Comparison of lipid profiles and lipoprotein (a) levels in patients with type 2 diabetes mellitus during oral hypoglycemic or insulin therapy

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ABSTRACT

Objective: The aim of this study is to compare lipid and lipoprotein (a) profiles in patients with type 2 diabetes mellitus (DM) on insulin and oral hypoglycemic therapy.

Methods: The study took place in the Department of Physiology, Army Medical College, Rawalpindi, Pakistan, during 2002. Ninety-seven type 2 DM patients participated in the study. We divided the patients according to the type of treatment into sulphonylurea (n=40), sulphonylurea plus metformin (n=33) and insulin (n=24) therapy groups as well as 40 healthy subjects served as controls. Fasting blood samples were analyzed for lipoprotein (a) [Lp (a)], total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), glucose, glycosylated hemoglobin (HbA_{1c}) and insulin.

Results: Different groups of diabetic patients showed elevated fasting blood glucose (FPG) levels ($p<0.0001$ for all), HbA_{1c} ($p<0.0001$ for all) compared with controls. Meanwhile, fasting insulin levels were elevated only in insulin treated group compared with oral hypoglycemic treated groups and controls ($p<0.0001$ for all). Patients on sulphonylurea and on sulphonylurea plus metformin groups showed significantly elevated TC ($p<0.001$, $p<0.0001$), TG ($p<0.001$, $p<0.01$), LDL-C ($p<0.01$, $p<0.001$) and LDL-C/HDL-C ($p<0.0001$, $p<0.0001$) compared with controls. Insulin therapy group showed significantly decreased TC, TG, LDL-C, LDL-C/HDL-C levels compared with sulphonylurea and sulphonylurea plus metformin treated groups, however, no significant difference was noted in the levels of above mentioned parameters and controls. Meanwhile, HDL-C levels were significantly lower in all diabetic groups compared with controls and were higher in insulin treated group compared with sulphonylurea plus metformin therapy group ($p<0.05$). Lipoprotein (a) levels were significantly higher in different diabetic groups compared with controls. While there was a non-significant difference in Lp (a) levels between different diabetic groups.

Conclusions: Patients with type 2 DM who are being treated on insulin have a better lipid profile (TC, HDL-C, LDL-C, TG) compared with those patients on oral hypoglycemic agents. Meanwhile, Lp (a) levels were raised in all diabetic patients and seem not to be affected either by insulin or by oral hypoglycemic treatment.

Saudi Med J 2006; Vol. 27 (2): 174-180

The progressive nature of type 2 diabetes mellitus (DM) makes choice and course of hypoglycemic treatment a challenge for researchers and physicians.[1] The dyslipidemic triad of high levels of low-density

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Received 19th July 2005. Accepted for publication in final form 12th December 2005.

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lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and lower levels of high-density lipoprotein cholesterol (HDL-C) leads to accelerated atherogenesis in DM.[2] It has been found that LDL-C lowering therapy reduces the risk for subsequent coronary events even in patients with advanced atherosclerotic disease.[3,4] In another study, small dense LDL particles have been suggested to be associated with an increased risk of coronary atherosclerotic diseases (CAD).[5] Strict metabolic control is recommended to reduce the risk of diabetic morbidity and premature mortality.[6] The United Kingdom Prospective Diabetic Study (UKPDS) has conclusively demonstrated that improved blood glucose control in type 2 diabetics reduced micro vascular complications by 25%.[7] However, the true pathogenic mechanism that leads to accelerated atherogenesis in DM is still not known. The Lp (a) may be one of the links to accelerated atherogenesis in DM patients, as its raised levels are associated with premature CAD.[8] It is structurally similar to plasminogen and competes with it for its receptors on endothelial cells and fibrin; thus, decreasing its fibrinolytic activity by decreasing formation of plasmin. This leads to a procoagulant state in the body.[9] Treatment progresses most of the time in a step-wise fashion as the insulin secreting capacity of the beta-cells decreases.[10] There are a number of oral hypoglycemic drugs (OHDs) to choose from, but the efficacy of all is influenced by beta-cell function.[11] Eventual progression to insulin therapy is inevitable after beta-cell failure and it is important that this is not delayed.[12] A subset of patients, called primary failures, who may be approximately 30% for sulphonylurea or <10% for biguanides, will not initially respond to oral agent therapy. Another set of patients, secondary failures, will initially achieve acceptable control of their diabetes with oral agent monotherapy which may not be effective with passage of time.[13] Insulin is currently used in approximately 30% of patients with type 2 diabetes. Apart from temporary use in acute conditions the indication for insulin therapy in type 2 DM is that adequate glycemic control can no longer be maintained with diet and oral antihyperglycemic agents.[14] Some workers advocate early use of insulin instead of oral drugs.[15] The European Diabetes Policy Group recommends oral agents before insulin and continuation of oral therapy when insulin is started. The UKPDS showed no advantages of insulin as initial pharmacotherapy.[16] Whether used alone or in combination, oral therapies become less effective over time and are unable to keep glycosylated hemoglobin (HbA_{1c}) in the recommended target range (HbA_{1c} < 7%).[17]

