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Original Research Article

Relationship between Serum Lipoprotein Ratios and Insulin Resistance in Iraqi Women with Type II DM

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Abstract

Type 2 diabetes confers an increased morbidity and mortality dueto macrovascular complicationssuch as CVDfor which dyslipidemia is themajor contributor. This study was designed toexplore the role of non-HDLcandlipoprotein ratios as CVD riskmarker in diabetic population. It was acase –control study , 68 female uncontrolled ($HbA_{1c} \geq 6.5$) diabetic were selected, 34 were diabetic who were treatment(Goup A) and 34 werediabetic without treatment (Group B)and 34 were non-diabetic subjects as control group . The lipidprofile including TC, TG and HDLc were measured and calculation of lipoprotein ratios.Lipoprotein ratios were significantly higher in group A, Non-HDL($P<0.001$), TC/HDL and TG/HDL($P<0.01$), LDL/HDL($P<0.05$) In group B; Non-HDLc($P<0.01$), TC/HDL, TG/HDL and LDL/HDL($P<0.05$) in contrast tocontrols. There is significantly positive correlation of TG/HDLc, TC/HDLc, LDL/HDLc and Non-HDLc with HOMA-IR in group A and in group B. Lipoprotein ratio provide a simple means of identifying insulin resistance which could be used as a possible risk factor ofCVD in uncontrolledtype 2 diabetic.

Key words: Type II diabetes mellitus, Triglyceride, Total cholesterol,lipoproteins, insulin resistance, cardiovascular disease.

الخلاصة

مرض السكري النوع الثاني يضفي زيادة على معدل الاعتلال والوفيات بسبب مضاعفات الشرايين الدموية الكبيرة مثل أمراض القلب حيث أن اضطراب الدهون هو المساهم الرئيسي لذلك.صممت هذه الدراسة للتناول دور الكولسترول غير الحميد ونسب البروتينات الدهنية كعلامة خطر لمرض القلب الوعائي في مرضى السكري. شملت الدراسة ٦٨ امرأة مصابة بالسكري وغير مسيطرة عليه, مجموعة أ تشمل٣٤ مريضةمع علاج, ومجموعة ب تشمل ٣٤مريضة بدون علاج, امامجموعة السيطرة تضمنت ٣٤ امرأة بدون سكري. تم قياس الدهون والدهون البر وتينة وحساب النسب. وأظهرت الدراسة زيادة ملحوظة في الكولسترول غير الحميد (Non−HDL($p < 0.001$) ,TC/HDLو TG/HDL($p < 0.01$), LDL/HDL($p < 0.05$) في مرضى السكري مجموعة أ عند مقارنتها مع مجموعة السيطرة.

أظهرت الدراسة زيادة ملحوظة في(Non−HDL($p < 0.01$) ,TC/HDLو (TG/HDL($p < 0.05$) ,LDL/HDL($p < 0.05$) في مرضى السكري مجموعة ب عند مقارنتها مع مجموعة السيطرة.وأظهرت ارتباط معنوي موجب لكل منTC/HDL, LDL/HDL ,,TG/HDL, Non− HDL مع ومقاومة الأنسولين في مجموعة أ ومجموعة ب. نسب البروتينات الدهنية قد تعطي تشخيص لمقاومة الأنسولين ويمكن استخدامها للتنبؤ بمخاطر امرض القلب الوعائية في مرضى السكري النوع الثاني غير المسيطر عليه.

الكلمات المفتاحية: داء السكري النوع الثاني, الكليسيريدات الثلاثية, الكولسترول الكلي, البروتينات الدهنية, مقاومة الأنسولين, إمراض القلب والأوعية الدموية.

Introduction

Type II diabeteshas become aworldwide epidemic and the number of cases is predicted to increase rapidly overthenext 10 years[1]. Patients withtype 2 diabetes are at greater riskof stroke and peripheral vascular disease, there are more likely todevelop CVD than patients without diabetes by two to four time[2].In addition, or perhaps as partof this high riskfor CVD, patients with diabetesoften have a dyslipidemic feature[3] or lipid abnormalities due to insulin resistance or insulin deficiency affect key enzymes and pathways in lipid metabolism[4].

