 2015 up to June 2015. As a control group, sixty-five healthy adults from the same area without a history of diabetes mellitus were randomly selected. Both qualitative and quantitative data were collected. The quantitative data consisted of Socio-demographic details like age (<18 years and >94 years), gender (male and female), occupation (Housewife, teacher, laborer, shopkeeper, student, farmer, retired, and others), religion, ethnicity, employment (employed and unemployed), monthly Income, history of severe disease, diabetes drugs and other drugs that patient received (essential or non-essential) were collected. The qualitative research was undertaken by personal interviews with the patients in Khartoum diabetic centers.

All participants were subjected to thorough clinical examination and detailed history to exclude recent infections, taking insulin supplements, bone diseases and fractures, malignancy, cardiovascular disease, hypertension, and hyperthyroidism (up to one year).

The height and weight of each participant were measured using standardized height and weight scales. The Body mass index (BMI) was calculated as weight (in kilograms)/height (in meters^2). Venous blood was collected and transfused, the plasma was used to estimate the level of fasting insulin, total osteocalcin, and undercarboxylated osteocalcin, fasting blood glucose, and lipid profile**.**

Result:-

The results in Table 1 demonstrate a highly significant difference in mean TOC level (p 0.001) in the underweight group between diabetes people and healthy control subjects, with greater levels in control subjects (13.8 ± 1.1 ng/ml) compared to diabetic participants (2.7 ± 0.7 ng/ml). The ucOC in the underweight group indicated a significant difference (p 0.01) between examined groups, with greater levels in healthy participants (2.3 ± 0.5 ng/ml)

than in diabetes patients (1.2 ± 0.5 ng/ml). In contrast, mean insulin was significantly greater (p 0.01) in diabetes participants (14.3 ± 0.5 ng/ml) than in control subjects (10.1 ± 2.0 ng/ml).

Table 1:- Mean concentrations of TOC, ucOC, and plasma Insulin according to BMI in diabetics and controls.

Variables	Underweight		Normal weight		Overweight		Obese	
	Diabetic	Control	Diabetic	Control	Diabetic	Control	Diabetic	Control
TOC ng/ml	2.7 ± 0.7	13.8 ± 1.1	2.4 ± 1.4	15.1 ± 2.5	2.4 ± 1.4	14.8 ± 1.7	2.4 ± 1.5	14.6 ± 0.8
p-value	0.00		0.00		0.00		0.00	
ucOC ng/ml	1.2 ± 0.5	2.3 ± 0.5	1.1 ± 0.6	2.7 ± 0.5	1.1 ± 0.6	2.6 ± 0.4	.1 ± 0.6	2.6 ± 0.56
p-value	0.013		0.00		0.00		0.001	
Insulin ml U/L	14.3 ± 0.5	10.1 ± 2.0	20.0 ± 0.4	9.7 ± 0.7	19.3 ± 5.6	9.0 ± 1.8	20.4 ± 6.8	10.0 ± 2.8
p-value	0.008		0.00		0.00		0.039	

The greater level was (15.1 ± 2.5 ng/ml) in healthy patients compared to (2.4 ± 1.4 ng/ml) in diabetic subjects, indicating a highly significant difference (p0.001). UcOC in the same group also showed a highly significant difference (p 0.001) in its mean level, with healthy participants (2.7 ± 0.5 ng/ml) having the highest level, followed by diabetes patients (1.1 ± 0.6 ng/ml). In this group, diabetes people had a significantly higher amount of insulin (p 0.001) than control subjects (9.7 ± 0.7 ng/ml).

TOC was substantially greater (p 0.001) in control patients (14.8 ±1.7 ng/ml) compared to diabetic subjects (2.4 1.4 n g/ml) in the overweight BMI group.

UcOC was also substantially greater (p 0.001) in controls (1.1 0.6 ng/ml) than in diabetics (2.6 0.4 ng/ml).

The insulin level, on the other hand, showed a highly significant difference (p 0.001) in both groups, with diabetic part icipants having a greater level (19.3 5.6 ng/ml) than control subjects (9.0 1.8 ng/ml).

