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Estimation of LCAT and Some Oxidative Stress in Type 2 Diabetic Patients in Kirkuk, Iraq

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Abstract: ***This study is the first to be conducted in Kirkuk City in terms of linking antioxidant parameters with the LCAT enzyme in type 2 diabetes patients. Oxidative stress has received a lot of attention in the field of human health, notably because of its link to diabetes. Oxidative stress is a state in which there is an imbalance between the creation of reactive oxygen species (ROS) and the ability of the body's antioxidant defense system to neutralize them. The purpose of this study was to evaluate the effect of LCAT and various biochemical parameters that were deemed oxidative stress indicators in patients with type II diabetes compared with normal healthy controls in Kirkuk City - Iraq. This study comprised 184 individuals (128 Type 2 diabetic mellitus (T2DM) patients and 56 healthy controls) ranging in age from 40 to 80 years old for both patients and controls. This study was divided into two groups of T2DM patients based on their HbA1c levels, which allude to the patient's diabetes control. The first group (G1) (70 instances) included patients whose HbA1c level was higher than 7% (poorly controlled or uncontrolled) and The second group (G2) contained individuals with HbA1c levels less than 7%, which included 58 instances compared to 56 healthy controls (G3). There was a significant decrease in PON1, LCAT, and NO in DM patients (G1, G2) compared with control groups (G3) (P-Value = 0.01). As well as Glutathione peroxidase and Melatonin significantly decreased in DM patients (G1, G2) compared with control groups (P-Value = 0.02, 0.03 respectively). While MDA was significantly increased in DM patients (G1, G2) when compared with the control group (P-Value 0.011).***

Keywords: ***Diabetes, LCAT, Glutathione Peroxidase, Melatonin, Oxidative Stress, Reactive Oxygen Species (ROS), Malondialdehyde.***

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1. INTRODUCTION

Metabolic syndrome, a combination of medical issues, increases the risk of developing Type 2 Diabetes and Cardiovascular Diseases [1], with oxidative stress being a significant contributor to its progression [2]. Hyperglycemia causes oxidative stress and reactive oxygen species (ROS), which are neutralized by the body's antioxidants to maintain balance [3]. Paraoxonase-1 (PON1), a highly conserved protein with 354 amino acids, is primarily found in HDL in serum and is highly conserved in mammals [4] ; the protective effects of PON-1 activity against LDL particle peroxidation were thought to be more substantial in T2DM patients than in nondiabetics [5] . PON1 genetics may influence the risk of T2D, as the disease can lower PON1 levels, indicating a reciprocal connection between the two [6] [7]. Serum paraoxonase 1 (PON1) is a liver enzyme and biomarker in toxicology that evaluates toxic organophosphate compounds. It binds to HDL and has antioxidant properties, elevated ROS levels can harm biochemical molecules and promote toxic compounds [8] PON-1 levels in metabolic syndrome and insulin resistance could predict Type 2 Diabetes progression[9]. LCAT activity declines with metabolic syndrome, and greater HbA1c levels are associated with reduced activity. Current research indicates an inverse association between LCAT activity and Type 2 diabetes and metabolic syndrome [10] . Glomset advocated for LCAT's promotion of reverse cholesterol transfer (RCT) after its discovery [11] . LCAT's protective effects against heart diseases may decrease over time. Advancements in testing methods like metabolomics and proteomics will help understand its role in disorders [12]. Nitric oxide (NO) is produced in Type 2 Diabetes Mellitus (T2DM) through nitric oxide synthase, which has three isoforms: NOS1, NOS2, and NOS3. These are involved in disrupting metabolic processes, affecting glucose and lipid balance, and promoting inflammation in insulin resistance [13] . Oxidative stress, which decreases the functionality and structure of healthy cells, significantly impacts vascular complications in T2DM patients [14] . Diabetes leads to high ROS levels due to reduced antioxidant activity or increased ROS production, causing tissue oxidative stress and complications [15] . Most diabetes-related deaths result from cardiovascular diseases, not just high blood sugar levels [16] . Individuals with Type 2 Diabetes (T2DM) have higher levels of malondialdehyde (MDA), a reactive byproduct produced when free radicals damage lipids [17] . The current study will measure and compare blood concentrations of Lecithin: Cholesterol acyltransferase (LCAT), PONI, Nitric oxide, melatonin, and GPx in T2DM (controlled and uncontrolled T2DM) to normal controls. The present study also looked at the current study's relationship between LCAT and other parameters.

