Turkish Journal of Endocrinology and Metabolism, (1999) 1 : 23-28 **ORIGINAL ARTICLE**

Relationship Between Serum Insulin Levels, Lipoprotein (a) Concentrations and Coronary Artery Disease in Patients with Impaired and Normal Glucose Tolerance

Ercan Tuncel* Kani Gemici Erdinç Ertürk* Ali Rıza Kazazoğlu** Nilgün Gürsoy* Şazi İmamoğlu* Nedim Çobanoğlu****

Uludağ University School of Medicine, Bursa

** Department of Endocrinology and Metabolism*

*** Department of Cardiology*

Increased lipoprotein (a) [Lp(a)] concentrations have been recognized as a risk factor for coronary artery disease (CAD) in nondiabetic individuals, although its contribution to CAD in subjects with impaired glucose tolerance (IGT) is not established.

We investigated the relationship between IGT and Lp(a) concentrations in 125 subjects suffering from anginal symptoms who had undergone the coronary angiography (96 male, 29 female, 28-75 years of age). They had no history of hyperglycemic symptoms, diabetes mellitus or hypertension. Subjects were divided into two groups according to the results of coronary angiogram: group 1 with CAD (n=90) and the group 2 with normal coronary arteries (n=35). Each group was divided into two subgroups according to the results of the oral glucose tolerance test (OGTT): subgroup a with IGT and subgroup b with normal OGTT.

Subjects of group 1 a and 1 b had significantly higher Lp(a) concentrations than group 2a and 2b respectively (p=0.0062, p=0.02). The Lp(a) concentration was also significantly higher in group 1a than in group 1b (p=0.035), whereas there was no difference between group 2 a and 2 b (p=0.8). In considering subjects with IGT there was no difference between the serum insulin levels of the group with CAD and the group with normal coronary arteries. There was also no significant difference between the serum insulin levels of groups 1b and 2b.

In conclusion, this study demonstrates that serum insulin levels are not associated with serum Lp(a) leves and that serum Lp(a) levels are higher in the CAD with impaired glucose tolerance than with normal glucose tolerance.

KEY WORDS Lipoprotein (a), coronary artery disease, impaired glucose tolerance

Introduction

Hyperinsulinemia and insulin resistance have been associated with coronary heart disease, dyslipidemia, NIDDM and hypertension, although the association of the latter with insulin resistance remains controversial. It is not certain whether insulin resistance may increase the risk of coronary heart disease through a direct effect on the arterial wall or through its association with other risk factors, such as NIDDM or dyslipidemia (1-3).

Recently, numerous studies have suggested that Lp(a) concentrations may be an independent risk factor for coronary heart disease (4-8). The relationship of NIDDM, an insulin-resistant condition, with Lp(a) concentrations remains controversial, with some studies showing increased concentra-

Correspondence address:

Prof Dr Şazi İmamoğlu

Department of Endocrinology and Metabolism, Uludağ University School of Medicine, Görükle 16384 Bursa, Turkey

tions (9-11), and other studies similar Lp(a) concentrations compared with normoglycemic subjects (12). In two studies of nondiabetic subjects, insulin concentrations have not been associated with Lp(a) concentrations (1). Lp(a) concentrations were not associated with insulin resistance in normoglycemic subjects, but Lp(a) concentrations were inversely related to first-phase insulin secretion(11). Increased Lp(a) concentrations have been recognized as a risk factor for CAD in nondiabetic individuals, although its contribution to CAD in subjects with impaired glucose tolerance is not established.

We investigated the relationship between IGT and Lp(a) concentrations.

Patient and Methods

The protocol was approved in June 1994 by the Ethical Committee of Uluda23 University (Bursa, Turkey). 125 nondiabetic, normotensive subjects (96 male, 29 female, aged 28-75 years) were recruited for the study. All subjects suffering from anginal symptoms had undergone coronary angiography. They were divided into two groups according to the results of coronary angiogram: group 1 with CAD (n=90) and group 2 with normal coronary arteries (n=35). Each group was divided into two subgroups according to the results of OGTT: subgroup a with IGT and the subgroup b with normal OGTT.

