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PLASMA LIPOPROTEIN(A) LEVELS

A comparison between diabetic and non-diabetic patients with acute ischemic stroke

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ABSTRACT - *Objective:* The aim of this study was to evaluate lipoprotein(a) (Lp(a)), total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), very low density lipoprotein cholesterol (VLDL), triglycerides , apolipoprotein A (apo A) and B100 (apo B100), uric acid, glycaemic and insulin plasmatic concentrations in patients affected by acute stroke. In this group of patients, we have compared the variables between type 2 diabetic patients and non-diabetic patients. *Method:* We evaluate a total of 34 non-diabetic patients (22 males and 12 females; mean age 66.71 ± 10.83 years) and a group of 26 type 2 diabetic patients (15 males and 11 females; mean age 66.35 ± 9.92 years) in a cross-sectional study. *Results:* Mean Lp(a) concentration did not significantly differ between type 2 diabetic patients and non-diabetic subjects (29.49 ± 23.09 vs 44.81 ± 44.34 mg/dl). The distribution of Lp(a)levels was highly skewed towards the higher levels in both groups, being over 30 mg/dl in 50%. Lp(a) concentration was positively correlated with abdominal adiposity, using waist-hip ratio(WHR)($p< 0.05$). No association was found between Lp(a) and others risk factors like sex, age, other lipidic parameters and the presence of stroke. *Conclusions:* Our results showed that there were no significant differences between diabetic and non-diabetic patients` serum Lp(a) levels, which indicates that elevated Lp(a) levels were associated with ischemic stroke, irrespective of the presence of type 2 diabetes mellitus (type 2 DM).

KEY WORDS: lipoprotein(a), stroke, type II diabetes.

Níveis plasmáticos de lipoproteína(a): uma comparação entre pacientes diabéticos e não-diabéticos com acidente vascular cerebral isquêmico agudo

RESUMO - *Objetivo:* O objetivo deste estudo foi avaliar os níveis de lipoproteína(a) (Lp(a)), colesterol total, lipoproteína de alta densidade (HDL), lipoproteína de baixa densidade (LDL), lipoproteína de muito baixa densidade (VLDL), triglicerídeos, apolipoproteína A (apo A) e B100 (apo B100), ácido úrico e concentrações plasmáticas de insulina e glicose em pacientes acometidos por acidente vascular cerebral isquêmico. Neste grupo de pacientes, comparamos as variáveis entre diabéticos tipo 2 e pacientes não-diabéticos. *Método:* Nós avaliamos um total de 34 pacientes não-diabéticos (22 homens e 12 mulheres, com idade média 66,71±10,83 anos) e um grupo de 26 pacientes diabéticos tipo 2 (15 homens e 11 mulheres, com idade média 66,35±9,92 anos) em um estudo transversal. *Resultados:* A concentração média de Lp(a) não variou significativamente entre os pacientes diabéticos tipo 2 e os não-diabéticos (29,49±23,09 vs 44,81±44,34 mg/dl). A distribuição dos níveis de Lp(a) foi altamente convergente em direção aos níveis mais altos em ambos os grupos, estando maior que 30mg/dl em 50%. A concentração de Lp(a) foi positivamente correlacionada com a adiposidade abdominal, usando a relação cintura-quadril (RAQ) ($P<0,05$). Nenhuma associação foi encontrada entre Lp(a) e outros fatores de risco, como sexo, idade, parâmetros lipídicos e a presença de acidente vascular cerebral. *Conclusão:* Nossos resultados mostraram que não houve diferenças significativas entre os níveis séricos de Lp(a) de pacientes diabéticos e não-diabéticos, o que indica que os níveis elevados de Lp(a) são especificamente associados com acidente vascular cerebral isquêmico, mas não com diabetes mellitus tipo 2 (DM tipo2).

PALAVRAS-CHAVE: lipoproteína (a), acidente vascular cerebral, diabete mellitus tipo 2.

