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Assessment of Serum Lipid Profile in Sudanese Diabetic Patients Treated with Insulin and/or Oral Hypoglycemic Medications

Elsadig Mohamed Ahmed[*1], Abdelrahim Osman Mohamed[2], Elrasheed Mohamed Salih[3], MutasimSiddig Mohamed Salih[4], Bader EldinHaroun Idris[5]

[*]1.Department of Clinical Biochemistry, Division of Medical Laboratory Science, Applied Medical Science, Faculty of Science and Art, King Khalid University- Elmahdi, Sudan.E-mail; alsadigmaf@yahoo.com
2.Department of Biochemistry, University of Khartoum, Sudan.
3.Department of Internal Medicine, University of El imam Elmahdi, Sudan.
4.Department of Pharmacology, University of El imam Elmahdi, Sudan
5.Department of Physiology, University of ElimamElmahdi, Sudan.
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ABSTRACT

Insulin resistance is the pathophysiological basis of dyslipidemia and hyperglycemia.Most lipid abnormalities in type 2 diabetes can be explained by reduced action of insulin at the tissuelevel.This cross sectional study was carried out to assess the impact of diabetes mellitus on lipid profile of Sudanesediabeticpatients treated with insulin and/or oral hypoglycemic agentsat Kosti teaching hospital, during October, 2008 – April, 2009.One hundred and sixty three diabetic patients aged between 15-85years were included. They were informed and consented to participate in this study. Subjected patients were classified into three groups according to their medication;group A (n=36)includes patientstreated with insulin, group B (n=113)were patients treated withhypoglycemic agents and group C (n=14), those whom wereusing combination of both insulin and oral hypoglycemic agent as treatment.Patientsblood samples were taken and examined for lipids profile and HbA_{1C} using spectrophotometric and chromatographic techniques, respectively. Obtained data were analyzed using SPSS program for windows, V,20. Usingstudent-'t' test. Patients results were compared with results of one hundred persons as controls.In this study there was an elevatedmean level ofcholesterol(4.88±1.55mmol/L),triglycerides(2.2±0.66mmol/L), LDL(3.1±1.76mmol/L), ApoB(1.48±0.6g/L),and HbA_{1C}(10.4±4.5%), and reduced mean levels of HDL(1.15±0.36mmol/L)and ApoA (1.62±0.1g/L)in all groupswhen compared with control. All patients were having HbA_{1C}>9%.Mean values ofcholesterol,triglycerides, LDL, HDL, ApoB, ApoA and HbA_{1C} of diabetic patients were found non-significant when compared with controls (*P* values were 0.340, 0.802, 0.489, 0.812, 0.342, 0.490 and 0.840), respectively. The assessment of lipid profile in serum of diabetic patients treated with insulin and/or oral hypoglycemic agents should be done to reduce the risk of fat gain to diabetic patients.Glycemic control and treatment of dyslipidemia reduces the development and progression of diabetic complications.