The aim of the present study was to compare lipid and Lp (a) profile in patients with type 2 DM treated by oral hypoglycemic agents (sulphonylurea or sulphonylurea plus metformin) or by insulin.

Methods. This study was carried out at the Department of Physiology, Army Medical College and Diabetes Clinic of Armed Forces Institute of Pathology, Rawalpindi, Pakistan during 2002. This study was approved by the Army Medical College Ethics Review Board and informed written consent was obtained from each participant. The study included 97 patients (49 males, 48 females) with a mean ± SEM age of 50.79 ± 1.19 suffering from type 2 DM and 40 age, gender and body mass index (BMI) matched healthy individuals (23 males and 17 females) with a mean ± SEM age of 44.67 ± 1.13 years) selected from the staff members of Army Medical College served as controls. The control subjects had normal lipid profile and fasting blood glucose levels <6.1 mmol/l (110 mg/dl). The patients participating in the study were diagnosed cases of type 2 DM on different modes of hypoglycemic therapy. Patients were divided into 3 groups according to their treatment types: sulphonylurea, sulphonylurea plus metformin and insulin therapy groups. Patients were using second generation sulfonylureas; glyburide (1.5-12 mg/day) and glimepiride (1-8 mg/day) and Biguanide Metformin (500-2000 mg/day). Those who were on insulin were using Neutral Protamine Hagedorn 70/30 twice daily. Patients using insulin were secondary failure patients. In all patients, hypoglycemic treatment program had been stable for at least 3 months. All groups were matched in gender, age, BMI, duration of disease and dietary habits. Clinical informations including date of diagnosis of DM and medical history were obtained by chart review and patients interview. In history of medication, name of drug, duration of treatment, dose of drug and regularity of treatment were recorded. Exclusion criteria included metabolic disorders, diabetic ketoacidosis, non ketotic hyperosmolar diabetes, history of familial hypercholesterolemia, nephrotic syndrome, acute or chronic renal failure, thyroid disorders, acute infections, stroke, ischemic or coronary heart disease or hypertension, irregularity of diabetic treatment, lipid lowering agents, oral contraceptives or steroids. No patients were taking other medications that may have influence on cardiovascular risk parameters

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded in sitting position in the right arm in mm Hg, by a mercury sphygmomanometer. Overnight fasting blood samples were taken from the antecubital vein, 5 ml blood

Table 1 - Demographic and clinical characteristics of different studied groups.

Variants	Control (n = 40)	Sulphonylurea (n = 40)	Sulphonylurea and metformin (n = 33)	Insulin (n = 24)
Gender (M/F)	23/17	21/19	16/17	12/12
Age (years)	44.67 ±1.13	52.23 ± 1.47	52.63 ±1.73	42.58 ± 3.66
BMI (kg/ m^2)	24.02 ± 0.38	26.49 ± 0.71	27.66 ± 0.81	25.33 ±1.14
Duration of illness (years)		4.81 ± 0.49	7.38 ± 0.98	8.50 ± 1.60
				^2p< 0.01
SBP (mm Hg)	125.67 ± 1.53	145.67 ± 2.51	145.33 ± 2.12	139.17± 4.68
		^1p<0.0001	^1p<0.0001	^1p<0.0001
DBP (mm Hg)	77.83 ± 1.19	88 ±1.14	87.67 ± 1.39	85.42 ± 4.37
		^1p<0.0001	^1p<0.0001	^1p<0.0001
Fasting serum glucose (mmol/l)	5.07 ± 0.09	9.93 ± 0.53	10.48 ± 0.49	9.88 ± 1.16
		^1p<0.0001	^1p<0.0001	^1p<0.0001
HbA_{1c} (%)	4.81 ± 0.08	7.65 ± 0.29	7.80 ± 0.25	6.99 ± 0.51
		^1p<0.0001	^1p<0.0001	^1p<0.0001
Fasting serum insulin (uIU/ml)	8.99 ± 1.01	9.88 ± 0.95	9.66 ± 1.24	45.23 ± 13.14
		^1p>0.05	1p>0.05	^1p<0.0001
				^2p<0.0001
				^3p<0.0001