Blood samples were drawn after an overnight fast for measurement of plasma glucose, insulin,total cholesterol, triglycerides, HDL-cholesterol, apolipoprotein A,B and Lp(a). A 75 g load of glucose was administered and blood samples were drawn at 30,60,90 and 120 minutes for the determination of plasma glucose and insulin levels. The definition of glucose tolerance was based on a 2-h OGTT according to the World Health Organization criteria (14). Glucose was determined by the glucose oxidase method (15) and insulin by RIA (Coat a count, Diagnostic Products Corp., San Diego, CA, USA). Total cholesterol, triglycerid levels were determined by an enzymatic method, HDL cholesterol after precipitation of apolipoprotein B-containing lipoproteins using dextran sulfate/magnesium chloride, apolipoprotein A and B by the immunoturbudimetric method and Lp(a) by the nephelometric method. Coronary angiography was performed by the Judkins technique and the severity of CAD was quantified in a modified Gensini score (16).

The data were expressed as means (SD and comparisons between groups were performed by Student's t-test (Instat 2 Software, San Diego, CA, USA).

Results

In this study;subjects of the CAD group with IGT and normal OGTT had significantly higher Lp(a) concentrations than the group of normal coronary arteries with IGT and normal OGTT (Table 1).

Although Lp(a) concentration was higher in the CAD group with IGT than in the group with normal OGTT (Table 3), there was no difference in the Lp(a) concentrations between of group of normal coronary arteries with IGT and those with normal OGTT (Table 2).

While there was no difference in the serum insulin levels between the CAD group and the normal coronary arteries with IGT (Table 4), there was also no significant difference between the serum levels in the CAD group and the normal coronary arteries with normal OGTT (Table 5).

Discussion

This study indicates that serum Lp(a) levels are higher in the CAD group with impaired glucose tolerance than with normal glucose tolerance. Hiraga et al, in their prospective study, found that the incidence of cardiovascular disease was significantly higher among NIDDM patients with a high serum Lp(a) level (17). As far as serum Lp(a) levels in diabetic patients are concerned, different results have been reported: Haffner et al showed that Lp(a) levels were higher in diabetic patients than in nondiabetic subjects (18). Concerning the relationship between Lp(a) and cardiovascular disease in diabetic patients, relatively fewer studies have been performed. Two studies have shown that Lp(a) is associated with increased CVD events

Table 1. Clinical and biochemical characteristics of the groups with CAD and normal coronary arteries.

	Group 1 (n=90)	Group 2 (n=35)	p
BMI(kg/m^2)	26,94±0.38	26.21±0.46	NS
W/H	1.00±0.01	0.92±0.01	<0.0001
C-peptide (ng/ml)	6.71±0.5	3.5±0.41	<0.0005
T. cholesterol (mg/dl)	246.94±4.64	208.58±6.79	<0.0001
LDL-cholesterol (mg/dl)	164.56±4.17	131.33±6.36	<0.0001
HDL-cholesterol (mg/dl)	36.19±0.73	38.85±1.02	NS
Triglyceride (mg/dl)	226.1±8.87	183.58±12.05	<0.01
ApoA1 (mg/dl)	121.52±2.89	132.82±5.14	<0.05
ApoB (mg/dl)	166.03±4.02	136.36±6.47	<0.0005
Lp(a)	33.3±2.1	19.3±2.5	<0.005

NS: Nonsignificant

Table 2. Clinical and biochemical characteristics of the normal groups with IGT and normal OGTT.

	Group 2a (n=36)	Group 2b (n=12)	p
BMI(kg/m^2)	27,89±2.76	25.31±2.16	<0.005
W/H	0.98±0.04	0.90±0.05	<0.0005
C-peptide (ng/ml)	4.15±1.98	3.1±2.36	NS
T. cholesterol (mg/dl)	215.16±35	203.43±39.97	NS
LDL-cholesterol (mg/dl)	128.41±30.93	131.52±38.51	NS
HDL-cholesterol (mg/dl)	40.75±6.28	38.52±4.94	NS
Triglyceride (mg/dl)	225.58±78.96	162±49.11	<0.01
ApoA1 (mg/dl)	132.83±32.68	128±12.46	NS
ApoB (mg/dl)	143.17±39.08	132.3±34.76	NS
Lp(a)	20.33±11.93	18.96±17.15	NS
Insulin(basal)	15±4.2	11.8±5.65	NS
Insulin (120.min.)	112±62.8	48.2±52.5	<0.005

NS: Nonsignificant

Table 3. Clinical and biochemical characteristics of CAD groups with IGT and normal OGTT.