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Lipoprotein(a) (Lp(a)) is a modified form of low density lipoprotein (LDL) in which a large glycoprotein, apolipoprotein(a) (apo(a)) is covalently bound to apo B by a disulfide bridge[1]. The role of excess of Lp(a) in atherosclerosis is propably relates to the observation that Lp(a) could promote the inhibition of the conversion of plasminogen to plasmin and then thrombus formation[2]. Another action of Lp(a) in atherosclerosis is recruitment of monocytes to the vessel wall and promotion of binding that could lead to foam cell formation and localization of Lp(a) at atherosclerotic plaques[3]. Many studies have investigated the possible effect of diabetes mellitus on Lp(a) concentrations in recent years[4,5]. Prospective studies that evaluated Lp(a) as a predictor of cardiovascular and cerebrovascular events in men have had conflicting results . Some studies suggested that Lp(a) was an independent risk factor for coronary heart disease (CHD), while others showed no significant association[6-12].

Strokes are one of the most common causes of mortality and long term severe disability. There is evidence that Lp(a) is a predictor of many forms of vascular disease, including premature coronary artery disease. Several studies have also evaluated the association between Lp(a) and ischemic (thrombotic) stroke. Several cross sectional and a few prospective studies provide contradictory findings regarding Lp(a) as a predictor of ischemic stroke[13]. Serum Lp(a), a risk factor for coronary heart disease in some non-diabetic populations, is largely under genetic control and varies among ethnic and racial groups[14]. Black children presented with higher values of serum concentrations of Lp(a) at each level of birth weight distributions than white children[15]. Recent studies confirm and extend previous evidence that Lp (a) plays a significant role in atherosclerosis and is one of the top five or six risk factors for cardiovascular disease. In Japanese patients, Lp(a) levels and apo phenotypes are significant predictors for myocardial infarction.

We have examined the distribution of serum Lp(a) levels in 60 patients affected by acute stroke and studying 34 patients with diabetes mellitus (DM) type 2 compared with 26 non-diabetic subjects. Furthermore , we evaluated the correlation with Lp(a) concentration and waist-hip ratio(WHR).

METHOD

A total of 60 patients with acute stroke (34 non-diabetics subjects and 26 DM type 2), were included in this study. The blood samples were analyzed in the first 24 hours. The diagnosis of cerebral infarction was confirmed by clinical signs and symptoms, a history of the disease and cerebral computerized axial tomography or nuclear magnetic resonance imaging. The diagnosis of carotid vascular disease was established by an abnormal doppler. We exclude the patients with nephropathy and smokers. The study was conducted with appropriate ethics committee oversight and patients informed consent.

Type II diabetes had been previously diagnosed according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus[12], mean age was 66.35 $\pm$ 9.92 years and mean of abdominal fat, according to the WHR, was 0.96 $\pm$ 7.28. We also studied a group of 34 non-diabetic subjects with acute stroke (22 males and 12 females). Mean age of 66.71 $\pm$ 10.83 years and mean of abdominal fat, according to the WHR, was 0.96 $\pm$ 8.55.

Triglyceride and cholesterol levels were determined by standard enzymatic methods. High-density lipoprotein (HDL) ,and low density lipoprotein and very low - density lipoprotein (VLDL) cholesterol levels were measured by the ultracentrifugation-precipitation combined technique recommended by the Lipid Research Clinical Program. Lp(a) concentration was measured by enzimoimmunoassay using a monoclonal antibody against Lp(a) (Terumo Medical, Elkton, MD, USA), with normal levels until approximately 30 mg/dl[2]. Insulin was measured by radioimmunoassay method.

Statistical analysis used the SPSS PC (9.0) program and data are expressed as mean $\pm$ S.D. Comparisons between groups were performed using the two-tailed t- test for unpaired data and the χ^2-test . Pearson correlation coefficients were used to assess the relationship between Lp(a) and different parameters.