KEYWORD:Lipoproteins, Glycosylated hemoglobin, cardiovascular disease

المستخلص

الانسلين المقاوم يعتبر الأساس المرضي لارتفاع معدلات الشحوم و السكر لدي مرضي السكري. أغلب حالات اعتلال الشحوم لدي مرضي السكري من النوع 2 يمكن أن تفسر بانخفاض فعالية الانسلين في الأنسجة.صممت هذه الدراسةالمقطعية للتعرف علي تأثير مرض السكري علي السودانيين المعالجين باستخدام الانسلين و الأدوية خافضة للسكر وذلك في وحدة الباطنية بمستشفي كوستي التعليمي خلال الفترة من أكتوبر 2008 و إلي أبريل 2009. وافق جميع المرضي كتابة أو شفاهة علي الاشتراك فيها. تم قياس مستوي الشحوم و مستوي HbA_{1C} بالدم في عينات مرضي السكري السودانيين (163) الذين أعمارهم مابين 15 و 85 عاما وعينات المقارنة (100). قسم المرضي المستهدفين بالدراسة إليثلاثة مجموعات بناءاً علي نوع العلاج المجوعة أ و عددهم (36)، المعالجين بالانسلين، المجموعة ب (وعددهم 113)، المعالجين بالأدوية الخافضة للسكر، والمجموعة ج (وعددهم 14)، المعالجين بالانسلين والأدوية الخافضة للسكر. استخدمت طريقة المطياف اللوني والاستشراب لتحليل العينات للتعرف علي مستويات الشحوم و HbA_{1C} علي التوالي. استخدم برنامج التحليل الإحصائي (SPSS students' T-test) لتحليل البياناتإحصائيا.هذه الدراسة أن هناك ارتفاع في متوسط قيمالكولسترول(4.88±1.55 ملي مول/ليتر) ثلاثي الجليسريد (2.2 ± 0.66ملي مول/ليتر)، البروتينات الشحمية منخفضة الكثافة LDL(3.1±1.76ملي مول/ليتر)، ApoB (1.48±0.6جرام/ل) و HbA_{1C}(10.4%). كما وجد انخفاض في مستويات البروتينات الشحمية عالية الكثافة HDL (1.15±0.36ملي مول/ليتر)و ApoA(1.62±0.1جرام/ل).جميع المجموعات لها مستوي مرتفع من HbA_{1C}(9%<).القيمالمتوسطة لكل من الكولسترول، ثلاثي الجليسريد، البروتينات الشحمية منخفضة الكثافة، البروتينات الشحمية مرتفعة الكثافة، ApoB، ApoAو HbA_{1C}وجد أنهاليس لها دلالة إحصائية عند مقارنتها بالعينات الضابطة ، حيث أنالقيم المعنوية لها هي (0.340، 0.802، 0.489، 0.812,0.342، 0.490 و 0.840)، علي التوالي،.قياس الشحوم لدي مرضي السكري المعالجين بالانسلين أو الأدوية خافضة للسكر أو الاثنين معا لابد من إجرائه، لمعرفة مستويات هذه الشحوم وذلك للتقليل من خطر الارتفاع في معدلات الشحوم لدي المرضي. التحكم في مستوي السكر في الدم ومعالجة الخلل في مستوي الشحوم بالدم يقلل من تطور واستمرار مضاعفات مرض السكري.

INTRODUCTION

Improved glycemic control has been shown to diminish the risk of long-term complications in patients with diabetes.[1] Treatment should begin with lifestyle modification, including meal planning and exercise, and pharmacologic therapy to improve prognosis and to reduce complications resulted from the use of insulin and/or sulfonylureas.[1]Cardiovascular disease (CVD) is currently the primary causeof morbidity and mortality in diabetes mellitus (DM).[2,3,4,5] Diabetic patients have two to four fold greater risk than do non-diabetic individuals of developing atherosclerosis and its complications, including vascular disease.[2]

Lipid disorders are common in DM, and play crucial roles in the development of diabetic cardiovascular complications.[5] The initial management of lipid disorders in diabetic patients without CVD is lifestyle intervention and glucose control. [5]

Due to lipoprotein abnormalities in diabetes, an easily measured composite indicator may be useful for treatment thediabetes.[2] The Diabetes Control and Complications Trial indicate that a tight control of glucose levels does not substantially reduce cardiovascular events in patients with diabetes.[4] All treatment strategies of diabetes should emphasize

cardiovascular risk reduction, focusing particularly on correction of dyslipidemia.(1) Diet, exercise and weight reduction are essential for the management.(1)

Insulin resistance is the pathophysiological basis of dyslipidemia and high blood sugar.(6) Most of lipid abnormalities in type 2 diabetes can be explained by reduced action of insulin at the tissuelevel.(7) Both type 1 and type 2 diabetes are characterized by a progressive decrease in beta-cell function and mass.(8) Chronic exposure to elevated glucose results in further deterioration of the beta-cell function.(8) Insulin regulates heart metabolism through the regulation of insulin-stimulated glucose uptake. Also insulin can regulate mitochondrial function.(9)