	Group 1a (n=36)	Group 1b (n=54)	p
BMI(kg/m^2)	26.5±3.66	27.21±3.64	NS
W/H	1.01±0.06	0.99±0.06	NS
C-peptide (ng/ml)	8.37±5.33	5.37±3.82	NS
T. cholesterol (mg/dl)	244.94±47.38	247.37±41.38	NS
LDL-cholesterol (mg/dl)	165.65±44.33	163.27±36.8	NS
HDL-cholesterol (mg/dl	35.34±7.3	36.83±6.79	NS
Triglyceride (mg/dl)	220.17±95.93	228.7±76.49	NS
ApoA1(mg/dl)	124.49±24.43	120.09±29.31	NS
ApoB(mg/dl)	173.71±35.15	160.19±39.24	NS
Lp(a)	38.54±20.79	29.69±18.57	<0.05
Insulin (basal)	12.23±7.62	10.28±5.73	NS
Insulin (120.min.)	105.4±68.5	50.83±37.1	<0.0001

NS: Nonsignificant

Table 4. Clinical and biochemical characteristics of CAD and normal group with IGT.

	Group 1a (n=36)	Group 2a (n=12)	p
BMI (kg/m^2)	26.5±3.66	27.89±2.76	NS
W/H	1.01±0.06	0.98±0.04	NS
C-peptide (ng/ml)	8.37±5.33	4.15±1.98	<0.05
T. cholesterol (mg/dl)	244±47	215±35	<0.05
LDL-cholesterol (mg/dl)	165±44	128±30	<0.01
HDL-cholesterol (mg/dl)	35.3±7.3	40.7±6.2	<0.05
Triglyceride (mg/dl)	220±96	225±78	NS
ApoA1(mg/dl)	124±24	132±32	NS
ApoB (mg/dl)	173±35	143±39	<0.05
Lp(a)	38.5±20.7	20.3±11.9	<0.01
Insulin (basal)	12.2±7.6	15.0±4.2	NS
Insulin (120.min.)	105±68	112±62	NS

NS: Nonsignificant

Table 5. Clinical and biochemical characteristics of CAD and normal group with normal OGTT.

	Group 1b (n=54)	Group 2b (n=23)	p
BMI(kg/m^2)	27.2±3.6	25.3±2.1	NS
W/H	0.99±0.06	0.9±0.05	<0.001
C-peptide (ng/ml)	5.37±3.82	3.10±2.36	<0.01
T. cholesterol (mg/dl)	247±41	203±39	<0.001
LDL-cholesterol (mg/dl)	163±36	131±38	<0.001
HDL-cholesterol (mg/dl)	36.8±6.7	38.5±4.9	NS
Triglyceride (mg/dl)	228±76	162±4.1	<0.001
ApoA1 (mg/dl)	120±29	128±12	NS
ApoB (mg/dl)	160±39	132±34	<0.005
Lp(a)	29.6±18.5	18.9±17.1	NS
Insulin (basal)	10.2±5.7	11.8±5.6	NS
Insulin (120.min.)	50.8±37.1	48.2±52.5	NS

