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Biochemical study of lipoprotein lipase enzyme and apo-lipoprotein-C2 in patients with and without type 2 diabetes mellitus

Amaal Adel Hashim

Department of Biochemistry, College of Medicine, University of Babylon, Iraq

Maha Fadhil Smaism

Department of Internal Medicine, College of Medicine, University of Babylon, Iraq

Mohammed Hassan

Department of Internal Medicine, College of Medicine, University of Babylon, Iraq

Abstract---Type two diabetes mellitus (T2DM) is the most common type of diabetes; it is characterized by hyperglycemia in the presence of hyperinsulinemia which is produced from beta cell insulin secretory malfunction and insulin resistance. This study was designed as a case-control study and was constructed to study the effect of type 2 diabetes mellitus on lipoprotein lipase and Apo lipoprotein C2 levels among lipid profiles in type 2 diabetes. The patient's ages ranged from (40-60) years. The serum sample of all groups was collected and used to measure the level of lipoprotein lipase and Apo lipoprotein C2 by using the ELISA method and to measure lipid profile by spectrophotometer technique. All samples were collected from Merjan Medical City at Babylon/ Hilla city. The study revealed that there was a significant decrease in the levels of lipoprotein lipase in patients with type 2 diabetes mellitus compared with the control group ($P < 0.001$), also there was a significant increase in the levels of Apo lipoprotein C2 in the patient's group compared with the control group ($P = 0.02$), There was a significant increase in plasma level of total cholesterol, triglyceride, low-density lipoprotein and very low-density lipoprotein with $P < 0.001$, < 0.001 , < 0.02 and < 0.001 respectively in patients group compared with the control group, and there was a decrease in levels of high-density lipoprotein in patients and control groups but non-significant ($P = 0.579$). Type 2 diabetes mellitus may be associated with decreased lipoprotein lipase concentration due to impaired insulin action. Increasing the level of apolipoprotein-C2 in type 2 diabetes mellitus may result in increased triglyceride levels. Decrease lipoprotein lipase enzyme activity in type 2 diabetes mellitus is probably a response to increase apolipoprotein-C2.

Keywords---type 2 diabetes mellitus, apo-lipoprotein C2, lipase.

Introduction

Diabetes Mellitus (DM) is one of the most common metabolic disorders that is increasing at an alarming rate all over the world (Kirkman et al., 2012). According to World Health Organization (WHO;2021), diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Diabetic patients are unable to metabolize glucose efficiently and cannot synthesize fatty acids and triglycerides from carbohydrates or amino acids, due to the failure of insulin secretion or action. Since the cells cannot detect and absorb glucose in the blood, enzymes in the glycolytic, lipogenic, and pentose phosphate pathways (PPP) are suppressed, while gluconeogenic, glycogenolytic, and lipolytic activities are elevated, reversing the metabolic pathway in non-diabetic individuals (Garcia-Garcia et al., 2020). Type 2 diabetes mellitus (T2DM), is a type of diabetes mellitus that was previously known as non-insulin-dependent diabetes mellitus or adult-onset diabetes mellitus (Hafiane & Genest, 2015). T2DM is caused by a combination of two basic factors: inadequate insulin secretion by pancreatic islet β -cells (β -cell dysfunction), and the failure of insulin-sensitive tissues to respond to insulin (insulin resistance). This an inadequate compensatory insulin secretory response cause the chronic dysregulation of the hyperglycemia state which leads over time to damage to the heart, vasculature, eyes, kidneys and nerves (Gutgsell et al., 2019). Lipoprotein lipase (LPL) was first discovered in 1943 by Paul Hanh in dogs as heparin-activated clearing factor , and renamed LPL by Edward Korn in 1955(Wolska et al., 2017). Lipoprotein lipase (LPL) is a member of the so-called lipase superfamily which includes hepatic lipase, pancreatic lipase and LPL itself (Albuquerque et al., 2015). The parenchymal cells of the heart, adipose tissue, and skeletal muscle are the first to synthesize LPL. LPL is subsequently secreted into the surrounding interstitial spaces and delivered to the vascular endothelium cells, where it attaches into the lumen of capillaries (Amundson & Mingjie, 1999). The main function of LPL is hydrolysis of lipoproteins which occurs at the surface of capillaries, mainly in skeletal muscle, heart, and adipose tissue provides fuel to vital tissues, such as the heart, and lipids for storage in adipose tissue (Bhowmik et al., 2018). Apolipoproteins are structural and functional proteins of the lipoprotein particles, which perform important functions for the lipoprotein metabolism as carriers of these hydrophobic molecules in the plasma aqueous medium, binding to the specific receptors on the cell surface to conduct the lipids correctly to the target organs and tissues of the organism. They also activate or inhibit the enzymes involved in the lipid metabolism (Davies et al., 2010). Apolipoprotein-C2 (Apo-C2) is a small exchangeable apolipoprotein found on triglyceride-rich lipoproteins (TRL), such as chylomicrons (CM) and very low-density lipoproteins (VLDL), and on high-density lipoproteins (HDL), particularly during fasting. Apo-C2 was subsequently discovered in 1970 as a protein bound to very low-density lipoproteins (VLDL) and other lipoproteins, and was initially called glutamic acid lipoprotein or Apo-LP-Glu based on its C-terminus amino acid (Glu). Apolipoprotein-C2, in humans, it is expressed in jejunal enterocytes at relatively high levels and in liver (Cerqueira et al., 2016). Apo-C2 on circulating lipoprotein particles activates LPL to hydrolyze TG in these particles into fatty