In type 2 diabetes, a diminished or absent first-phase insulin release is the earliest metabolic defect, which is accompanied by lack of prandial suppression of hepatic glucose production, increased postprandial glucose excursion and late insulin hyper-secretion.(8) In type 1 diabetes autoimmune destruction results in rapid loss of beta-cell function therefore insulin therapy is essential to maintain normal glycemia.(8) Early and intensive glycemic control, using regimens which re-create a physiological insulin profile, controlling postprandial as well as fasting glucose levels, offers the most promise for preserving beta-cell function, decreasing disease progression, and reducing the chronic complications of diabetes.(8) Reliable indices of coronaryrisk assessment and targets for drug treatment are importantto the management of diabetes patients.(3)

Current clinical guidelines require measurement of total cholesterol, LDL, HDL and triglycerides to assess the lipid-related risks. (6) All the four parameters are targets of therapy and therefore must be measuredinitially and at the follow-up. (6)

This study was conducted to assess serum lipid profile inSudanese diabetic patients treated with Insulin and/or oral hypoglycemic agentsso that therapeutic strategies can be established to reduce the risk of fat gain.

MATERIALS and METHODS

This study was designed as prospective cross-sectional study, carried out atinternal medicine unit, Kosti teaching hospital, Kosti, White Nile State, Sudan, during the period of October, 2008 – April, 2009. One hundred sixty three diabetic patients aged 15-85years old were included. The Study subjects were consentedto participate,each patient was asked for the type of medication he/she used. Then patients were divided into three groups; Group A (n=36), includes those who treated with insulin, group B (n=113), were patients who treated with hypoglycemic agents and Group C (n=14), treated with combination of insulin plus oral hypoglycemic agents.Lipids and glycosylated hemoglobin (HbA_{1C}) were tested for allpatients.Blood samples of 100 individuals with no personal or family history of diabetes were examined for lipids and HbA_{1C} to compare the means and cut-off values with results of patients.

Five milliliters of venous blood samples were collectedfrom patients and control subjects and divided into two parts, one was transferred in an EDTA tube for the immediate analysis of HbA_{1C}, and the second part was transferred to a plan container,centrifuged 3000/rpm for 5mins using Lab tech centrifuge, India.Serum was obtained and kept at -20°C for the analysis of lipid parameters.HbA_{1C} was extracted using chromatographic spectrophotometric ion-exchange method from Cypress Diagnostic, Belgium.And the concentration was determined by colorimeter (Lab Tech, India). Turbidimetric immunoassay technique was applied to measure the apolipoprotein B

(ApoB) and apolipoprotein A (ApoA) concentration using commercially available test kits obtained from Human Gesellschaft for Biochemica and DiagnosticambH, Germany and the standard procedure was followed using spectrophotometer (Hitachi photometer 4020 from Boehringer Mannheim, Japan).Enzymatic colorimetric test using kits obtained from Human Gesellschaft for Biochemica and diagnosticambH, Germany, was used to determine the concentration of triglycerides, cholesterol, LDL and HDL. The standard procedure was followed using spectrophotometer (Hitachi photometer 4020 from Boehringer Mannheim, Japan).

Statistical analysis: Data were analyzed using SPSS program for windows, v20. Student-'t' test, Results of diabetic patients and their groups were correlated using Bivariate correlation, Pearson coefficient, two tailed test of significant. Results were compared as mean and standard deviation. *P* value was considered significant when it is<0.05.

Quality control: All samples were analyzed as duplicate analysis and the average of each two readings was obtained for quality control purposes.Control sera purchased with reagent kits was used and applied with each run.

RESULTS

In this study there was an elevatedcholesterol (4.88±1.55mmol/L), triglycerides (2.2±0.66mmol/L), LDL (3.1±1.76mmol/L), ApoB (1.48±0.6g/L),and HbA_{1C} (10.4±5.7%), and reduced HDL (1.15±0.36mmol/L),and ApoA (1.62±0.1g/L) mean valuesin all groups when compared with control subjects, table 1. Diabetic patients in all groups were having HbA_{1C}>9%, figure, 1.

Mean values ofcholesterol,triglycerides, LDL, HDL, ApoB, ApoAand $HbA_{1C}$of diabetic patients were found non-significant when compared with controls(*P* values were 0.340, 0.802, 0.489, 0.812, 0.342, 0.490 and 0.840), respectively, Table 1.