Table 3 shows that in the Obese group, the TOC level was substantially greater (p 0.001) in control people (14.6 0.8 n g/ml) than in diabetes patients (2.4 1.5 ng/ml).

In the same group, the ucOC level in healthy participants (2.6 0.56 ng/ml) was substantially higher (p 0.001) than in di abetic subjects (1.1 0.6 ng/ml).

In the obese, insulin exhibited a significant difference (p 0.05) in its mean level between diabetic individuals and contr ol subjects, with diabetic participants having a greater level (20.4 6.8 ng/ml) than control subjects (10.0 2.8 ng/ml).

Table 2:- Pearson's correlation between plasma TOC, ucOC concentrations, and lipid profile parameters.

		TOC ng/ml	TCHOL mg/dl	TG mg/dl	HDL mg/dl	LDL mg/dl	ucOC ng/ml
TOC ng/ml	**Pearson correlation**	1	-0.220**	-0.142	0.715**	-0.121	0.859**
	Sig. (2-tailed)		0.003	0.057	0.000	0.105	0.000
	N	180	180	180	180	180	180
TCHOL mg/dl	**Pearson correlation**	0.220**	1	0.307**	-0.052	0.520**	-0.213**
	Sig. (2-tailed)	0.003		0.000	0.491	0.000	0.004
	N	180	180	180	180	180	180
TG mg/dl	**Pearson correlation**	-0.142	0.307**	1	-0.277**	0.859**	-0.096
	Sig. (2-tailed)	0.057	0.000		0.000	0.000	0.200
	N	180	180	180	180	180	180
HDL	**Pearson**	0.715**	-0.052	-0.277**	1	-0.156*	0.531**

mg/dl	**correlation**						
	Sig. (2-tailed)	0.000	0.491	0.000		0.037	0.000
	N	180	180	180	180	180	180
LDL mg/dl	**Pearson correlation**	-0.121	0.520**	0.859**	-0.156*	1	-0.094
	Sig. (2-tailed)	0.105	0.000	0.000	0.037		0.208
	N	180	180	180	180	180	180
ucOC ng/ml	**Pearson correlation**	0.859**	-0.213**	-0.096	0.531**	-0.094	1
	Sig. (2-tailed)	0.000	0.004	0.200	0.000	0.208	
	N	180	180	180	180	180	180

**** Correlation is significant at the 0.01 level (2-tailed).**

*** Correlation is significant at the 0.05 level (2-tailed).**

A Pearson's product-moment correlation was run to assess the relationship between plasma TOC, ucOC concentration, and lipid profile parameters. When the test was done between TOC and lipid profile, there was a moderate negative correlation between TOC and TCHOL. Which was statistically significant (P = 0.003). There was a moderate negative correlation between TOC and TG. Which was statistically non-significant (P = 0.057). There was a strong positive correlation between TOC and HDL. Which was statistically significant (P = 0.000). There was a weak positive correlation between TOC and LDL. That is statistically non-significant P = 0.105. When the test was done between ucOC and lipid profile, there was a moderate negative correlation between ucOC and TCHOL. Which was statistically significant (P = 0.004). There was a weak negative correlation between ucOC and TG. Which was statistically non-significant P = 0.200.

There was a moderate positive correlation between ucOC and HDL. Which was statistically significant (P = 0.000). There was a weak negative non-significant correlation between ucOC and LDL, (P = 0.208). (Table 2).