2. RELATED WORKS

The study of [18] found that lifestyle modification is highly effective in preventing diabetes in older individuals due to weight loss and physical activity. However, metformin's effectiveness may be limited due to age-related differences in insulin action and secretion. A lifestyle modification program is recommended for high-risk individuals. A study on the cardiovascular effectiveness of newer glucose-lowering drugs added to metformin in type 2 diabetes mellitus found that most participants were men, with a larger proportion of males

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using metformin monotherapy compared to the healthy group [19]. A study on metformin adverse drug reactions found that sex differences were observed in the first weeks after initiation, while significant differences in self-reported prescribed dosing were observed after several months. The study suggests that patients, particularly women, may benefit from lower metformin doses at treatment initiation, which could guide future studies and sex-specific management of ADRs in clinical practice [20]. [21] studied correlation between oxidative stress and glycated hemoglobin and lp (a) in patients with diabetes mellitus, he concluded antioxidant levels were lower in patients with diabetes compared to healthy subjects, patients with diabetes have a high risk of developing and progression of different vascular diseases correlated with hyperglycemia, hyperglycemia and high lp (a) were correlated with low antioxidants levels. [22] studied Association of serum nitric oxide metabolite level with mortality in patients undergoing coronary angiography, and they concluded an increase in serum NOx level does not herald a benign clinical course but is an independent predictor of high risk of any-cause mortality and heart failure. [23] studied the Melatonin as a natural ally against oxidative stress: a physicochemical examination and they concluded that melatonin efficiently protects against oxidative stress by a variety of mechanisms. Moreover, it is proposed that even though it has been referred to as the chemical expression of darkness, perhaps it could also be referred to as the chemical light of health.

3. METHODOLOGY

Subjects

This study included 184 cases (128 patients and 56 control) with 40-80 years of age, separated into three groups of T2DM patients, these groups were classified according to the HbA1c of the patients which refers to controlling the diabetes by the patients. The first group (G1) (70 cases) included the patients who their HbA1c value was more than 8% (poorly controlled) whom taken ether Glucophage or Metformin. While the second group (G2) was included the patients with HbA1c level less than 7% (good controlled with Glucophage and metformin) which included 58 cases, As well as Third group included Healthy Controls (G3) which included 56 cases All patients were attending at the Kirkuk Teaching Hospital and Azadi Teaching Hospital and private clinics in Kirkuk/Iraq during the period from November 2023 until May 2024. They were diagnosed proven under the supervision of specialists. All of them have not been diagnosed to any other disease, Patients with liver, kidney, vascular and cardiovascular diseases were excluded.

Sample Collection

Following an overnight fast, the individuals' venous blood samples were taken aseptically by venipuncture. 5ml was collected and split into two portions, and 4ml was stored in a simple tube without any anticoagulant at room temperature for 30 minutes. The tube was centrifuged at 3000×g for 10 min. The clear serum was pipetted into clear dry Eppendorf tubes and stored at (-20) ^{o}C until used for various investigations (FBS, melatonin, HbA1c, LCAT, PON1, Nitric oxide, glutathione peroxidase enzyme, and malondialdehyde level). The lipid profile was estimated fresh, while 1 ml of whole blood was kept in an anticoagulant tube (EDTA) and used for HbA1c determination.

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Determination of Fasting Blood Sugar (FBS)
Fasting serum glucose has been measured using kit from spinreact, Spain.