When mean values were compared between groups, patients ingroup A were having the highest HbA_{1C} level (11.2%). Also they were having mean value of cholesterol less than group B and increased mean value than group C (4.7mmol/L). However, this group have the lowesttriglycerides mean value (2mmol/L). Patients in group C were having the lowest cholesterol and the lowest ApoB mean values (4.2mmol/L, 1.28g/L, respectively), table 2. However they were having high ApoA mean values (1.76mmol/L) when compared with other groups, Table 2. The frequencies of parameters among diabetic patients are listed in Table 3.

All parameters were correlated using Bivariate correlation, Pearson coefficient, two tailed test of significant. Correlations were outlined in tables 4, and 5(for all diabetic patients, and diabetic patients group B), respectively.

Table 1: Means ± standard deviations of parameters of diabetic patients and controls

	Diabetic Patients (n=163)	Controls (n=100)	*P* value
Age (years)	56..03±13	55.2±12.2	0.619
HbA_{1C} %	10.4±4.5	4.3± 0.7	0.840
Cholesterol (mmol/L)	4.88±1.55	4.11±0.82	0.340
Triglycerides (mmol/L)	2.2±0.66	1.16±0.55	0.802
LDL (mmol/L)	3.1±1.76	1.18±0.47	0.489
HDL (mmol/L)	1.15±0.36	1.93±0.95	0.812
ApoB g(/L)	1.48±0.6	1.34±0.12	0.342
ApoA (g/L)	1.62±0.1	1.75±0.23	0.490

Table 2: Means ± standard deviations of parametersamong groups of diabetic patients

	Group A (n= 35)	Group B (n= 113)	Group C (n= 14)
Age (year)	47.7±14.3	58.8±10.4	55.7±14.4
Duration (year)	10.7±6.3	10±5.2	12.9±7.8
HbA_{1C}%	11.2±5.4	10.1±4.5	10.4±4.6
Cholesterol (mmol/L)	4.7±1.6	4.9±1.5	4.2±0.9
Triglyceride (mmol/L)	2.0±0.56	2.2±0.7	2.22±0.12
LDL (mmol/L)	2.85±1.6	2.98±1.22	2.93±1.22
HDL (mmol/L)	1.17±0.35	1.12±0.35	1.14±12
ApoB (g/L)	1.46±0.74	1.45±0.58	1.28±0.46
ApoA (g/L)	1.64±0.47	1.70±0.71	1.76±0.48

Table 3: Frequencies of parameters among diabetic patients and their groups

	Percentages			
	All diabetics (n=163)	Group A (n=35)	Group B (n=113)	GroupC(n=14)
Cholesterol				
≥ 3.8mmol/L	75%	68%	78%	64%
≥ 5.2mmol/L	34%	26%	38%	38%
Triglycerides				
≥ 1.7mmol/L	83%	80%	84%	85%
≥2.25mmol/L	55%	54%	57%	46%
LDL				
≥ 2.6mmol/L	66%	48%	58%	57%
≥3.9mmol/L	17%	15%	20%	15%
ApoB				
≥ 1.0g/L	77%	71%	80%	65%
≥1.5g/L	37%	37%	39%	35%
HDL				
≤1.07mmol/L	43%	32%	45%	50%
≤0.80mmol/L	17%	20%	17%	7%
ApoA				
≤1.5g/L	33%	37%	37%	23%
≤1.0g//L	14%	9%	16%	14%
HbA_{1C}				
≥6%	81%	91%	92%	86%
≥ 9%	47%	51%	48%	43%

Table 4: Correlation of parameters of diabetic patients in all groups (n=163)

		Cholesterol	LDL	ApoB	HDL	ApoA	HbA_{1C}	Triglycerides
Cholesterol	Correlation	1	.247**	.353**	.274**	.156*	.178*	-.056-
	Significance		.002	.000	.000	.046	.023	.474
LDL	Correlation	.247**	1	.387**	.118	-.095-	.160*	.041
	Significance	.002		.000	.132	.229	.041	.607
ApoB	Correlation	.353**	.387**	1	.087	.027	-.096-	-.068-
	Significance	.000	.000		.271	.730	.224	.390
HDL	Correlation	.274**	.118	.087	1	.227**	-.065-	-.098-
	Significance	.000	.132	.271		.004	.413	.215
ApoA	Correlation	.156*	-.095-	.027	.227**	1	-.047-	-.158-*
	Significance	.046	.229	.730	.004		.550	.043
HbA_{1C}	Correlation	.178*	.160*	-.096-	-.065-	-.047-	1	.064
	Significance	.023	.041	.224	.413	.550		.418
Triglycerides	Correlation	-.056-	.041	-.068-	-.098-	-.158-*	.064	1
	Significance	.474	.607	.390	.215	.043	.418	