NS: Nonsignificant

in NIDDM patients (19,20) whereas Haffner et al, Nikanen et al have found no association between Lp(a) and cardiovascular disease(17,21).In another study Velho et al showed that there was no difference between the diabetic patients and their relatives and the control group in Lp(a) levels and that Lp(a) levels were higher in the diabetic group with a history of myocardial infarctus (20). Ramirez et al determined in their study that Lp(a) levels were elevated in poorly controlled diabetic patients (8). In the study by Terres et al Lp(a) concentrations were clearly elevated in patients with rapid angiographic progression compared with patients without progression and Lp(a) concentrations in the study group as a whole were higher than in healthy subjects and are typical for patients with manifest coronary disease (22). Steven et al and Haffner suggested that concerning the relationship between Lp(a) and CAD in diabetes little current evidence shows that Lp(a) is a risk factor for CHD in diabetes, more studies, especially prospective studies with larger numbers of subjects, need to be done (18). Watts et al found that plasma lipoprotein(a) was a strong and independent correlate of the extent of angiographic CAD in symptomatic patients with NIDDM (23), while James et al reported in their study that Lp(a) was an independent risk factor for ischemic heart

disease and macroangiopathy in NIDDM patients (24).

In this study the serum total cholesterol, LDL-cholesterol, triglyceride, apoA1 and apoB levels were significantly more different in the group with CAD than in the group with normal coronary arteries. In considering subjects with impaired glucose tolerance the CAD group had a significantly higher serum level of total cholesterol, LDL-cholesterol and apoB level and a significantly lower level of HDL-cholesterol level than the normal group. There was no difference in the serum triglyceride and apoA1 level between both groups. Fujiwaara et al showed that the CAD group had a significantly lower plasma level of HDL-cholesterol and apoA1 and a significantly higher plasma level of total cholesterol, triglyceride and apoB than the normal group (25). Hiraga et al found that the patients in the high Lp(a) group had lower serum triglyceride and higher HDL cholesterol compared with those in the low Lp(a) group and suggested that the NIDDM patients who experienced clinical events had higher serum triglyceride and lower HDL cholesterol levels than the mean values of the high Lp(a) group (17). Terres et al reported that the serum concentrations of LDL cholesterol, HDL cholesterol, triglycerides, and apolipoprotein B were similar in the two groups of patients with and without rapid progression of coronary artery disease and concluded that the classic cardiovascular risk factors did not appear to be risk factors for rapid progression (22). Ramirez et al found that plasma cholesterol, LDL colesterol, and plasma triglyceride levels did not differ between the two diabetic groups with poor and better glycemic control and in their study no correlation between the levels of Lp(a) and LDL cholesterol was determined (9).

In this study, there was no difference in the elevation of serum insulin levels during the oral glucose tolerance test period between the CAD and normal group and between the CAD and normal group with IGT although Fujiwara et al found the plasma insulin levels during the test were higher in the CAD group than in the normal group (25). Their conclusion was that hyperinsulinemia appeared to be associated with changes in lipid and apolipoprotein that predisposed toward coronary atherosclerosis not only in nondiabetic subjects, but also in those with IGT (23). In two studies of nondiabetic subjects, insulin concentrations have not been associated with Lp(a) concentrations (1). Sidhu et al suggested that Lp(a) concentrations were not associated with insulin resistance (measured by the intravenous glucose tolerance test) in normoglycemic subjects, but Lp(a) concentrations were inversely related to first-phase insulin secretion (13). Haffner et al found that normoglycemic insulin-resistant subjects did not have elevated Lp(a) concentrations (1).

In conclusion, this study demonstrates that the serum insulin levels are not associated with serum Lp(a) levels and that serum Lp(a) levels are higher in the CAD group with impaired glucose tolerance when compared with the normal glucose tolerance group.

References

1. Haffner SM, Karhapaa P, Rainwater DL, et al. Insulin sensitivity and Lp(a) concentrations in normoglycemic men. *Diabetes Care* **18:** 193-199, 1995.
2. De Fronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM: a balanced overview. *Diabetes Care* **15:** 318-368, 1992.
3. Ferrannini E, Buzzigoli G, Bonadonna RC, et al. Insulin resistance in essential hypertension. *N Eng J Med* **317:** 350-357, 1987.
4. Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg AL. Lp(a) lipoprotein as a risk factor for myocardial infarction. *JAMA* **256:** 2540-2544, 1986.
5. Durrington PN, Ishola M, Hunt L, Arrol S, Bhatgnar D. Apolipoproteins(a), A1, and B and parenteral history in men with early onset ischemic heart disease. *Lancet* **I:** 1070-1073, 1988.
6. Dahlen GH, Guyton JR, Attar M, et al. Association of levels of lipoprotein Lp(a), plasma lipids and other lipoproteins with coronary artery disease documented by angiography. *Circulation* **74:** 758-765, 1986.
7. Seed M, Hopplicher F, Reavley D, et al. Relationship of serum lipoprotein(a) concentration and apolipoprotein phenotype to coronary heart disease in patients with familial hypercholesterolemia. *N Eng J Med* **322:** 1494-1499, 1990.
8. Schwarzman RA, Cox ID, Poloniecki J, et al. Elevated plasma lipoprotein(a) is associated with coronary artery disease in patients with chronic stable angina pectoris. *J Am Coll Cardiol* **31:** 1260-6, 1998.

