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## Insulin sensitivity and Lp( $\alpha$ ) concentrations in normoglycemic offspring of type 2 diabetic parents

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### Abstract

**Background:** Offspring of at least 1 parent with type 2 diabetes are more resistant to the insulin action, exhibit higher incidence of dyslipidemia and are more prone to cardiovascular diseases. The association between Lp( $\alpha$ ) and coronary heart disease is well established. An association between Lp( $\alpha$ ) concentration and insulin sensitivity was examined in this study.

We investigated the serum LP( $\alpha$ ) in 41 offspring of 41 families of type 2 diabetic subjects (group I) with normal glucose tolerance, compared to 49 offspring who their parents had no history of type 2 diabetes, matched for sex, age, BMI, WHR and blood pressure (group II). Serum Lp( $\alpha$ ), triglycerides, insulin resistant index, HDL, LDL-cholesterol and insulin were measured.

**Results:** The offspring of type 2 diabetic subjects had higher fasting serum triglycerides (mean  $\pm$  SD  $199.3 \pm 184.2$  vs.  $147.1 \pm 67.9$  ng/dl,  $p < 0.05$ ) lower HDL-cholesterol ( $37.3 \pm 9.0$  vs.  $44.6 \pm 7.8$ ,  $p < 0.001$ ) and particularly higher Insulin resistance Index (HOMA-IR) ( $2.84 \pm 1.39$  vs.  $1.67 \pm 0.77$ ,  $p < 0.001$ ).

They also had higher serum LP( $\alpha$ ) concentration ( $15.4 \pm 6.7$  vs.  $8.6 \pm 6.0$ ,  $p < 0.001$ ). By simple linear analysis in the offspring of type 2 diabetic parents there was no correlation of Lp( $\alpha$ ) concentration with insulin resistance index Homa-IR ( $r = 0,016$   $p = NS$ ).

**Conclusions:** We conclude that serum LP( $\alpha$ ) is significantly increased in offspring of type 2 diabetic subjects but was not related to insulin sensitivity.

### Background

Patients with type 2 diabetes mellitus are characterized by resistance to insulin-stimulated glucose uptake [1,2], dyslipidemia (especially increased triglyceride and decreased high-density lipoprotein (HDL) levels [3,4], hypertension [5] and coronary heart disease [6,7].

Lipoprotein ( $\alpha$ ) [Lp( $\alpha$ )], first described by Berg [8] in 1963, is a low density lipoprotein (LDL) - like substance

with a specific apoprotein, apoprotein ( $\alpha$ ) [apo ( $\alpha$ )], bound to apo- $\beta$  100 by disulfide bridges [9,10].

Numerous studies have suggested that lipoprotein ( $\alpha$ ) concentrations may be an independent risk factor for coronary heart disease [11-15]. However, the molecular mechanism by which Lp( $\alpha$ ) might promote atherosclerosis has not been clarified.

**Table 1: Clinical characteristics of the offspring of type 2 diabetes parents (Group 1) and offspring of normal parents (Group 2).**

Parameter	Group 1	Group 2	P value
Number (M/F)	41 (28/13)	49 (31/18)	NS
Age (Yr)	41.4 ± 6.8	43.5 ± 5.5	NS
BMI (Kg.m <sup>-2</sup> )	28.1 ± 4.8	27.6 ± 3.5	NS
WHR	0.87 ± 0.1	0.8 ± 0.08	NS
Systolic BP (mmHg)	119.4 ± 15.5	120.8 ± 10.8	NS
Diastolic BP (mmHg)	72.1 ± 12.8	73.9 ± 10.1	NS

**Table 2: Laboratory profile of the offspring of type 2 diabetes parents (Group 1) and offspring of normal parents (Group 2).**

Parameter	Group 1	Group 2	P value
Triglyceride (mg/dl)	199.3 ± 184.2	147.1 ± 67.9	< 0.05
Cholesterol (mg/dl)	215.4 ± 41.6	199.2 ± 29.8	< 0.05
HDL-cholesterol (mg/dl)	37.3 ± 9.0	44.6 ± 7.8	< 0.001
LDL-cholesterol (mg/dl)	143.7 ± 31.7	124.6 ± 25.1	< 0.01
Lp(α) (mg/dl)	15.4 ± 6.7	8.6 ± 6.0	< 0.001

The relationship of Lp(α) concentrations with insulin resistance remains controversial. Some studies have shown increase Lp(α) concentration in subjects with NIDDM [16–18] whereas other studies have showed similar Lp(α) concentrations in type 2 diabetic subjects compared with normoglycemic subjects[19]. In other studies of nondiabetic subjects, insulin concentrations have not been associated with Lp(α) concentrations [20,21]. One study showed no elevated Lp(α) concentrations in normoglycemic insulin-resistant subjects [22].

In this report, we examine the association of Lp(α) concentrations to insulin sensitivity, calculated using the Homeostasis model Assessment (HOMA-IRI) in normoglycemic offspring of at least 1 parent with type 2 diabetes.