RESULTS

Table 1 shows analytical characteristics of the diabetic patients and the control subjects studied in this report. The controls patients exhibited increased Lp (a). Mean Lp(a) concentrations in DM type 2 patients (29.49$\pm$23.09 mg/dl)and in control group (44.81$\pm$44.34mg/dl) were not significantly different (t-test=1.16 and p=0.115).

The frequency distribution of Lp(a) levels in both groups was highly skewed towards the higher levels in both groups, being over 30 mg/dl in 50% (Fig 1). The proportion of subjects with Lp (a) concentration above 30 mg/dl was 18,3% in DM type 2 patients and 31,7% in control subjects (Fig 2). The value of the χ^2-test , comparing the proportion of patients, was 21,73 and p= 0,000, so the proportions of the Lp(a) levels showed in Figure 2 are statistically different.

Our results showed that serum Lp(a) levels are increased in the patients with stroke, like the results of Morrisett[16], but there were no significant differences between diabetic and non-diabetic patients.

Lp(a) concentration positively correlated with WHR (r=0.545; P=0.001), but no correlation was found between Lp(a) and total cholesterol, HDL, LDL and VLDL cholesterol, trygliceride, glycaemic and insulin plasmatic concentrations in patients affected by acute stroke. Neither did we observe differences in Lp (a) levels in relation to age and sex.

DISCUSSION

Lp(a) levels are significantly higher in ischemic stroke patients than in controls. However, plasma concentrations of Lp(a) are not predictive of ischemic cerebral infarction in either men or women. Serum Lp(a) levels are significantly higher in patients with carotid plaques or measurable intima-media thickness than in controls without[16]. Lp(a) is recognized as a new coronary risk factor, but few studies have quantitatively assessed the relationship of serum Lp(a) levels with other

Table1. Mean ± S.D.values of the analytical parameters measured in type 2 DM and non-diabetic control subjects

Parameters	Diabetic group	Control group	t-Test	p value
Glycaemia(mg/dl)	178.27 ± 72.34	98.50 ± 25.60	5.97	0.000*
Insulin (µIU/ml)	14.40±8.38	12.91±6.67	0.76	0.448
Total- cholesterol (mg/dl)	212.85±45.70	195.12±39.36	1.61	0.112
HDL-cholesterol (mg/dl)	49.38±8.72	50.59±8.43	0.54	0.591
LDL-cholesterol (mg/dl)	125.84±36.19	110.66±37.68	1.57	0.121
VLDL-cholesterol (mg/dl)	41.70±35.10	30.90±16.04	1.59	0.117
Triglycerides (mg/dl)	198.58±125.02	156.15±78.57	1.61	0.113
Lp (a) (mg/dl)	29.49±23.09	44.81±44.34	1.16	0.115

*Significative - $p < 0.05$

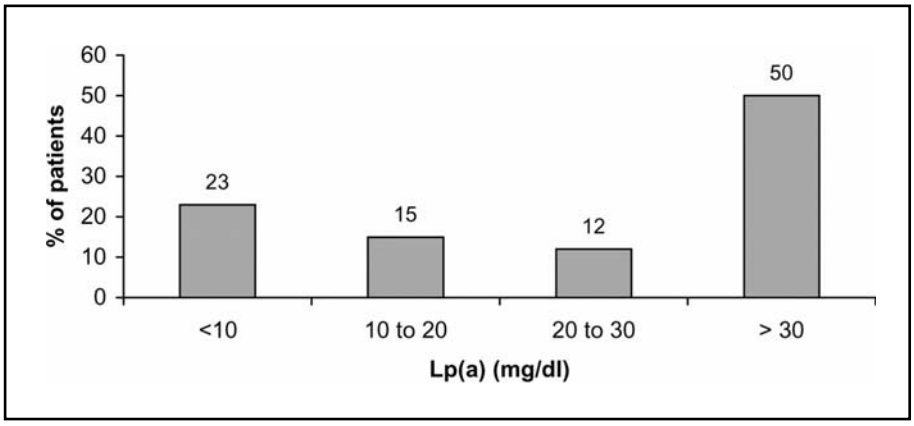

Fig 1. Frequency distribution of plasma lipoprotein(a) levels in type 2 DM patients and control subjects