When grouping was based on BMI, in controls mean TCHOL concentrations were highest in underweight (156 ± 5 mg/dl) and overweight subjects (154 ± 18 mg/dl) compared to normal weight (143 ± 23 mg/dl) and obese subjects (130 ± 49 mg/dl). These differences were statistically significant in normal weight (P = 0.005) and were not statistically significant in underweight subjects (P = 0.887), overweight (P = 0.490), and obese (P = 0.211). In diabetics mean TCHOL concentration was highest in normal weight (161 ± 28 mg/dl) and was nearly similar in overweight subjects (159 ± 42 mg/dl) and obese subjects (160 ± 32 mg/dl) and the least value was observed in underweight subjects (151 ± 43 mg/dl), also these differences were not statistically significant (P = 0.887). Mean TCHOL concentrations were higher in all BMI groups of diabetic subjects compared to their control peers except in the underweight subjects' group, and the differences were only significant between normal-weight groups (P = 0.005), but not statistically significant in overweight (P = 0.490) and obese subjects (P = 0.211). (Figure 1)

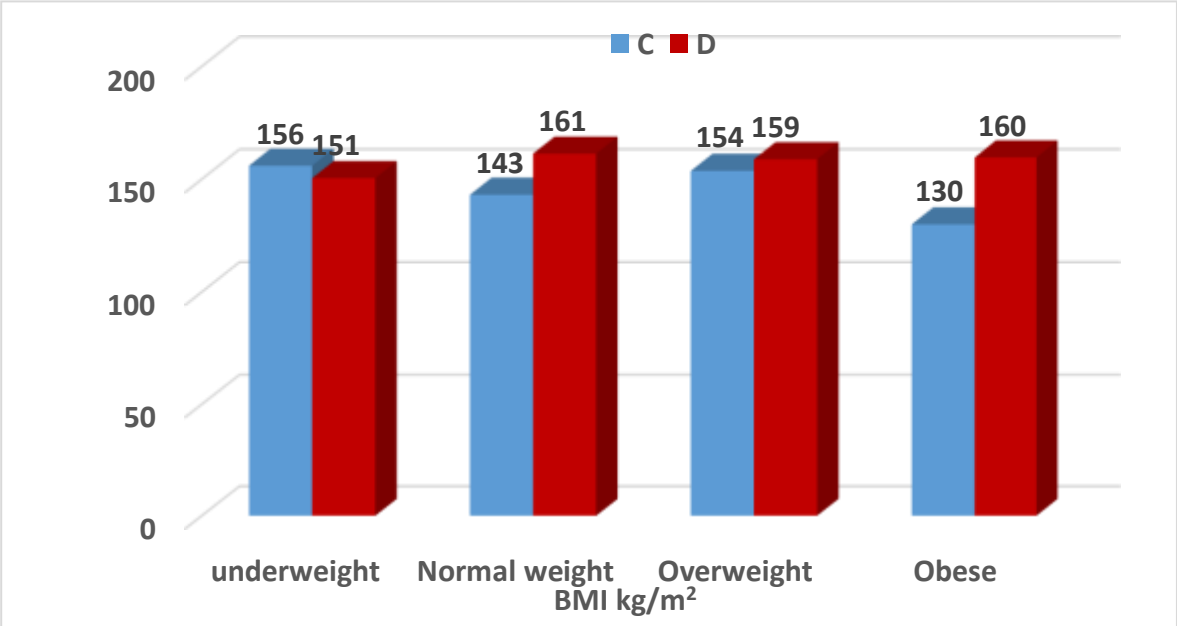

Figure 1:- Mean plasma concentrations of TCHOL among different BMI subgroups in control (C) and diabetic (D) subjects.

The differences in mean plasma concentrations of TG were not statistically significant, if the BMI groups were compared within controls or diabetics separately or if the groups were compared as diabetics versus controls.

The interesting observation was that the mean TG concentration decreased progressively from underweight subjects to obese subjects in both diabetic and control subgroups. The mean TG concentrations were higher in all diabetic BMI groups compared to their respective controls. (Figure 2).