Hemoglobin A1c (HbA1c) is the attachment of a glucose molecule to the N-terminal amino acid of the hemoglobin molecule in non-enzymatic reaction. the HbA1c level reflects the mean glucose concentration over the previous period (8-12 weeks). HbA_{1c} is assessed glycemic status [5]. Persistent hyperglycemic patients accelerates the formation of advanced glycation end products (AGEs) which modifies extracellular matrix molecules and causes cellular dysfunction, that lead to inflammatory cytokines were released and causes vascular pathology[6].

Dyslipidemia encompasses changes inHigh density lipoprotein cholesterol (HDLc), the size and density of Low density lipoprotein cholesterol (LDLc), very low density lipoprotein cholesterol (VLDLc) and triglyceride level[7]. Although levels of LDLc are the primary focus of dyslipidemia screening, where in people with diabetes since they produce highly atherogenic VLDLc and IDLc lipoproteins as well as small dense atherogenic LDLc particles, in spite of normal values of LDLc. So, relying on LDLc targets alone can be misleading in DM patients[8], therefore, LDLc is not only atherogenic lipoprotein but apoprotein-B represents the total numberof atherogenic particles (chylomicron remnants, VLDLc, IDLc and LDLc) [9].Directly can be assessed by measuring Apo-B serum level, but its measurement is not widely available in commercial laboratories.TGRLPs may be partly depleted of their triglyceride content In the presence of hypertriglyceridemia and become enriched with cholesterol from LDLc. The modified remnant lipoproteins which produce are believed to be highly atherogenic because of their small size, high cholesterol content, and increased residence time in plasma[10]. Smaller LDL particles more easily penetrate into the arterial intima exhibit increased binding to arterial wall proteoglycans [11] and are more prone to oxidative stress. These small and dense LDL particles are lower binding affinity for the LDL receptor, so have a prolonged plasma half-life. The presence of small, dense LDL particles in plasma is therefore considered pro-atherogenic[12].

The amount of cholesterol in both the TG-rich lipoproteins and LDL represented by Non-HDLc[13], measurement of non-HDL cholesterol is accepted as a surrogate marker for apo B in routine clinical practice, and considered more practical, reliable, and inexpensive[10]. Non-HDL cholesterol is more significant than LDLc in the presence of postprandial hypertriglyceridemia[14].

Insulin resistance is oneof the pathogenic markers of diabetes mellitus[15], which associated with atherogenic lipoprotienphenotype that increase the risk of CVD complications. Several atherogenic indices including (TC/HDLc, TG/HDLc, LDL/HDLc) are calculated from measured values of plasma lipids. The association between TG, TC, LDL and HDL cholesterol in this ratios reflect the balance between risk and protective lipoproteins forces[16].

Obesity may be responsiblefor high level of the remnant cholesterol, high TG levels and decline inHDLc level, as a consequent result of high BMI values[17]. In the presence of the hypertriglyceridemia it is recommended to measure non-HDLc levels as additional tool to assess next to LDLc levels.This is particularlyvital in

diabetic patients, in whom LDL levels may not be significantly increased[18].

Materials and Methods

Subjects

This study was performed in the laboratories of Biochemistry Department in faculty of Medicine/ University of Babylon. The present study was performed on 34 patients of type 2 diabetic with oral hypoglycemic agent (glibenclamide) and 34 patients without treatment.All uncontrolled diabetics ($HbA_{1c} \geq 6.5\%$)were selected from the patients attending the Diabetic Consultation Unit at Merjan Teaching Hospital in Hilla city. Apparently healthy subject include 34 control group were collected from relatives and medical staff.All groups were taking gradient values of body mass index (BMI).

The patient with type 1 Diabetes Mellitus, male, infection diabetic foot, chronic kidney disease, pregnant women, smokers, alcoholicswere excluded from the current study.

Sample Collection

Venous blood samples were drawn from patients and control in fasting state, (5 mL) of blood obtained by venipuncture using disposable syringe. 2 ml of the blood pushed slowly into EDTA tube for HbA_{1c}estimation, the remainder pushed slowly into gel tubes for other tests. Blood in gel tube was allowed to clot for 10-15minutes at 37˚C and then centrifuged at 2000Xgfor approximately 10-15 minutes, then the sera were used for analysis.