acids and glycerol (Henderson et al., 1999). Lipids are biomolecules that are only found in living beings. The way and degree of interaction of these biomolecules with water determine important aspects in some biological processes. For example, the amphipathic character of phospholipids favors the efficient formation of micelles and bilayers. On the other hand, the nonpolar characteristic of fatty acids and triglycerides requires specific transport mechanisms in the blood, through plasma lipoproteins (Panarotto et al., 2002). Cholesterol is the major sterol present in animal tissues. This molecule is almost planar and rigid and contains a steroid nucleus of four fused rings, three of which have six carbons and a fourth that has five. The molecule is amphiphilic, having a hydrophobic hydrocarbon body and a hydrophilic hydroxyl headgroup (Ferrier, 2014). Triglyceride is the most concentrated energy form found in biological tissues. It is an ester consisting of three fatty acids and one glycerol backbone. Fatty acids are the essential substrates for membrane lipids and lipids involved in cellular signaling. However, high concentrations of non-esterified fatty acids (NEFA) distort the integrity of cellular membranes, alter the intracellular pH balance and evoke the production of harmful bioactive lipids (Dilworth et al., 2021).

Materials and Method

There are two groups in this a case-control study: the first one includes patients with type 2 diabetes mellitus, and the second one is the control group includes apparently healthy individuals. The present study was completed in the laboratory of Clinical Biochemistry Department in College, of Medicine, University of Babylon. The collection of samples was directed during the period from 1st of November 2021 until 24th of February 2022. Questionnaires were created to collect data from the control and patients group. All subjects were selected in fasting state.

Group Distributions

The patient's group that consisted of 45 patients with type 2 diabetes (22 male + 23 female). The patients' ages between (40-60) years, and a duration of (5-20) years, and with BMI between (25-39.9) Kg/m². All patients were diagnosed by physicians and according to especially criteria. They were enrolled to the Diabetic and Endocrinology Center in Marjan medical city at Babylon / Hilla city. The control group consists of 45 individuals (22 male + 23 female) who seemed to be healthy, they were taken from out people and relative. This group's age between (40-60) years old, BMI between (25-39.9) Kg/m², and with FBG < 100 mg/dl. They were devoid of any illness symptoms and indicators.

Exclusion criteria

Duration of diabetes >20 and <5, age >60 and <40, smoker, renal failure, thyroid disease, malignant disease, hepatic disease, patients on statins or any hypolipidemic drug, type 1 diabetes mellitus and pregnant women.