## Results

The clinical characteristics of the study population are shown in Table 1 and the laboratory profile of the study population are shown in Table 2.

The group of offspring with type 2 diabetes parents as well as the control group had a similar distribution of age, sex, BMI, WHR systolic and diastolic BP. As expected the mean fasting serum triglycerides, cholesterol, and LDL-cholesterol were significantly higher in group 1 compared to the control group. HDL-cholesterol was significantly lower in group 1 compared to the control group.

The glucose and insulin concentrations in the fasting state and after an oral glucose challenge are shown in Table 3.

The mean fasting glucose and insulin concentrations were significantly higher in group 1 compared to group 2:

fasting glucose: 4.5 ± 0.6 vs. 4.3 ± 0.6 mmol/l (p < 0.05)

fasting insulin: 14.0 ± 6.4 vs. 8.6 ± 3.2 μU/ml (p < 0.005)

Serum insulin concentration 30 min post glucose challenge was significantly higher in the offspring group 1 (122.2 ± 94.3 vs. 81.7 ± 51.6 μU/ml, p < 0.005) as well at 60 min post glucose challenge (134.4 ± 103.1 vs. 99.9 ± 48.9 μU/ml, p < 0.05) whereas there was no difference at 120 min.

In the offspring of the diabetic parents the insulin resistance index was significantly higher compared to control group (2.84 ± 1.39 vs. 1.67 ± 0.77, p < 0.001). 22 (53.6%) of the 41 subjects of group 1, had HOMA-IR values > 2.5 indicating that they were insulin resistant [23–29], compared to only 6 (12.2%) of the 49 subjects of group 2.

Lp(α) concentration was significantly higher in group 1 compared to group 2 (15.4 ± 6.7 vs. 8.6 ± 6.0 ng/dl, p < 0.001).

In the offspring of the diabetic parents the insulin resistance index was positively correlated with serum triglycer-

**Table 3: Serum insulin and glucose and insulin resistance index in offspring and control subjects in the fasting state and after an oral glucose challenge (120 min)**

	<b>Group 1 no 41</b>	<b>Group 2 no 49</b>	<b>P value</b>
<b>Glucose (mmol/l)</b>			
Fasting	4.53 ± 0.62	4.26 ± 0.56	0.036
30 min	8.4 ± 2.0	8.3 ± 1.5	NS
60 min	8.4 ± 3.0	8.9 ± 2.5	NS
120 min	5.4 ± 1.3	5.6 ± 1.2	NS
<b>Insulin (μU/ml)</b>			
Fasting	14.0 ± 6.4	8.6 ± 3.2	< 0.001
30 min	122.2 ± 94.3	81.7 ± 50.6	0.013
60 min	134.4 ± 103.1	99.9 ± 48.9	0.042
120 min	76.9 ± 8.1	70.5 ± 40.7	NS
Insulin Resistance Index (HOMA-IR)	2.84 ± 1.39	1.67 ± 0.77	< 0.001

**Table 4: Correlation (r) and significance (P) of HOMA-IR with serum concentration of Lipids and Lp(α).**

<b>Parameter</b>	<b>Group 1</b>		<b>Group 2</b>	
	<b>r</b>	<b>P value</b>	<b>r</b>	<b>P value</b>
Cholesterol	0.177	NS	0.231	NS
Triglycerides	0.319	p < 0.01	0.099	NS
HDL	0.304	p < 0.05	0.055	NS
LDL	0.342	p < 0.02	0.161	NS
Lp(α)	0.016	NS		

ides and LDL. There was no correlation of HOMA-IR with any of the above parameter in the control group (Table 4).

There was no correlation of HOMA-IR with Lp(α) concentration in the offspring of the diabetic parents.

### Discussion

Resistance to insulin-stimulated glucose uptake is a characteristic finding in patients with type 2 diabetes [1,2]. The observation that concordance for type 2 diabetes approaches 100% when one identical twin has the disease, strongly suggests that the decisive component of this syndrome is genetic in nature [30]. Several studies have shown that offspring of at least one parent with type 2 diabetes display hyperinsulinism and are more resistant to insulin action than offspring of parents whose glucose tolerance was normal [31–34].

The result of our study supports and expands those findings. We found that offspring of patients with type 2 diabetes when compared with normal individuals whom their parents had no history of type 2 diabetes matched for sex, age and BMI, were relative hyperinsulinemic, had

higher fasting serum triglycerides, lower HDL-cholesterol and higher insulin resistance index.

Moreover, the serum Lp(α) concentration was significantly higher compared with control group. The overall impression from the large number of publications on diabetes mellitus and Lp(α), is that neither insulin dependent nor non-insulin dependent diabetes has a direct effect on serum Lp(α) [16–19,31–34]. Some reports of increased levels in non-insulin dependent diabetes may result from the inclusion of patients with established CHD in the population studied. However, there does appear to be an increase in serum Lp(α) in insulin-dependent diabetes when nephropathy is present and this may be the case even when this is at the stage of microalbuminuria [35–42]. Thus the rise seems to occur with much less marked proteinuria than in primary renal disease. Possibly this is because there is some specific feature of the nephropathy in diabetes, which triggers the Lp(α) response early in the disease or perhaps microalbuminuria in diabetes is a marker for a more extensive vasculopathy which is the major stimulus for Lp(α) to increase.