Determination of HbA1c (AFIAS HbA1c Neo)
The test employs a sandwich immunodetection strategy. The detector antibodies in buffer bind to antigens in the sample, generating antigen-antibody complexes, which move to the nitrocellulose matrix and are captured by the other immobilized streptavidin on the test strip. More antigens in the sample produce more antigen-antibody complexes, resulting in a stronger fluorescence signal by detecting antibodies. This signal is processed by the equipment for AFIAS testing to calculate the quantity of glycated hemoglobin in the sample as a percentage of total hemoglobin.

The following items were tested for assessment in accordance with manufacturer instructions:
1- Human Paraoxonase1 (PON1) ELISA Kit (Cloud-Clone Crop\ USA)
2- Human Lecithin Cholesterol Acyltransferase (LCAT) ELISA Kit(Cloud-Clone Crop\ USA)
3- Human Nitric oxide (A012) ELISA Kit (Cloud-Clone Crop\ USA)
4- Serum level Melatonin by ELISA (Cloud-Clone Crop\ USA)
5- Serum level of glutathione peroxidase (GPx) by ELISA (Cloud-Clone Crop\ USA)
6- Serum malondialdehyde level was measured using human enzyme-linked immunosorbent assay kits (Human malondialdehyde kit; Catalog No. CSBA082431 America).

Statistical Analysis
All data were analyzed using the Minitab application with the ANOVA test. However, the mean when challenged by the ducun multiple range test under the P-value of 0.05.

4. RESULTS AND DISCUSSIONS

Age Range (Years) Categorization among Studied Group
The results of this study showed that equal cases of diabetes mellitus cases the current study is divided into three parts , uncontrolled DM patients (G1) and Controlled DM patients (G2) compared with healthy controls (G3), under the age groups (40-50) and (51-60), (61-70) and **>70** respectively with 12 (17%),15 (21%), 25 (36%),18 (26%),respectively uncontrolled DM patients (G1) when compared with healthy controls (G3). In the same age groups with controlled DM patients (G2) with 11 (19%),20 (34%), 18(31%),9 (16%),respectively when compared with healthy controls (G3), Statistically these differences were non significant (P-value=0.2) as arranged in Table 1 .

Table 1 Age range (Years) categorization among studied group

Group		**Age range (Years)**				**Total**
		(40-50)	**(51-60)**	**(61-70)**	**70-80**	
Diabetes mellitus cases	uncontrolled DM patients (G1)	12(17%)	15 (21%)	25 (36%)	18 (26%)	70

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No.(128)	Controlled DM patients (G2)	11(19%)	20 (34%)	18 (31 %)	9 (16 %)	58
healthy controls (G3)		10(18%)	13(23 %)	16 (29%)	17 (30%)	56
Total		33	43	54	44	184
P-value		0.2 (N.S)				

Gender Categorization among Studied Group

The results of the current study recorded there were non-significant differences(P-value=0.2) in the number and percentages of gender among Diabetes mellitus cases groups who uncontrolled DM patients (G1) Male recorded that 31 (44 %) , Female 39 (56 %).While Controlled DM patients (G2) Male recorded that 30 (52 %), Female 28 (48 %) compared with healthy controls (G3) Male recorded that 24 (43 %), Female 32 (57 %) as arranged in Table 2 .

Table 2 Gender categorization among studied group

Group		Gender		Total
		Male	Female	
Diabetes mellitus cases	uncontrolled DM patients (G1)	31(44 %)	39(56 %)	70(38 %)
	Controlled DM patients (G2)	30(52%)	28(48%)	58(32%)
healthy controls (G3)		24(43%)	32(57 %)	56(30%)
Total		85(46 %)	99(54 %)	184(100%)
P-value		0.2 (N.S)		

Compared of Concentrations of FBS and Hbac1 for Patients with Controlled DM and Patients with Uncontrolled DM.