The values in control subgroups were (141 ± 60 mg/dl) in underweight, (117 ± 45 mg/dl) in normal weight, (116 ± 36 mg/dl) in overweight, and (106 ± 13 mg/dl) in obese, and respective values in diabetic subgroups were (172 ± 118 mg/dl), (136 ± 53 mg/dl), (132 ± 41 mg/dl) and (123 ± 17 mg/dl). (Figure 2)

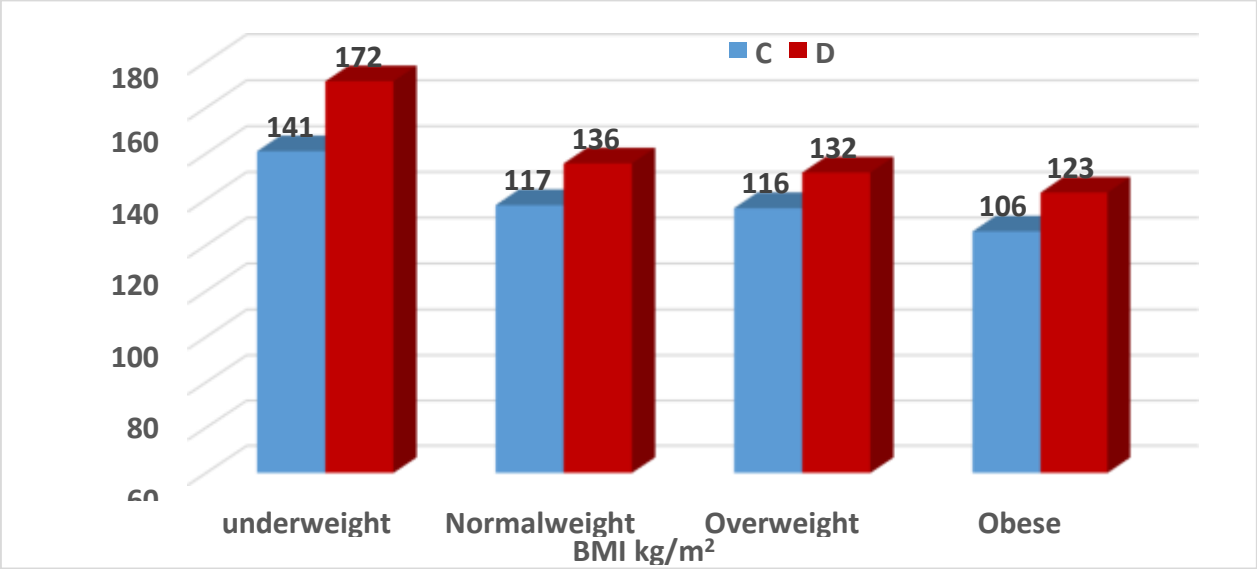

Figure 2:- Mean plasma concentrations of TG among different BMI subgroups in control (C)and diabetic (D) subjects.

A correlation between TOC concentration and TG showed a weak positive correlation that is statistically non-significant P = 0.674. The same test was done to assess the correlation between ucOC and TG, it revealed a weak positive correlation that is statistically non-significant P = 0.426

The mean HDL plasma concentrations in the subgroups of BMI of control subjects showed a nearly inverted U-shaped, but in the diabetic subgroups, these concentrations increased progressively from underweight subjects toward obese ones to reach their maximum. (Figure 3). In controls, the highest levels were observed in normal weight (34 ± 7 mg/dl) and overweight subjects (31 ± 6 mg/dl), and the lowest levels were noticed in obese subjects (31 ± 1 mg/dl) and underweight (29 ± 7 mg/dl). In diabetics, the values of mean HDL concentrations increased progressively from underweight (15.0 ± 5 mg/dl) to normal weight (19 ± 6 mg/dl) to overweight (21 ± 5 mg/dl) to reach its maximum level in the obese group (21 ± 6 mg/dl). When the diabetic subgroups were compared versus their respective control ones, the differences were statistically significant in normal-weight (P = 0.000), overweight (P = 0.000), and obese (P = 0.034). (Figure 3) A correlation between TOC concentration and HDL showed a weak negative correlation that is statistically significant P = 0.050. The same test was done to assess the correlation between ucOC and HDL, it revealed a weak negative correlation that is statistically non-significant P = 0.062.