Methods

Blood glycohemoglobin HbA_{1c} assay by Stanbio Glycohemoglobin (USA) kit.By Plasmatic spectrophotometric kit(France) are determined the concentration of Serum glucose. Serum insulin levels are determined by Monobind (USA) ELISA kit. By Biolabo SA spectrophotometric kit (France) determination of serum total cholesterol, TGs and HDL-cholesterol concentration. VLDLc and LDLc serum level was obtained by calculations. The Non-HDLc can be calculated as total cholesterol minus HDLc.

Insulin resistance was calculated by usingHomeostasisModel Assessment (HOMA) [19].

Statistical analysis

The data was analysed using Software Pachage for Social Science (SPSS-18 version). The data was presented as a mean ± standard deviation (SD), the differences between each groupof patientsalone and control group in means ± SD were compared using t- test. The associations between insulin level and insulin resistance with lipoprotein ratios were tested by using Pearson, s correlation coefficient.

Results

The characteristics of the present study groups are shown in table (1) which include age, body mass index (BMI), waist circumference , and duration of disease.The baseline characteristic of diabetic patients included in the study had poor glycemic control, The mean difference of age between control and patients in groups A and B are statistically nonsignificant($p > 0.05$), and show significant increase in BMI ($p < 0.05$) and waist circumference ($p < 0.01$) in group A and B as compared to control subjects.

Table1: Comparison of demographic of type II diabetic patient and control group

Parameter		Patients		Control		p-value
		Mean±SD	Range	Mean±SD	Range	
No.	Group A	34		34		-
	Group B	34				
Age (year)	Group A	41.06±2.71	38-45	40.85±3.44	35-45	> 0.05
	Group B	42.13±2.13	39-45			> 0.05
BMI (kg/m^2)	Group A	28.19±4.84	19- 36	25.35±4.44	19-34.3	<0.05
	Group B	27.65±4.87	18.2-37			<0.05
Waist circumfer-ence(cm)	Group A	93.79±6.34	82-106	89.02±4.98	80-100	<0.01
	Group B	92.76±6.27	83-106			<0.01

In the present study results revealed increased significantlyin mean values of glucose, $HbA_{1c,}$ insulin, HOMA-IRof group A and group B, when compared to those of the control group which ($p < 0.001$), as described in table (2).

Table 2: Mean HbA_{1c} , Fasting Serum Glucose, Insulin, HOMA-IR in type 2 diabetic patients and control group

Parameter		Patients		Control		p-value
		Mean±SD	Range	Mean±SD	Range	
Glucose (mmol/l)	Group A	7.42±1.08	6.4 -13	4.64±0.73	3.3-5.9	< 0.001
	Group B	9.22±1.9	7 – 13			< 0.001
HbA_{1c} %	Group A	9.22±1.13	7.3 -12.6	4.81±0.57	3.5-5.8	< 0.001
	Group B	8.25±1.25	6.9 -12			< 0.001
Insulin(µU/ ml)	Group A	10.7±3.46	5.4-20	7.85±2.39	0.94-13	< 0.001
	Group B	10.4±3.61	4.8-20			< 0.001
HOMA-IR	Group A	4.36±1.51	2.4-8	1.64±0.67	3.47-0.21	< 0.001
	Group B	3.4±1.23	1.68-6.66			< 0.001

In group A was found that total cholesterol (TC), TG, and VLDL cconcentration were significantly higher ($p < 0.001$) and significant increase ($p < 0.01$) in LDLc, while HDLc was significantly lower ($p < 0.05$) in sera of patients when compared to those of the control subjects. Also, in this group show significant increase ($p < 0.001$) in non-HDL, TC/HDL and TG/HDL were significant increase ($p<0.01$), LDL/HDL was significantly ($p<0.05$) as compared to control subjects, as shown in table (3).

It was found that TC, TG, and VLDLc were significant increase ($p<0.01$), and LDLc was significantly increased ($p<0.05$), While the HDLc concentration was found to be non-significantly decreased ($p > 0.05$). Andthe results showed significant increase($p < 0.01$) in non-HDL, TC/HDL, TG/HDL and LDL/HDL showe dsignificant increase ($p<0.05$) in group Bpatients as compared to subjects of control, as shown in table (3).