Data expressed as mean ± SEM, M - male, F - female, BMI - Body mass index, SBP - systolic blood pressure, DBP - diastolic blood pressure, HbA_{1c} - glycated hemoglobin, ^1p - significance versus control, ^2p- significance versus sulphonylurea therapy group. ^3p - significance versus sulphonylurea and metformin therapy group

was transferred to ethylene diamine tetra acetic acid (EDTA) added tubes for estimation of HbA_{1c} and 5 ml was collected in plain test tubes, centrifuged at 3000 rpm for 15 minutes and sera were aliquoted and then frozen at –70^{O}C. All the tests were run in duplicate and the average of the 2 readings was taken as the final result. Fasting blood glucose was assayed by glucose oxidase phenyl ampyrone method (GOD–PAP) (Linear Chemicals, Spain). Ion exchange resin separation method was used for estimation of HbA_{1c} (Stanbio Glycohemoglobin, USA). Fasting insulin levels were measured by Chemiluminescence procedure (Immulite system, Diagnostic Products Corporation, USA). The immulite system utilizes assay specific antibody coated plastic beads as the solid phase, in a specifically designed test unit. The test unit serves as the reaction vessel for the immune reaction, incubation, washing and signal development. Light emission from the chemiluminescent substrate, which reacts with the enzyme conjugate bound to the bead is proportional to the amount of insulin originally present in the sample. Total cholesterol (TC), HDL-C and LDL-C were estimated colorimetrically by cholesterol oxidase phenol ampyrone (CHOD-PAP) method (Linear Chemicals, Spain and Merck Systems, USA). Glycerol phosphate oxidase (GPO-PAP), an enzymatic colorimetric kit was used for serum triglycerides estimation (Linear Chemicals, Spain). Measured parameters were determined color metrically on a clinical chemistry analyzer Selectra 2 (Vital Scientific NV, Dieren, The Netherlands). Lp (a) was estimated by enzyme linked immunoabsorbent assay (ELISA) kits (Innogenetics Biotechnology for Health Care, Belgium).

Statistical Analysis. The data were analyzed by computer software program Statistical Package for Social Sciences (SPSS version 10, Chicago). Data were expressed as mean and standard error of mean (SEM). The tests applied for statistical analysis were one way analysis of variance (ANOVA), Bonferroni (Multiple comparisons) for comparison differences between studied groups and Spearman's correlation coefficient. A p<0.05 was considered as statistically significant.

Results. **Table 1** shows demographic data, clinical characteristics and glycemic status of the diabetic and control subjects. Both SBP and DBP were significantly higher in all diabetics as compared with control subjects (p<0.0001). Among different diabetic groups, there was no difference in both SBP and DBP. Fasting serum glucose levels and glycated hemoglobin levels were significantly elevated in all the diabetic groups compared with

Table 2 - Serum Lp (a) and lipid profile of control and DM Patients on different modes of treatment (Mean ± SEM).

Parameters	Control (n = 40)	Sulphonylurea (n = 40)	Sulphonylurea and metformin (n = 33)	Insulin (n = 24)
TC (mmol/l)	4.36 ± 0.11	5.12 ± 0.16 $^1p<0.001$ $^2p<0.05$	5.30 ± 0.06 $^1p<0.0001$ $^2p<0.01$	4.44 ± 0.32 $^1p>0.05$
TG (mmol/l)	1.35 ± 0.07	1.92 ± 0.14 $^1p<0.001$ $^2p<0.01$	2.17 ± 0.28 $^1p<0. 01$ $^2p<0.05$	1.25 ± 0.11 $^1p>0.05$
LDL -C (mmol/l)	2.72 ± 0.10	3.30 ± 0.15 $^1p<0.01$ $^2p>0.05$	3.46 ± 0.15 $^1p<0.001$ $^2p<0.05$	2.75 ± 0.31 $^1p>0.05$
HDL-C (mmol/l)	1.21 ± 0.03	0.98 ± 0.05 $^1p<0.0001$ $^2p>0.05$	0.90 ± 0.04 $^1p<0.0001$ $^2p<0.05$	1.04 ± 0.06 $^1p<0.001$
LDL-C/HDL-C	2.27 ± 0.09	3.86 ± 0.37 $^1p<0.0001$ $^2p>0.05$	4.19 ± 0.35 $^1p<0.0001$ $^2p<0.05$	2.76 ± 0.37 $^1p>0.05$
Lp (a) (mg/dl)	20.80 ± 3.54	56.81 ± 9.35 $^1p<0.001$ $^2p>0.05$	47.74 ± 9.07 $^1p<0.01$ $^2p>0.05$	41.29 ± 12.47 $^1p<0.05$