The results of the current study recorded there were significant differences(P value=0.01) (mean ± SD)of FBS (mg/dl) among Diabetes mellitus cases groups who uncontrolled DM patients (G1)recorded that 231.7±16.7 compared with Patients with controlled DM (G2) 124.67±2.31 and healthy controls (G3) 99.12±13.71. As well as HbAc1(%) (mean ± SD) in among Diabetes mellitus cases groups who uncontrolled DM patients (G1)recorded that 10.13±2.01compared with Patients with controlled DM (G2) 6.21±0.3 and healthy controls (G3) 4.6±0.7 showed significant differences(P value=0.01) as arranged in Table 3 .

Table 3 Concentrations of FBS and HbAc1 for patients with controlled DM and patients with uncontrolled DM.

Variable	DM patients		Apparently Healthy Controls (G3)	P-Value
	Patients with uncontrolled DM (G1)	Patients with controlled DM (G2)		
FBS (mg/dl) (mean ± SD)	231.7±16.7[a]	124.67±2.31[b]	99.12±13.71[c]	0.01
Maximum	200	128	180	
Minimum	124	119	87	

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HbAc1(%) (mean ± SD)	10.13±2.01 [a]	6.21±0.3 [b]	4.6±0.7 [c]	0.01
Maximum	15	6.7	5.6	
Minimum	4.4	5.2	3.0	

Compared of Concentrations of PON1, LCAT, NO, Glutathione Peroxidase and Melatonin for Patients with Controlled DM And Patients with Uncontrolled DM.

The results of the current study recorded that PON1(ng/ml) (mean ± SD) in among Diabetes mellitus cases groups who uncontrolled DM patients (G1)recorded that 64.8±9.7compared with Patients with controlled DM (G2) 64.9±9.4 and healthy controls (G3) 154.13±7.9 showed significant differences(P value=0.01) ,While LCAT (mean ± SD) in among Diabetes mellitus cases groups who uncontrolled DM patients (G1) recorded that 66±8.1compared with Patients with controlled DM (G2) 88.8±5.1 and healthy controls (G3) 117±7 showed significant differences (P value=0.01) as arranged in Table 4 . As well as NO (µ mole/L) (mean ± SD) in among Diabetes mellitus cases groups who uncontrolled DM patients (G1)recorded that 59.15±5.33compared with Patients with controlled DM (G2) 124.39±4.44 and healthy controls (G3) 126.67±7.38showed significant differences(P value=0.01) . Glutathione peroxidase (mean ± SD) in among Diabetes mellitus cases groups who uncontrolled DM patients (G1)recorded that 4.30±1.18compared with Patients with controlled DM (G2) 5.61±1.07 and healthy controls (G3) 6.81±2.014 showed significant differences(P value=0.02). However Melatonin (mean ± SD) in among Diabetes mellitus cases groups who uncontrolled DM patients (G1)recorded that 11.76±2.16 compared with Patients with controlled DM (G2) 13.56±1.20 and healthy controls (G3) 18.14±2.90showed significant differences(P value=0.03). However MDA (mean ± SD) in among Diabetes mellitus cases groups who uncontrolled DM patients (G1)recorded that 115.0±2.06compared with Patients with controlled DM (G2) 31.72±1.19and healthy controls (G3) 23.04±1.06 showed significant differences(P value=0.03)as arranged in Table 4 .

Table 4 Compared of concentrations of PON1, LCAT ,NO , Glutathione peroxidase and Melatonin for patients with controlled DM and patients with uncontrolled DM.