Table 3: Comparison of biochemical characteristics between two group of typeII diabetic patients with control group

Parameter	Patients			Control		p-value
		Mean±SD	Range	Mean±SD	Range	
TC (mmol/l)	Group A	4.98±0.73	3.2-6.2	4.25±0.59	2.6-5.2	<0.001
	Group B	4.75±0.71	2.8-6.1			<0.01
HDLc (mmol/l)	Group A	1.02±0.14	0.64-1.33	1.11±0.22	0.85-1.71	<0.05
	Group B	1.06±0.16	0.67-1.45			>0.05
TG (mmol/l)	Group A	1.92±0.43	0.9-3.5	1.52±0.31	0.87-2.1	<0.001
	Group B	1.79±0.48	1-3.4			<0.01
VLDLc (mmol/l)	Group A	0.86±0.2	0.4-1.57	2.46±0.62	0.54-3.4	<0.001
	Group B	0.81±0.22	0.45-1.53			<0.01
LDLc (mmol/l)	Group A	2.99±0.83	1.1-4.3	0.68±0.14	0.39-0.9	<0.01
	Group B	2.88±0.71	1.06-4.3			<0.05
Non–HDL	Group A	3.95±0.77	2.1-5.46	3.14±0.67	1.6-4.25	<0.001
	Group B	3.69±0.76	1.76-5.36			<0.01
TC/HDL	Group A	5.0±1.24	2.6-9.53	4.02±1.25	2.1-7.5	< 0.01
	Group B	4.65±1.18	2.5-8.24			<0.05
TG/HDL	Group A	1.87±0.65	1-3.75	1.43±0.46	0.62-0.6	<0.01
	Group B	1.74±0.58	0.62-3.4			<0.05
LDL/HDL	Group A	3.03±1.14	1.05-6.8	2.38±1.09	0.54-5.7	<0.05
	Group B	2.86±0.83	0.88-5.9			<0.05

In uncontrolled diabetic group A were observed a positive significantly correlated of TG/HDLc, TC/HDLc, LDL/HDLc and Non-HDLc with insulin level (r=0.424, p=0.01; r=0.399, p=0.02; r=0.353, p=0.04; r=0.377, p=0.02, respectively), and with HOMA-IR (r=0.474, P=0.002; r=0.437, p=0.02; r=0.379, p=0.02; r=0.392, p=0.02, respectively)Table (4), Figure (1).

Also in group B has significant positive correlation of TG/HDLc, TC/HDLc, LDL/HDLc, Non-HDLc with insulin level (r=0.432, p=0.01; r=0.396, p=0.01; r=0.339, p 0.02; r=0.350, p=0.04, respectively), and with HOMA-IR (r=0.435,p=0.01;r=0.436, p=0.01; r=0.399, p=0.04; r=0.347, p=0.04, respectively), Table(4), Figures (2).

Table 4: Correlation of lipoprotein ratios with insulin level and insulin resistanse (HOMA-IR) in T2DM patients

Parameter	Patients	Insulin level		Insulin resistance HOMA-IR	
		r	p-value	R	p-value
TG/HDLc	Group A	0.424	0.01	0.474	0.002
	Group B	0.432	0.01	0.435	0.01
TC/HDLc	Group A	0.399	0.02	0.437	0.01
	Group B	0.396	0.01	0.436	0.01
LDL/HDLc	Group A	0.353	0.04	0.379	0.02
	Group B	0.339	0.02	0.399	0.04
Non-HDLc	Group A	0.377	0.02	0.392	0.02
	Group B	0.350	0.04	0.347	0.04

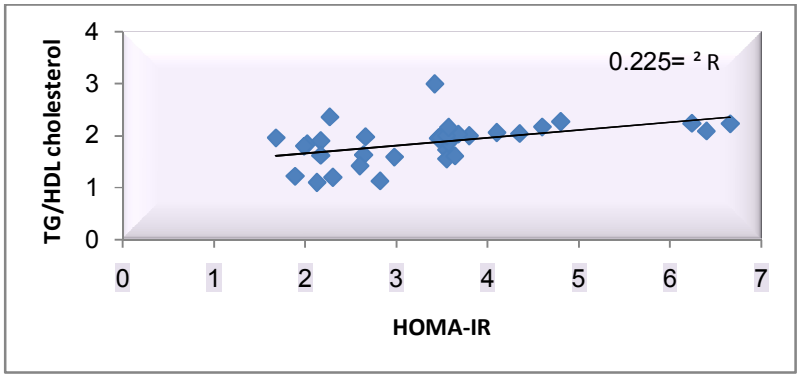

Figure1: Correlation of serum TG/HDLc with insulin resistance in Group A, r= 0.474, p= 0.002