Data expressed as mean ± SEM, TC - total cholesterol; TG - triglyceride; LDL-C - low density lipoprotein cholesterol, HDL-C - high density lipoprotein cholesterol, Lp (a) - lipoprotein (a), ^1p - significance versus controls, ^2p - significance versus insulin group.

controls ($p<0.0001$ for all), meanwhile, there were no statistically significant differences in glycemic status between different diabetic groups. Patients on insulin therapy tended to have lower mean values of HbA_{1c} as compared to sulphonylurea or sulphonylurea and metformin therapy group albeit difference was non-significant ($p>0.05$). Fasting insulin levels were not significantly different between, either sulphonylurea or sulphonylurea plus metformin group compared with controls, meanwhile, in insulin therapy group, fasting serum insulin was significantly raised compared with other groups ($p<0.0001$ for all) (**Table 2**). Patients in sulphonylurea and sulphonylurea and metformin groups had significantly elevated TC ($p<0.001$, $p<0.0001$), TG ($p<0.001$, $p<0.01$), LDL-C ($p<0.01$, $p<0.001$) and LDL-C/HDL-C ($p<0.0001$, $p<0.0001$) compared with controls. Meanwhile, serum HDL-C levels were significantly lower in all diabetic groups compared with controls ($p<0.0001$). The difference in TC, TG, LDL-C and LDL-C/HDL-C between insulin group and control group was non significant ($p>0.05$). Serum TC ($p<0.05$) and TG $p<0.01$) levels were significantly lower in insulin group as compared with sulphonylurea. In sulphonylurea and metformin group, serum levels of TC, TG, LDL-C and LDL-C/HDL-C were significantly elevated ($p<0.01$, $p<0.05$, $p<0.05$, $p<0.05$), meanwhile, HDL-C levels were significantly decreased ($p<0.05$) compared with insulin therapy group. The Lp (a) levels were significantly higher in different diabetic groups as compared with controls. While there was a non-significant difference in Lp (a) levels between different diabetic groups. Patients on sulphonylurea therapy had higher mean levels of Lp (a) as compared with those receiving sulphonylurea and metformin therapy or insulin but the difference was non significant ($p>0.05$ for both).

Discussion. The major clinical objective in the management of DM is to control hyperglycemia and the long-term objective is to prevent microvascular and macro vascular complication glycemic control improves and may even normalize triglyceride and HDL-C levels in type 1 DM patients.[18] It is well known that blood glucose optimization influences lipoprotein metabolism positively in type 2 diabetic patients, but a complete normalization in lipoprotein concentration and composition is seldom obtained.[19] The positive effects of near normalization of glucose levels in DM have been shown in many clinical trials.[20-23] To achieve optimal outcomes in type 2 diabetics, clinical trial data suggest that near normal glycemic control should be targeted.[6]

Metformin acts primarily by decreasing hepatic glucose output, largely by inhibiting gluconeogenesis. It also induces weight loss, preferentially involving

adipose tissue.[24] In peripheral tissues metformin increases insulin-mediated glucose uptake and oxidative metabolism.[25] Metformin improves lipid levels also.[26] Sulphonylureas act by stimulating insulin secretion from the pancreas and augmenting glucose-stimulated insulin secretion. Some, such as glibenclamide and glimepiride, are long acting and have metabolites that are excreted renally. Others, such as gliclazide and glipizide, are shorter acting and do not have active metabolites.[27] Lipoprotein Lipase (LpL) is synthesized primarily by adipocytes and myocytes and is transferred to the luminal side of capillary endothelial cells, where it can interact with circulating triglyceride-rich lipoproteins such as VLDL and chylomicrons and converts lipoprotein triglycerides into free fatty acids. The LpL is stimulated by insulin therapy. Insulin inhibits the breakdown of fat in adipose tissue by inhibiting the intracellular lipase that hydrolyzes triglycerides to release fatty acids.[28] The LpL activity is low in patients with diabetes and is increased with insulin therapy.[29] The release of stored fatty acids from adipocytes requires conversion of stored triglyceride into fatty acids and monoglycerides that can be transferred across the plasma membrane of the cell. The primary enzyme that is responsible for this is hormone-sensitive lipase (HSSL). The HSSL is inhibited by insulin, which decreases phosphorylation of HSSL and its association with the stored lipid droplet.[30] A second regulatory process may be a direct effect of insulin on liver production of apo B and other proteins involved in degradation of circulating lipoproteins. In some studies, insulin directly increased degradation of newly synthesized apo B.[31]