Collection of blood samples

Venous blood sample were pulled from control and patients by utilizing the dispensable syringe as a part of the sitting position and in fasting status. Three ml of blood were got from every subject by vein cut, this 3 ml drawn gradually into dispensable tubes containing isolating gel. The blood in gel - containing tubes was let to clot at room temperature for 30 minutes and after that centrifuged at 1000 rpm for 10 min, then partitioned into little aliquots and kept in (-20) °C until analysis for estimation of LPL, Apo-C2 and lipid profiles.

Determination of Human Lipoprotein Lipase

It was calculated by using ELAZA kit according to Manufacture Company/ Solar biotech/USA.

Determination of Human Apo lipoprotein - C2

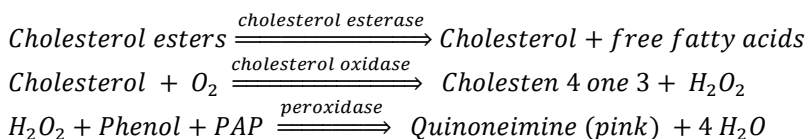
It was calculated by using ELAZA kit according to Manufacture Company/ Solar biotech/USA.

Plasma Lipid Measurements

Quantitative analyses of lipids were performed on 45 fasting type 2 diabetic patients and 45 fasting controls. Plasma levels of Total-C, TG and HDL-C were measured by enzymatic colorimetric methods, LDL-C level was measured by Fried Ewald formula.

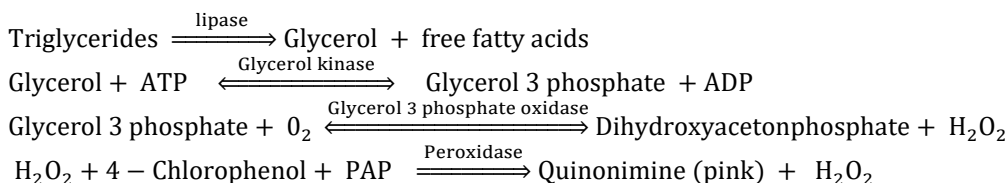
Determination of Serum Total Cholesterol

Plasma levels of total cholesterol was measured by an enzymatic colorimetric method. Enzymatic method described by Álvarez-López, (Álvarez-López et al., 2021). Which reaction scheme as follows.



Determination of serum triglyceride

Serum triglyceride was measured by Fossati and Prencipe method related with Trinder reaction. As shown in the following reactions:



Determination of serum HDL-Cholesterol

The standard measure of HDL is the cholesterol content in HDL particles after precipitation of Apo-B containing lipoproteins from serum by using phosphotungstic acid (PTA) and magnesium chloride $MgCl_2$. Chylomicron, very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) were precipitated from the specimens by phosphotungstic acid and $MgCl_2$ (Huanget al., 2013). HDL-cholesterol which obtained in the supernatant after centrifugation was measured with total cholesterol reagent

Determination of Serum Very Low-Density Lipoprotein

Very low-density lipoprotein-cholesterol (vLDL.C) was measured by divided the results of TG on five number.

$$VLDL.C \text{ (mmol/L)} = (TG/5)$$

Statistical analysis

The data was analyzed using Software Package for Social Science (SPSS-26.0 version). The data was presented as a mean and standard deviation (SD). Continuous variables were tested for normality according to the t- test and linear regression analysis that have been used to determine the significant difference between the groups.