Variable	**DM patients**		**Apparently Healthy Controls (G3)**	**P-Value**
	Patients with uncontrolled DM (G1)	**Patients with controlled DM (G2)**		
PON1(ng/ml)	64.8±9.7b	64.9±9.4b	154.13±7.9a	0.01
Maximum	90	160	165	
Minimum	54	128	134	
LCAT	66±8.1[c]	88.8±5.1[b]	117±7[a]	0.01
Maximum	81	99	133	
Minimum	45	77	100	
NO (µ mole/L)	59.15±5.33[c]	124.39±4.44[b]	126.67±7.38 [a]	0.01
Maximum	71	133	137	
Minimum	45	109	100	
Glutathione peroxidase	4.30±1.18c	5.61±1.07b	6.81±2.014a	0.02

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Maximum	3.5	3.9	7.5	
Minimum	2.3	2.1	6.2	
Melatonin	11.76±2.16c	13.56±1.20b	18.14±2.90a	0.03
Maximum	12.5	14.4	19.8	
Minimum	9.2	8.5	17.2	
MDA	115.0±2.06a	31.72±1.19b	23.04±1.06c	0.011
Maximum	73.96	23.92	9.84	
Minimum	14.3	13.1	12.4	

Discussion

T2DM in older adults is associated with insulin resistance, obesity, β-cell dysfunction, and sarcopenia [16]. Metformin is a first-line therapy for type 2 diabetes due to its potent glucose-lowering properties. Controlled diabetes patients (G2), well-established safety profile, and reasonable cost [17]. The results of the present study showed no significant differences between the studied groups according to the age. [18] in their study showed the number of diabetic patients in 45-59 years old that Controlled DM patients were more than the same age that was dependent on lifestyle therapy and healthy persons compared to other age groups.

Among the cases Controlled DM patients with diabetes mellitus demonstrated that (46% women), diabetes event incidence was lower in women than in males (66%), compared with uncontrolled DM patients (G1) and healthy controls (G3) [19]. [24] found that their managed DM patients (G2) had a somewhat larger proportion of males than females (55.5% vs. 44.5%) who used metformin monotherapy compared to the healthy group .Men were (69.1%) on average at the time of metformin commencement, compared to women were (20.9%) in the study of [20] which contradicts the conclusion of the current investigation. In a research by [25], type 2 diabetics treated with metformin had a mean FBS of 163.14±38.61, compared to 177.70±28.59 in the control group who did not receive metformin. The difference between the two is substantial (p=0.035) and is consistent with the current investigation. The comparison of following treatment HBA1C testing indicated normal results in 82.3% of metformin-treated patients (19). The primary and secondary goals used to assess group efficacy are glycated hemoglobin (HbA1C), fasting blood sugar levels (FBS), and random blood sugar levels (RBS). [26] the difference in HbA1C, FBS, and RBS levels from baseline to end follow-up was 0.50%, 20mg/dl, and 85mg/dl in the metformin group . In keeping with [21] results , there was a substantial link between PON1 and the diabetic phase in DM. This is corroborated by prior research, which found a robust link between diabetes duration and an increased chance of developing CHD as an independent risk factor. The findings imply that PON1 is a key early predictor of CVD in diabetics. It is strongly advised that researchers investigate the significance of PON1 genetic variants in Sudanese diabetes and how they may influence CHD complications. As the fundamental constraint of this research is the limited sample size, the current findings must be validated in a bigger study [26]. In this study, people with DM G1 and DM G2 showed lower levels of LCAT activity than those with T2DM, this may be due to relation its concentration with lipid level that decrease in HDL level decreased. These findings are consistent with previous study that found a decrease in LCAT activity among diabetics with insulin-dependent or non-insulin-dependent DM [21]. Prior findings, showed that LCAT activity was lower in those with T2DM than in those