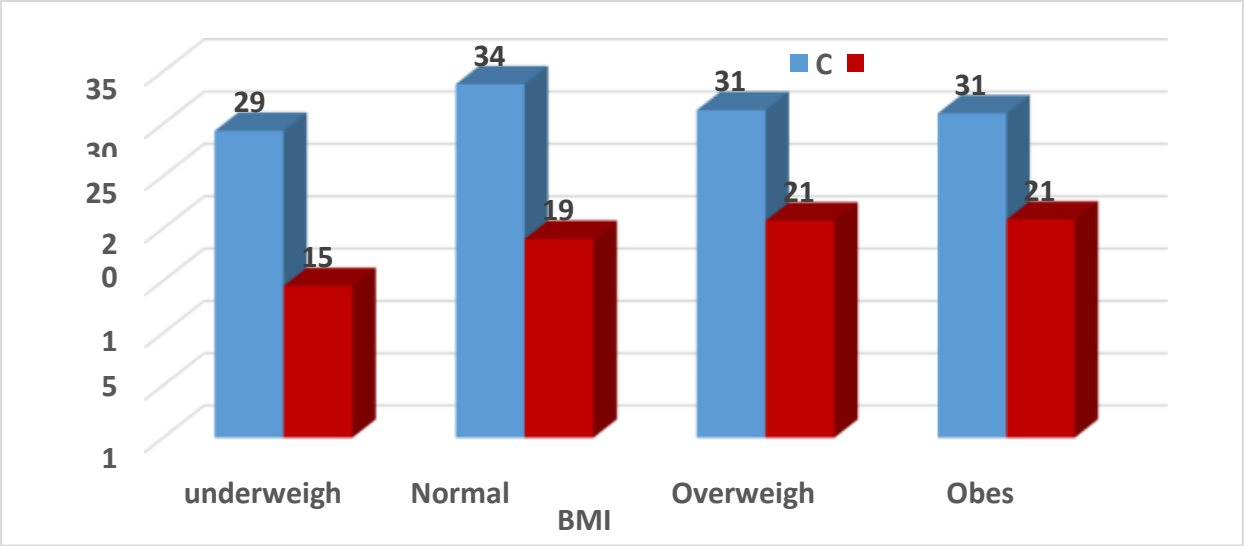

Figure 3:- Mean plasma concentrations of HDL among different BMI subgroups in control (C) and diabetic (D) subjects.

The pattern of LDL means in both control and diabetic was nearly similar as shown in (Figure 4). The highest values were noticed in underweights and the lowest was observed in obese subgroups, while normal weights and overweight had nearly similar values in both groups. In controls, the respective values were (56 ± 17 mg/dl) in underweight, (49 ± 12 mg/dl) in normal weight, (48 ± 10 mg/dl) in overweight, and (41 ± 13 mg/dl) in obese subjects. In diabetics, the respective values were (61 ± 31 mg/dl) in underweight subjects, (52 ± 14 mg/dl) in normal weight, (53 ± 14 mg/dl) in overweight subjects, and (50 ± 14 mg/dl) in obese subjects. (Figure 4). When the subgroups of diabetics were compared against their respective controls, the mean LDL concentrations were higher in diabetic BMI subgroups, but these differences were not statistically significant in underweight (P = 0.836), normal-weight (P= 0.325), overweight (P = 0.161), and in the obese (P = 0.369). (Figure 4)