Results and Discussion

The mean difference of age and body mass index (BMI) between patients' group and control group were statistically non-significant ($p > 0.05$). As shown in Table 1:

Table 1
Mean $\pm$ Standard Deviation and p value of age and BMI in patients and control groups

Parameter	group	N	Mean $\pm$ SD	P value
Age (Years)	Patients	45	55.24 $\pm$ 5.37	0.199
	Control	45	53.73 $\pm$ 5.69	
BMI (Kg/m ²)	Patients	45	30.21 $\pm$ 4.51	0.54
	Control	45	29.60 $\pm$ 4.92	

The matching between patients and control in age and BMI is important to eliminate the variation in the results that may arise from the differences in these parameters and to obtain good statistical results (Kirkman et al., 2012) showed that, about diabetes and age that there is a strong relationship between T2DM and age, older adults are at high risk for both diabetes and prediabetes, with surveillance data suggesting that half of older adults have the latter. The Academy of Nutrition and Dietetics recommends that overweight adults with risk factors and all adults aged ≥ 45 years be screened in the clinical setting every 1–3 years using either an FPG test, HbA1C, or oral glucose tolerance test (Kei et al., 2012). In this study, the selection of diabetics was within present age and duration to

attempt excluded the interference of complications. The level of LPL in patients' group was significantly decreased when compared with the control group ($P > 0.001$) as shown in Table 2.

Table 2
Mean $\pm$ Standard Deviation and p value of LPL concentration in patients and control groups

Parameter	Group	N	Mean $\pm$ SD	P value
LPL	Patients	45	93.52 $\pm$ 33.49	<0.001
(U/L)	Control	45	135.57 $\pm$ 66.78	

Lipoprotein lipase (LPL) was a pivotal role involved in lipid metabolism as rate-limiting enzyme hydrolyzing plasma TG-rich lipoproteins (TRLs) including chylomicron (CM) and very-low-density lipoprotein (VLDL), producing non-esterified fatty acids (FAs) and 2-monoacylglycerol for tissue uptake or into the blood circulation (Kirkpatrick et al., 2012). In this study, patients with T2DM have reduce lipoprotein lipase level as we expected. This result agree with several studies; one of these studies by Álvarez-López; they were found that lipoprotein lipase levels are reduced in patients with diabetes mellitus (Álvarez-López et al., 2021). This finding may due to impaired of insulin action which important and common feature in T2DM and that agreement with D. Panarotto, et al (2002) they reported that regulation of adipose tissue LPL is affected in insulin-resistant individuals in the postprandial period. This presumed impaired effect of insulin on LPL postprandially could be an important contributor to the atherogenic dyslipidemia described in insulin resistance syndrome (Li et al., 2020). Another possible reason for this present result was due to overproduction of Apo-C2, as the result of this study, this interpretation agrees with P. Zhang and J. Gao, et.al;(2017) they were found that at intermediate concentrations, Apo-C2 activates LPL. However, both very high and very low concentrations of Apo-C2 have been associated with decreased LPL activity and hypertriglyceridemia (Zhang et al., 2017). The level of Apo-C2 in patients' group was significantly increase when compared with the control group ($P= 0.022$) as shown in Table 3.

Table 3
Mean $\pm$ standard deviation and p value of APO-C2 concentration in patient group and control group

Parameter	group	N	Mean $\pm$ SD	P value
APO-C2	Patients	45	10.40 $\pm$ 4.971	0.022
(mg/dL)	Control	45	8.42 $\pm$ 2.789	

The main role of Apo-C2 secreted by the liver into the plasma was to enhance TG hydrolysis of VLDL and CM for energy delivery or storage, Plasma levels of Apo-C2 were approximately 4.5 μ mol/L (40 mg/L) in normolipidemic individuals but can be considerably higher when there was an accumulation of TRL in plasma (Alam et al., 2021). In normolipidemic, Apo-C2 was observed to be for the most part distributed in the HDL, whereas in hypertriglyceridemia, mostly distributed in the LDL and VLDL (Béliard et al., 2009). In this stud, increase level of Apo-C2 in patients group may be associated with elevated triglyceride-rich (TG-rich)

particles as reported in the study by Béliard (Béliard et al., 2009) they were reported that plasma concentration levels of Apo-C2 to be markedly higher in patients with T2DM, and this increase was associated with elevated TG-rich particles. However, the results show that, the levels of total cholesterol P value (< 0.001), TG P value (< 0.001), VLDL P value (< 0.001) and LDL P value (0.022) were significantly increased, while HDL P value (0.579) non-significant in patients' group when compared with the control group as shown in Table 4.