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Table 5:Correlation ofparameters of diabetic patients treated with hypoglycemicagents, group B (n=113)

		cholesterol	LDL	ApoB	HDL	ApoA	HbA_{1C}	Triglycerides
cholesterol	Correlation	1	.363**	.367**	.211*	.212*	.190*	.002
	Significance		.000	.000	.025	.024	.044	.987
LDL	Correlation	.363**	1	.437**	.151	.059	.246**	.135
	Significance	.000		.000	.110	.538	.009	.156
ApoB	Correlation	.367**	.437**	1	.095	.083	-.058-	.086
	Significance	.000	.000		.316	.381	.545	.368
HDL	Correlation	.211*	.151	.095	1	.304**	-.169-	-.190-*
	Significance	.025	.110	.316		.001	.073	.045
ApoA	Correlation	.212*	.059	.083	.304**	1	-.015-	-.060-
	Significance	.024	.538	.381	.001		.876	.532
HbA_{1C}	Correlation	.190*	.246**	-.058-	-.169-	-.015-	1	.122
	Significance	.044	.009	.545	.073	.876		.201
Triglycerides	Correlation	.002	.135	.086	-.190-*	-.060-	.122	1
	Significance	.987	.156	.368	.045	.532	.201	

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

DISSCUSSION

Diabetic patients in this study were having HbA_{1C}mean value >9%. In this study 47% of diabetic patients were having HbA_{1C}>9%. Our results to some extent weresimilar to results of study conducted by Khatab, *et al*. in 2010,[10] in Jordanian population. Diabetic patients were having $HbA_{1C}\geq7\%$.[10]. She and her colleague reported that the glycosylated hemoglobin level vary among populations.[10] It was ≥8% in Kuwaiti diabetics. However,in Pakistani, and in United Kingdom populationsthe HbA_{1C} level in types 2 diabetics was >7.5%.[10] From our results 91% of the diabetic patients theirs HbA_{1C} level >6%. In the literature, the level of HbA_{1C} ≥6.0% was associated with increased risk of diabetic complications.[11]. The development of diabetic complications was associated with the level of glycemic control, that is to sayHbA_{1C} level.[12]. Nearly half of the diabetic patient in all groups have HbA_{1C}>9%.So that patients in this study were at high risk of diabetic complication.

It is reported that, patients withHbA_{1C}>7% had higher values of cholesterol and LDL when compared with patients with HbA_{1C}<7%.[13] These findings to some extentsimilar to ourresults, because our patients were having HbA_{1C} mean level> 9% and elevated cholesterol and LDLmean levels.One third of our patients have cholesterol level exceed 5.0mmol/L, and ≥15% of the diabetic patients in all groups have LDL level ≥3.9mmol/L.

In this study the diabeticpatients had high triglycerides mean levels (>2mmol/L).However, greater than 46% of the diabetic patients in all groups (nearly half of the patients) their triglycerides levels were ≥2.25mmol/L. Ahmed, and his colleague in 2008,[14]found that 78% of their study population type 2 diabetics were having high triglycerides level.It is reported that lipid abnormalities in type2 diabetes were characterized by high triglycerides concentration.[7]

Dyslipidemia is one of the major risk factors for cardiovascular disease in diabetes mellitus.[15]The characteristic features of diabetic dyslipidemia are high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles. [15]

In this study the diabetic patients were having high cholesterol mean level in all groups. Our results differed from results in the literature, where normal total cholesterol concentrations were reported in diabetic patients.[7]