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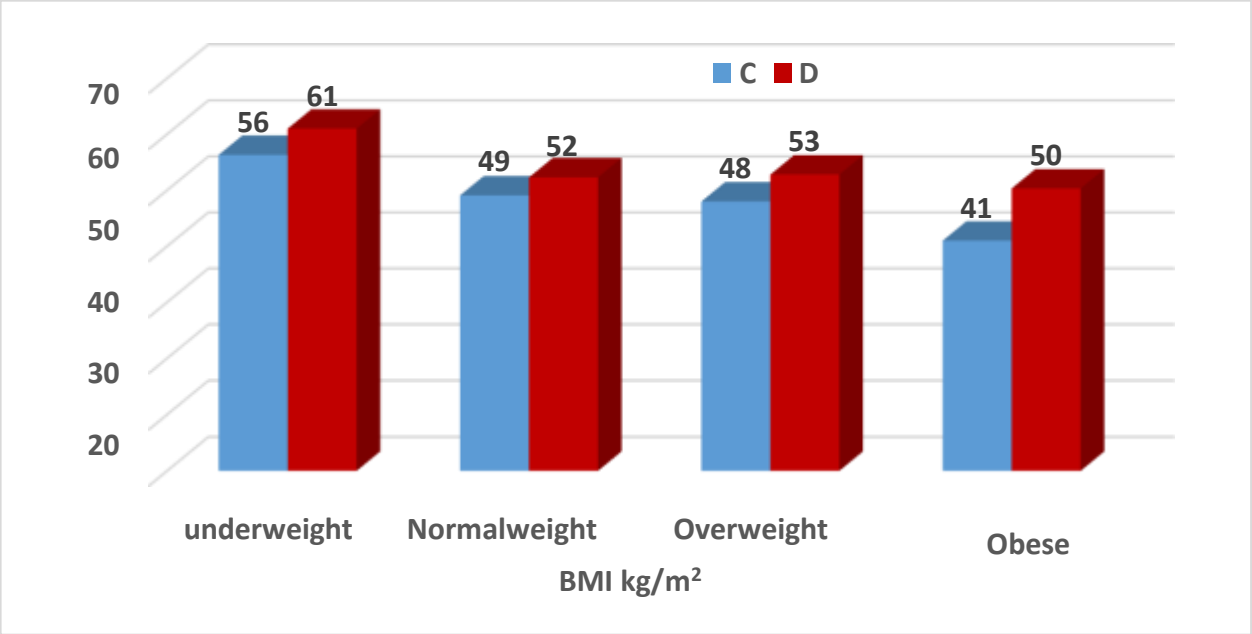

Figure 4:- Mean plasma concentrations of LDL among different BMI subgroups in control (C) and diabetic (D) subjects.

Discussion: -

Osteocalcin, a noncollagenous protein hormone is known to play a crucial role in the modulation of the body's metabolic activity (16). Studies revealed that the hormone, i.e. the uncarboxylated form affects the functions of the pancreas, fat, muscle, testes, and brain (17). In the pancreas, it was studied to trigger the release of insulin from the beta cells. Besides, it is also known to induce adiponectin secretion from the fat cells which in turn increases the sensitivity to insulin (16)

The results of our study confirm that there is a highly significant difference in the mean TOC level of the underweight group, diabetic group, and healthy control subjects respectively. Higher levels were observed in the controls as compared to the diabetic participants. A significant difference was also observed in the ucOC levels of the underweight group indicating greater levels in healthy participants than in diabetes patients. In contrast, mean insulin was significantly greater in diabetes participants than in control subjects as depicted in table 1. Thus, our study indicates a relationship between serum osteocalcin and glucose metabolism.

The moderate negative correlation that is statistically significant between plasma TOC concentration and FI, FBG level shown in this study was found to be consistent with previous reports that showed an inverse association of total serum osteocalcin with glucose and visceral fat mass, parameters of insulin secretion and its sensitivity in patients with type 2 diabetes (18).

Osteocalcin has shown no significant correlation with BMI as depicted in table 4.5, and our findings were inconsistent with many previous studies, as several studies have shown that osteocalcin is associated with lipid metabolism, and metabolic syndrome (19).

Moreover, it is reported that osteocalcin concentrations in obese people are lower than in normal controls (20). In some studies, a negative and inverse relationship between osteocalcin with body mass index (BMI) and waist circumference has been shown (21, 22) and others demonstrated a positive association between osteocalcin with BMI (23).

Regarding the undercarboxylated osteocalcin, some recent studies have shown that serum ucOC is related to T2DM in different racial groups (24) and that serum ucOC was inversely correlated with adiposity, blood glucose, insulin resistance, and triglycerides. Consistent with these results, we found that the serum ucOC concentrations were significantly lower in diabetics than in controls. Diabetics had lower plasma undercarboxylated osteocalcin concentrations than controls throughout all age groups, and these differences were statistically significant across all

age groups. When comparing each age group with controls or diabetics, the results were not statistically significant in either instance.