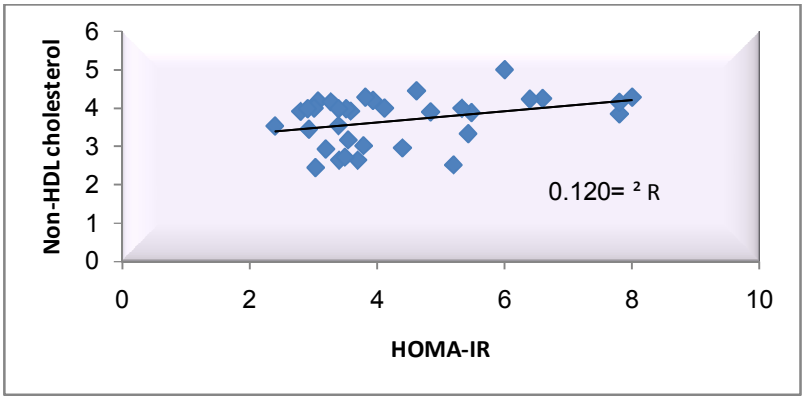

Figure2: Correlation of serum Non-HDLc with insulin resistance in Group B, r= 0.347, p=0.04

Discussion

Type II diabetes mellitus is a chronic degenerative disease, in treating diabetes should be prevent hyperglycemia from causing damage to organs. But when glucose fluctuation occur all thetime, hyperglycemia and hyperinsulinemia both of them can impair insulin sensitivity and body became more resistant to insulin [20].

Relative risk for coronary heart disease give high level of risk factor of blood pressure and atherogenic dyslipidemia in diabetic female than in diabetic male[21]. Type 2 diabetes patients often have raised triglycerides and low HDLc. The ratios calculated from the lipid and lipoproteins may be useful to known the status of the CVD complication in type 2 DM[16]. In diabetic subjects, insulin fails to suppress synthesis of VLDL particles. Insulin resistance in the type 2 DM is increased lipolysis of adipocytes leading to increased nonesterified fatty acid (NEFA) secretion. Increased delivery of NEFA to the liver also increases gluconeogenesis, as well as production of lipid,and decreased clearance of very low-density lipoprotein (VLDL) particales [22].

Insulin resistance isoneof the pathogenic factor for type 2 diabetes and is associated with cardiovascular disease riskstates[23], some studies suggesting insulin resistance can predict CVD independently of other risk factors, including hypertension, visceral obesity orlipid disorders [24,25]. Metabolic insulin resistance is characherized by pathway specific impairment in phosphatidylinositol 3-kinase (PI3-K) dependent signaling induced by proinflammatory cytokines, which in the endothelium may cause imbalance between production of nitric oxide (NO) and glucose uptake, resulting in insulin resistance and endothelial dysfunction[26]

The type 2 diabetic patients are at increased risk of cardiovascular diseases which may be due to the increased levelsof lipids and lipoproteins or it may be seen dueto increased insulin resistance[27]. Also hyperglycemia inhibits production of NO, lead to elevated free fatty acids (FFA) level due to impairment in insulin antilipolytic effect, and increases the production of reactive oxygen species, contributing to the reduction of NO synthesis [28]. Hyperglycemia also increases the production of endothelin-1[29]. In addition diabetes lead to abnormal vascular smooth muscle cell function due to impaired NO-mediated vasodilation, increased levels of endothelin-1, angiotension II, and plasminogen activator inhibitor-1[30]. Therefore, in hyperglycemia the PI3-kinase pathway and the Shc/Ras/MAP-kinase pathway even is down regulated[26].

Theresults of the present study are in consistent with Tangvarasittichai *et al*.[31], and Momin AA. *et al*.[15] showed the correlation between lipoprotein ratios with insulin resistance and canbe used as the marker of insulin resistance and cardiovascular disease risk in diabetic patients.

Conclusion

Our study showed that TC/HDLc, TG/HDLc, LDL/HDLc, and non-HDLc were significantly correlated with insulin resistance in diabetic patients, and does not mean that insulin resistance is a predictor of CVD, but, the combination of these evaluated markers may be important in identifying patients with risk of cardiovascular disease. The lipoprotein ratios are a simple, low cost, and easily available tool to the clinicians to get an idea about suspected CVD risk, and help them in treatment modification.

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