9. Ramirez LC, Arauz-Pacheco C, Lackner C, et al. Lipoprotein(a) levels in diabetes mellitus:relationship to metabolic control. *Ann Intern Med* **117:** 42-47, 1992.
10. Ishiday, Kazumi T, Yoshida M, et al. Serum lipoprotein (a) in patients with non-insulin-dependent diabetes mellitus (Abstract). *Diabetes* **40** (Suppl.1): 188A, 1991.
11. Çömlekçi A, Biberoğlu S, Kozan O, et al. Correlation between serum lipoprotein(a) and angiographic coronary artery disease in non-insulin-dependent diabetes mellitus. *J Intern Med* **242:** 449-54, 1997.
12. Haffner SM, Morales PA, Stern MP, Gruber MK. Lp(a) concentrations in NIDDM. *Diabetes* **41:** 1267-1272, 1991.
13. Sidhu M, Crook D, Godsland IF, Walton C, Wynn V. Inverse relationship between serum Lp(a) levels and first-phase insulin secretion. *Diabetes* **41:** 1341-1345, 1992.
14. World Health Organization: Diabetes Mellitus: Report of a WHO Study Group. Geneva, World Health Org., (Tech. Rep. Ser., no.727), p.9-25, 1985.
15. Hoffman WS. A rapid photoelectric method for the determination of glucose in blood and urine. *J Biol Chem* **120:** 52-55, 1937.
16. Gensini GG. A more meaningful scoring system for determination the severity of coronary heart disease. *Am J Cardiol* **51:** 606-607, 1993.
17. Hiraga T, Kobayashi T, Okubo M, Nakanishi K, Sugimoto T. Prospective study of lipoprotein(a) as a risk factor for atherosclerotic cardiovascular disease in patients with diabetes. *Diabetes Care* **18:** 241-244, 1995.
18. Haffner SM.Lipoprotein(a) and diabetes. *Diabetes Care* **16:** 835-840, 1996.
19. Jenkins AJ, Steele JS, Junus ED, Santamaria JD, Best JD. Plasma apolipoprotein(a) is increased in type 2 (non-insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia* **35:** 1055-1059, 1992.
20. Velho G, Erlich D, Tuppin E, et al. Lipoprotein(a) in diabetic patients and normoglycemic relatives in familial NIDDM. *Diabetes Care* **16:** 742-747, 1992.
21. Haffner SM, Moss SE, Klein BEK, Klein R. Lack of association between lipoprotein(a) concentrations and coronary heart disease mortality in diabetes: Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Metabolism* **41:** 194-197, 1992.
22. Terres W, Tatsis E, Pfalzer B, et al. Rapid angiographic progression of coronary artery disease in patients with elevated lipoprotein(a). *Circulation* **91:** 948-950, 1995.
23. Watts GF, Gwilym RM, Mazurkiewicz J, Coltart J. Independent correlation between plasma lipoprotein(a) and angiographic coronary artery disease in NIDDM. *Diabetes Care* **18:** 234-236, 1995.
24. James RW, Boemi M, Sirolla C, et al. Lipoprotein(a) and vascular disease in diabetic patients. Diabetologia **38:** 711-714, 1995.
25. Fujiwara R, Kutsumi Y, Hayashi T, et al. Relation of angiographically defined coronary artery disease and plasma concentrations of insulin, lipid, and apolipoprotein in normolipidemic subjects with varying degrees of glucose tolerance. *Am J Cardiol* **75:** 122-126, 1995.