Our patients were having increased levels of triglycerides and cholesterol mean levels. Greater than 80% of patients in all groups their triglycerides levelswere>1.7mmol/L. However, 60% of the diabetics in all groups have cholesterol level>3.8mmol/L. Patients in this study must lower these levels to reduce the risk of diabetic complications. American Diabetes Association guidelines for diabeticdyslipidemia, and the Australian guidelines recommendlowering of triglycerides to <1.5mmol/L in high risk diabetic individuals.[3] The desirable level of triglycerides is <1.95mmol/L.[15]

In this study there were high LDL and low HDL mean levels in serum of diabetic patients.Unlike our finding Ahmed, *et al* in 2008,[14] concluded that HDL level was normal in type 2 diabetic patients with dyslipidemia. [14]

In this study HDL level ≤1.07mmol/L was found in more than one third of diabetic patientsin all groups. However, in groups A and B, 20% and 17%, andin group C, 7% of patients were having HDL level less than 0.8mmol/L.Raising plasma HDL to a level >1.2mmol/L are desirable in high-risk individuals, as it was recommendedby the American Diabetes Association (ADA)

guidelines.[3] Lipid management has been considered as an effective approach to reduce rissks in diabetic patients, including reduced HDL.[16] A low plasma concentration of HDL constitutes one of the characteristic lipoprotein abnormalities in type2 diabetes.[17]

From our findings more than 46% of diabetic patients in all groups have LDL level greater than 2.6mmol/L. Findings in this study indicated the need for therapeutic attention for diabetic patients.Current guideline treatment were needed to reduce LDL level in diabetic patients.[18] Shen,[5] in 2007, wrote that the abnormalities in the metabolism of LDL or HDL in diabetic patients often require pharmacological intervention.[5] It is recommended that LDL level of diabetic patients should be kept at less than 1.81mmol/L to reduce coronary artery disease and cardiovascular risks.[15]

Although their HbA_{1C} mean values were greater than other groups, group (A) showed the lowest triglycerides andhigh levels of HDL when these values were compared between groups. These findings indicated that patients in group (A) were at poor glycemic control and having better lipids profile thanother groups. Patients on insulin therapyin this study were neededgood control of glycemic status to prevent the developing of diabetic complications.

HbA_{1C} is used as a screening test because it is used to define treatment targets in diabetes, and it predicts complications of diabetes.[11] HbA_{1C} in diabetic patients should be maintained at 6.5% or less. The lifestyle intervention should be reinforced at every physician visit, and HbA_{1C} should be monitored every three months until it dropped to <7.0% and then it is better to be investigated every six months.[19] The adjustments in intervention should be made if the HbA_{1C} level is 7.0% or higher.[19] The $HbA_{1C}$of diabetic patients in all groups needed to be adjusted androutinely monitored because the level exceeded 7.0%. Although therapeutic management for diabetic patients varies among groups, they were at same distance of increased risk of diabetic complications.Glycemic control and treatment of dyslipidemia including dietary style, practicing of exercise and using of lipids lowering drugsreduce the development and progression of diabetic complications. [15]

The availability of multiple lipid-lowering drugs and supplements provides new opportunities for patients to achieve target lipid levels. However, the variety of therapeutic options poses a challenge in the prioritization of drug therapy.[15]Hypolipidemic treatment leads to the significant lowering of cardiovascular risk, however despite treatment cardiovascular risk remains still very high. [20] In this study, types of medications of all subjected groups were associated with lipids and HbA_{1C} increased levels. These findings may be due to lifestyle of subjected patients. Also in Sudan exercise was not routinely practiced, especially for diabetics. Depending on antidiabetic medications only was not enough to treat diabetic patients, lipids lowering agents were also needed.

CONCLUSIONS

The management of dyslipidemiain diabetic patients should be based on patients' predominant phenotypic feature and include therapeutic agents with a proven ability to reduce cardiovascular disease events.Diabetic patients in this study were at increased risk of cardiovascular disease associated with dyslipidemia and hyperglycemia. The assessment of lipid profile in serum of diabetic patients using insulin and/or oral hypoglycemic agents should be encountered to reduce the risk of fat gain at diabetic patients. And to insure that diabetic patients were not at risk of cardiovascular complications.Although

the decision to initiate drug therapy must be individualized, patients with diabetes mellitus who are considered to be at high risk for cardiovasculardisease events are in need oflipids lowering therapy, not only antidiabetic agents.

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