There has been little published data on insulin sensitivity and Lp( $\alpha$ ) concentrations. Lp( $\alpha$ ) concentrations were not significantly related to insulin sensitivity measured by the intravenous glucose tolerance test in nondiabetic subjects [43]. Haffner et al [22] demonstrated that insulin-resistant normoglycemic men did not have elevated Lp( $\alpha$ ) concentrations and that Lp( $\alpha$ ) concentrations are principally controlled at the locus encoding apo ( $\alpha$ ) in agreement with the data of other studies [44–47].

Moreover, Haffner et al suggested that the relationship between insulin sensitivity and Lp( $\alpha$ ) concentrations might be at least partially dependent on apo ( $\alpha$ ) phenotype [22]. One possibility for such an association could be that genes for apo ( $\alpha$ ) genotype and insulin sensitivity could be in linkage disequilibrium.

To our knowledge this is the first report in which the levels of Lp( $\alpha$ ) concentration and insulin sensitivity in normoglycemic offspring of type 2 diabetic parents were studied. Our study demonstrates that Lp( $\alpha$ ) concentrations were not significantly correlated with HOMA-IR ( $r = 0.016$ ). The impression from this finding and in agreement with previous studies [16,19–21,35–43], is that serum Lp( $\alpha$ ) concentration is not related to insulin sensitivity. However, Lp( $\alpha$ ) concentration was significantly higher in the group of offspring of diabetic parents compared to the control group ( $p < 0.001$ )

## Conclusions

We conclude that serum LP( $\alpha$ ) is significantly increased in offspring of type 2 diabetic subjects but was not related to insulin sensitivity.

## Methods

### Subjects

We studied 54 healthy offspring of 54 separate families with type 2 diabetes parents. The subjects were Caucasians of Greek origin. They all had a parent who had developed type 2 diabetes mellitus after 50 years of age. Two patients were the offspring whom both parents were diabetic. Maturity-onset diabetes of the young was excluded on the basis of the late onset of diabetes. The 54 subjects (group 1) were matched to 54 subjects with no family history for diabetes and were used 95 controls (group 2). The subjects in both groups were matched for sex, age, Body Mass Index (BMI) and waist-to-hip ratio (WHR).

All subjects had normal physical examination and normal values for routine laboratory parameters including hematology, c-reactive protein, HbA1c (upper limit of normal 6.5%), adrenal, kidney, liver and thyroid function. The subjects were not under any medication known to affect carbohydrate or lipoprotein metabolism and all denied alcohol intake.

After an appropriate carbohydrate diet for one week, an oral Glucose Tolerance test (OGTT) was performed and patients with impaired glucose tolerance or type 2 diabetes were excluded from the study. Forty one subjects remained for group 1 and 49 for group 2. Informed consent was obtained from all participants in the study.

### Study design

After 12-h overnight fast, blood samples were drawn for serum glucose, insulin, lipids, lipoprotein and Lp( $\alpha$ ). The subjects then ingested 75 g of glucose load over a 2-min period. Blood samples were drawn at 30, 60 and 120 min thereafter for measurement of serum glucose and insulin concentrations. Plasma glucose was measured with an automatic analyzer by the glucose oxidase method. Immunoreactive insulin (IRI) was measured with an insulin radioimmunoassay (RIA) kit.

We used the homeostatic model to assess insulin resistance, where HOMA-IR = fasting plasma insulin ( $\mu\text{U/ml}$ )  $\times$  fasting plasma glucose (mmol/l) / 22.5 [23–25]. HOMA-IR provides a reliable estimate of insulin resistance across the range of glucose tolerance using either the frequently sampled intravenous glucose tolerance test (FSIGTT) with minimal model analysis or the glucose clamp technique as the gold standard measure of insulin sensitivity [26,27].

Total serum cholesterol, serum triglyceride and HDL-cholesterol were assayed with a commercial kit (Boehringer Mannheim, Germany). LDL cholesterol was calculated according to the Friedewald equation [28]. Lp( $\alpha$ ) was estimated by enzyme immunoassay (Macra Lp( $\alpha$ ), Strategic Diagnostic, Newark, NJ).

The study design was approved by the ethical and scientific committee of the Hospital.

### Statistical analysis

Results are expressed as mean  $\pm$  SD. Data were analyzed according to the unpaired student's t-test or by the non-parametric Mann-Whitney U test of Wilcoxon's test. Pearson's correlation coefficient or the Spearman's test were used depending on the normal distribution of the variables. A p-value of less than 5% was considered statistically significant.

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