The early institution of insulin therapy in type 2 DM patients have been recommended by many researchers,[12,15] and some of them have even stopped treating type 2 diabetics with oral hypoglycemic agents. It has been proved that in patients with type 2 DM, insulin treatment can be safely used to achieve near-normal HbA_{1c} levels (<7-7.5%) if prevention of diabetic microangiopathy is indicated, or to maintain HbA_{1c} levels <8.5-9% if catabolic symptoms due to insulin deficiency are to be prevented.[15] Diabetic patients on insulin therapy showed a positive lipid profile as compared with diabetics on oral hypoglycemic therapy. There were non significant differences in TC, TG, LDL-C and HDL-C between insulin treated type 2 DM patients and control subjects. The lipoprotein profile of the patients with type 2 DM, matched for level of fasting hyperglycemia, was similar irrespective of treatment with different types of oral hypoglycemic therapy and thus, no changes in lipoprotein metabolism could be identified that could account for differences in risk of CAD as a function of treatment. We have similar findings as far as oral hypoglycemic therapy is concerned, but in the present study insulin treated type 2 diabetics had significantly better lipid profile as far as TC, TG, LDL-C and HDL-C are concerned. While Lp (a) levels were similar in all diabetics irrespective of treatment.[32] If diet, physical activity, and oral hypoglycemic agents fail to achieve the individual treatment goal, insulin therapy must be considered. Insulin therapy in patients with type 2 diabetes should not be initiated too late.[33]

Diabetes is a coronary heart disease equivalent and confers an increased risk of cardiovascular morbidity and mortality even with good glycemic control. This may be attributed to other atherogenic factors and one of them is Lp (a). The Lp (a) levels were significantly higher in all diabetic groups compared with controls. Patients on sulphonylurea therapy had higher mean levels of Lp (a) compared with those receiving sulphonylurea plus metformin or insulin therapy but the difference did not reach significant level. Lp (a) levels have no differences between different diabetic groups. The association of Lp (a) with diabetes has been a matter of controversy. Some workers have not noticed any difference in the Lp (a) levels between healthy subjects and diabetic patients[34-36] while others reported raised levels in diabetics.[37,38] Even there are some studies in which lower levels of Lp (a) have been found in diabetic patients.[39,40] The major reasons for the discrepant results of different studies have been attributed to the variation in study design, collection and storage of samples, methods used for statistical analysis and population differences that reflect the known ethnic variability in the distribution of Lp (a) levels and apolipoprotein (a) [apo (a)] size isoform.[41] In previous reports, plasma Lp (a) levels in Turkish type 2 DM patients with and without vascular diabetic complications were studied.[42] The plasma Lp (a) levels were found to be significantly increased in type 2 diabetics compared with the healthy subjects and showed no correlation between Lp (a) levels and the mode of treatment.[43] Conversely, in a study on Chinese type 2 DM patients, comparison of Lp (a) levels with age and gender matched healthy control subjects revealed no significant difference.[35] Similarly, Haffner et al[43] found no significant difference in Lp (a) concentrations between diabetic subjects and normoglycemic controls in the San Antonio Hearty Study, a population based study of diabetes and cardiovascular risk factors.

Previous studies[38] found an inverse relationship between serum Lp (a) concentrations and molecular mass of apo (a) isoforms. Secondly, low molecular weight isoforms have a higher prevalence in type 2

DM and thus, higher levels of Lp (a). Hypolipidemic drugs have little if any effect on Lp (a) levels.[44] Nicotinic acid has been found to have a Lp (a) lowering effect but its role in diabetic patients is uncertain as it can worsen insulin resistance and glycemic control.[45] Effect of ciprofibrate treatment on Lp (a) levels has been found to be non significant.[46] After starting insulin, metabolic control may significantly improve in oral hypoglycemic treated diabetic patients. It is therefore, prudent to initiate insulin at an early stage in the course of type 2 diabetes. Insulin treatment may restore insulin sensitivity in type 2 DM patients resistant to OHDs treatment and after 3 years there is no exhaustion of B-cell function.[47]

In conclusions, patients with type 2 DM who are being treated on insulin have a better lipid profile (TC, HDL-C, LDL-C, TG) compared with those patients on oral hypoglycemic agents. Meanwhile, raised Lp(a) seems not to be affected by type of treatment of diabetes and was high in all diabetic patients and did not improve by insulin therapy. Insulin therapy appears to significantly decrease cardiovascular disease risk factors in patients with type 2 DM. This study suggested that insulin treatment should be initiated earlier in type 2 DM to improve lipid profile and minimize the burden of cardiovascular complications.

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