Table 4
Mean $\pm$ standard deviation and P value of lipid profile in patients' group and control group

Parameter	Group	N	Mean $\pm$ SD	P value
T.Cholesterol	Patients	45	5.826 $\pm$ 1.363	<0.001
mmol/L)(	Control	45	4.835 $\pm$ 0.801	
TG	Patients	45	2.202 $\pm$ 0.948	<0.001
mmol/L)(	Control	45	1.606 $\pm$ 0.391	
HDL-C	Patients	45	0.766 $\pm$ 0.287	0.579
mmol/L)(	Control	45	0.798 $\pm$ 0.252	
LDL-C	Patients	45	4.059 $\pm$ 1.349	0.022
mmol/L)(	Control	45	3.307 $\pm$ 0.779	
VLDL-C	Patients	45	1.001 $\pm$ 0.430	<0.001
mmol/L)(	Control	45	0.730 $\pm$ 0.177	

Lipid abnormalities are common in diabetic patients and frequently seen in type 2 diabetic patients. Dyslipidemias make diabetic patients prone to develop cardiac heart disease and other complications of atherosclerosis (Saydah et al., 2004). Several studies agreed with this study (Saydah et al., 2004; Taxiarchis, 2019; Díaz-Aragón et al., 2021) they reported that T2DM is usually implicated in dyslipidemia, because insulin resistance affects the enzymes that are involved in lipid metabolism. This study exhibit highly significant increase plasma triglycerides (TG) and VLDL, these results agree with most studies, as researches established by Vergès and Bruno; (Vijayaraghavan, 2010) patients with T2DM show increased plasma triglycerides (TGs) as a result of both increased hepatic production of VLDLs and decreased catabolism of TG-rich lipoproteins (VLDL, IDL). In this study, it was demonstrated that non-significant difference in HDL-C level between patient group with control group, both of them have mean of HDL-C concentration under normal range which was below 1.2 mmol/L (45 mg/dL) in men and 1.4 mmol/L (55 mg/dL) in women. This result do not agree with several studies that showed a significant decrease in HDL-C level in type 2 diabetic patient group with control group, this result might related to life style that dependent by control group in region of this study and this is agree with many studies have assessed the relationships of lifestyle factors to circulating HDL particles levels, especially in healthy individuals (Windler et al., 2007). Lifestyle factors such as losing weight and increasing physical activity have been proven to raise HDL-cholesterol concentrations, even moderate weight loss by 5–10%, combined with exercise, significantly decreases serum triglycerides and increases plasma concentrations of HDL-cholesterol (Wu & Klaus, 2014). Zeqollari et al; [33] found that, Type 2 diabetes was associated with a cluster of interrelated plasma lipid and lipoprotein abnormalities. The lipoprotein abnormalities commonly

present in type 2 diabetes include an abnormally high level of triglycerides (TG), a high proportion of small dense low-density lipoprotein cholesterol (LDL), low high density lipoprotein cholesterol (HDL), and postprandial lipemia. This pattern of lipid profile in diabetes mellitus type 2 is termed diabetic dyslipidemia. Several factors are likely to be responsible for diabetic dyslipidemia: insulin effects on liver Apo protein production, regulation of lipoprotein lipase (LpL), actions of cholesterol ester transfer protein, and peripheral actions of insulin on adipose and muscle (Wu et al., 2021).

Conclusion

Type 2 diabetes mellitus may be associated with decrease Lipoprotein lipase concentration due to impaired insulin action. Increase the level of apolipoprotein-C2 in type 2 diabetes mellitus may be result as a response to increase triglyceride level. Decrease lipoprotein lipase enzyme activity in type 2 diabetes mellitus probably response to increase apolipoprotein-C2. Diabetic-dyslipidemia may be due to decrease plasma level of lipoprotein lipase enzyme.

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