Notably, our results showed that there was a moderate negative correlation that was statistically significant between plasma ucOC level and fasting plasma insulin.

A study by Alfadda AA, (25) reported that there was no correlation between plasma ucOC concentration and BMI. Our study revealed that there was a significant correlation between plasma ucOC level and BMI. Though there is a paucity of published data on undercarboxylated osteocalcin levels in humans and their possible changes in diabetes, so the estimated number might be too low to reveal the trend.

Our findings suggested that decreased osteocalcin levels were associated with abnormal lipid profiles which are in line with a recent animal study that reported a beneficial effect of osteocalcin on fat mass and serum triglyceride concentration (26).

The interesting observation was that the mean TG concentration decreased progressively from underweight subjects to obese subjects in both diabetic and control subgroups. A correlation between TOC concentration and TG showed a weak positive correlation that is statistically non-significant. The same test was done to assess the correlation between ucOC and TG, and it revealed a weak positive correlation that was statistically non-significant. In contrast to our findings, a few other reports also showed a negative association between osteocalcin levels and triglycerides in blacks and non-Hispanic whites (27) and in older men (28).

The mean HDL plasma concentrations in the subgroups of BMI of control subjects showed a nearly inverted U-shaped, but in the diabetic subgroups, these concentrations increased progressively from underweight subjects toward obese ones to reach their maximum. When the diabetic subgroups were compared with their respective controls, the differences were statistically significant.

A correlation between TOC concentration and HDL showed a weak negative correlation that was statistically significant, whereas the correlation between ucOC and HDL, is assessed to be a weak negative correlation that was statistically non-significant. In previous studies, HDL cholesterol was found to be negatively (29), positively (30) correlated, or was found to be not associated at all (27) with osteocalcin levels in different populations.

The pattern of LDL in both control and diabetic were nearly similar. The highest values were noticed in underweight and the lowest was observed in obese subgroups, while normal weight and overweight had nearly similar values in both groups. When the subgroups of diabetics were compared against their respective controls, the mean LDL concentrations were high in diabetic BMI subgroups, but these differences were not statistically significant in underweight, normal-weight, overweight, or obese.

Thus, a strong positive correlation was established between TOC and HDL in our study. The findings align with a recent study in the Chinese male population indicating that osteocalcin was positively correlated with HDL-C (22).

Moreover, our findings also revealed that the mean fasting plasma insulin (FI) concentration was significantly high in the diabetic group compared to the control group. The mean plasma insulin concentration in diabetes females and diabetic men was found to be considerably higher than in control females and control males. These results were supported by a couple of previous studies (31, 32). Similarly, our results also showed a statistically significant negative correlation between plasma insulin ucOC along with this a significant negative correlation between plasma insulin TG was also observed. A negative correlation, that was not significant between FI and TOC, age, and LDL was also studied. Similarly, the correlation between FI and TCHOL showed positive statistically significant. The correlations of other predictors with FI were positive, but all of them were not statistically significant. Our results are similar to some of the earlier studies (33) and at the same time contraindicated a few of them (34).

Conclusion: -

Our findings showed a statistically highly significant negative correlation between TOC and fasting blood glucose concentration. Similarly, the correlation between FBG and ucOC, age, BMI, TCHOL, and HDL showed a negative correlation that was not significant.

Conflicts of interest:
The authors state that they do not have any conflicts of interest.

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Ethical clearance:
The Standing Committee for Scientific Research - Shendi University School of Medicine granted ethical approval on February 24, 2015, and all methods were performed in accordance with the provisions of the approval.

Authors Contributions:
OYD, MAA, and MMM conceptualized and designed the study. ABE,AAO, and AMA analyzed and interpret the data. Wrote the manuscript.

All authors have critically evaluated and approved the final text, and they are responsible for the manuscript's content and similarity index.

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Reference: -

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