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without, and it was inversely related to HbA1c levels. Glycemia-induced glycation of HDL lowers LCAT activity. HbA1c is a reliable glycemic marker capable of representing glycated HDL levels explains the link discovered in the current investigation. Finally, HbA1c is a simple and reliable biomarker of LCAT activity in DM2 [27]. Increased LCAT activity in both G1 and G2, may be due to study's limitations include: Small sample size and the absence of a control group suffering only from metabolic syndrome. In this study, there was a significant difference (P-value = 0.01) in blood nitric oxide levels between patients with uncontrolled DM and control DM against healthy controls. This may be due to development of endothelial dysfunction and atherosclerotic complications in DM, but may also affect insulin-mediated postprandial glucose disposal and possibly contribute to the development of insulin resistant. A Turkish study employed the Griess reaction to compare baseline blood nitric oxide levels in T2DM with different stages of diabetic retinopathy to non-diabetic controls. Patients with T2DM exhibited significantly higher serum NOx levels than those without diabetes [28]. A study of T2DM and healthy controls discovered that T2DM had greater blood and urine NO levels than controls in early diabetes [29]. Namba and Takayuki observed that untreated patients had significantly higher plasma NOx levels. Previous research reveals that antioxidant therapy which are complex compounds with vital properties that act as a protective shield against many diseases [30]. protects the beta-cell from oxidative stress-induced apoptosis and maintains beta-cell function, and antioxidants reduce diabetes complications [31] . In the [32] study, showed NOx was measured in adults, and it was much higher in T2DM, supporting the current theory that NO overproduction limits insulin's metabolic activities. In addition, the findings of this study showed that diabetic patients had significantly lower levels of melatonin compared to the control group. This decrease in melatonin levels was found to be parallel to the decrease in the activities of the GPX enzyme. A decrease in the level of glutathione in patients with type 2 diabetes compared to the control due to the occurrence of oxidative stress resulting from hyperglycemia in the case of diabetes. Oxidative stress leads to a decrease in the level of antioxidants in general, including glutathione and melatonin. Other study suggested that the antioxidant action of melatonin may be related to its ability to enhance the activities of antioxidants, as supported by previous studies [33]. Melatonin exerts its effects through multiple mechanisms to mitigate oxidative stress. Melatonin has the ability to remove harmful oxygen species [34], and it also has other activities that counteract free radicals. One way melatonin might neutralize a free radical is by redistributing one of its electrons [34]. However, it is commonly recognized that the capacity of melatonin to decrease oxidative stress can be influenced by its connection with melatonin receptors, that are found in many, if not all, cells [35] [23]. Melatonin's antioxidant properties depend on its interactions with cell membrane or intracellular organelle membrane receptors [32]. These melatonin receptors are likely to be found in all organisms [13]. Melatonin's activities on receptors are mediated indirectly, potentially through the activation of antioxidant enzymes such GPX, SOD1, 2, SIRT3, and other enzymes [36]. Melatonin can have antioxidant effects at much lower doses via acting through receptors rather than directly as a free radical scavenger. The results of our study also showed a statistically significant level of MDA in the group of individuals with diabetes. This finding aligns with the research conducted by Whiting et al. [37], who concluded that long-term high blood sugar levels can impact the production of free radicals, leading to higher levels of lipid

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peroxidation, increased consumption of antioxidants, and elevated oxidative stress in individuals with diabetes. [38] did a clinical study conducted to identify blood oxidative stress in individuals with diabetes discovered a notable increase in lipid peroxidation. This increase was found to be associated with elevated glucose levels, as measured by fasting glucose and HbA1c measurements. Contrary to our own results, a previous study found no significant association between MDA levels and fasting blood sugar (FBS) or glycated hemoglobin in both the cases and control group. However, those with diabetes had significantly higher MDA levels compared to the control group, which supports our findings.

5. CONCLUSIONS

Type 2 diabetics with uncontrolled (G1) and managed DM showed lower LCAT levels than the control group. Melatonin levels were much lower in diabetes individuals, which may contribute to a reduction in the ROS defense system by inhibiting the activity of the GPx enzyme. Malondialdehyde is a non-invasive biomarker that may be used to distinguish T2DM patients from healthy controls. Individuals with type 2 diabetes who have uncontrolled diabetes (G1) and those who have managed diabetes had lower levels of LCAT compared to the control population. Diabetic patients exhibited a notable decrease in melatonin levels, potentially leading to a reduction in the defense mechanism against reactive oxygen species (ROS) by impacting the functioning of the GPx enzyme.

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