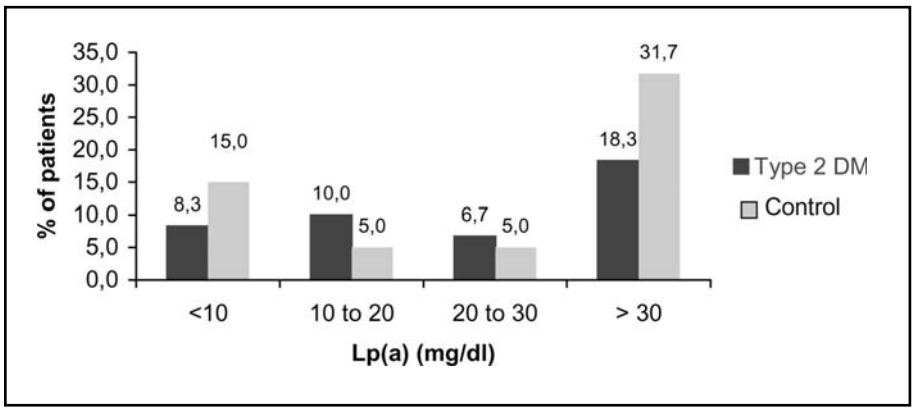

Fig 2. Frequency distribution of plasma lipoprotein(a) levels in type 2 diabetic patients comparing with control

coronary risk factors in many patients undergoing coronary cineangiography. Among many coronary risk factors that were quantified (i.e., age, gender, hypertension, impaired glucose tolerance, cerebrovascular accident, hyperuricemia, smoking, family history of ischemic heart disease (IHD), history of hyperlipidemia, Lp(a), total cholesterol, high density lipoprotein (HDL)-cholesterol, triglyceride, low density lipoprotein-cholesterol, apo A-I,B, E), Lp(a) is an independent, potential, and modifiable coronary risk factor, and its reduction is important in the clinical management of patients with ischemic heart disease and stroke[8-11]. Newer risk factors were described, including homocysteine and chronic infection (Chlamydia pneumoniae and periodontal disease), are being studied as predictors of ischemic stroke. With these recent advances in the un-

derstanding of risk factors, the ability to detect or modify the risk for ischemic stroke should lead to a substantial reduction in the number of people killed or disabled by stroke each year[17].

In this study , mean Lp(a) levels in diabetic and non-diabetic subjects was high in the 60 patients (mean=38.17±37.20 mg/dl), according to the laboratory measurements. The distribution of Lp (a) levels in both populations was highly skewed towards the higher levels similar to the distribution observed in other non-diabetic and diabetic population[18] and different from other reports[11,19]. This appeared not to be related to sex, age and the lipids parameters.

A relationship exists between obesity and non-insulin-dependent diabetes mellitus. Central abdominal obesity carries a particularly high risk that is most likely associated with enlargement of visceral fat deposits. A multiple endocrine perturbation is associated with visceral obesity[20].

In our study, only WHR was associated with Lp(a) levels. Lp(a) concentrations positively correlated with WHR (r=0.545; p=0.001). This finding was previously reported and consider the WHR as an independent determinant of Lp(a) concentrations in both type 1 and type 2 diabetes[21,9]. In contrast, in non diabetic subjects, this correlation has not been found[22].

CONCLUSION

Stroke places a tremendous burden on health resources throughout the world. Improved detection and modification of risk factors could reduce the impact of this disease. In our study, elevated Lp(a) levels were associated with ischemic stroke, irrespective of the presence of type 2 DM, so if the Lp(a) level is elevated, it seems reasonable to check the other major vascular risk factors.

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