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Is Apolipoprotein-(a) an Important Indicator of Vasculogenic Erectile Dysfunction?

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We aimed to investigate whether high peripheral and cavernosal plasma levels of apolipoprotein-(a) [Lp (a)] is an indicator for vasculogenic erectile dysfunction. We determined Lp (a), total cholesterol (TC), triglyceride (TG) and high density lipoprotein (HDL) levels in peripheral and cavernosal blood in 39 patients with erectile dysfunction. Thirty-nine impotent patients have been divided into two groups: vasculogenic erectile dysfunction (VED) and nonvasculogenic erectile dysfunction (NVED), according to colour Doppler ultrasonic flowmetry, dynamic infusion cavernosometry, and the pressure difference between the brachial arterial systolic pressure and cavernosal arterial systolic pressure measurements. Biochemical values were compared in both groups. Lp (a) and TC levels were higher in both peripheral and cavernosal samples of VED group than in NVED group, with no differences between peripheral and cavernosal blood levels within the same groups. There were no significant changes in TG and HDL levels in either group. The detection of more than 31 mg/dl in Lp (a) level solely shows the vascular origin with a sensitivity and specificity of 95 and 82.3%, respectively. High Lp (a) levels can be considered an indicator of vasculogenic erectile dysfunction.

Introduction

Apolipoprotein-(a) [Lp (a)] is a low-density lipoprotein (LDL) particle in which apolipoprotein B-100 is attached to a glycoprotein called apolipoprotein-(a). Lp (a) shares sequence homology and structural elements with plasminogen. The physiological function of Lp (a) currently remains uncertain. One hypothesis states that Lp (a) can bind to fibrin, thus supporting wound healing during inflammatory processes by supply of cholesterol. This may facilitate and enhance fibrous plaque formation in atherosclerotic lesions. Due to the genetic link between Lp (a) and plasminogen it is also possible that Lp (a) competes with plasminogen, thus interfering in the process of fibrinolysis. Lp (a) levels have been suggested to be an independent risk factor for atherosclerosis, although its mechanisms of action are still uncertain [1].

The haemodynamic basis of erection results from increased arterial inflow, sinusoidal smooth muscle relaxation and decreased venous return [2]. Failure of any of these vascular mechanisms may lead to erectile dysfunction.

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The increase in the frequency of impotence with age has been associated with atherosclerotic changes in penile arteries and the majority of cases are associated with vascular risk factors such as diabetes, smoking, hyperlipidaemia, hypercholesterolaemia and hypertension [3, 4]. These factors impair endothelium-mediated relaxation of blood vessels and cavernosal activity in both experimental animals and humans [5, 6, 7].

Experimentally it has been shown that impaired lipid metabolism plays a major role in vascular/cavernogenic erectile dysfunction [8] but this has not yet been confirmed clinically.

The aim of this study was to determine whether peripheral and cavernosal blood lipid profile and especially high Lp (a) level solely will show the nature of erectile dysfunction as vasculogenic or nonvasculogenic.

Patients and methods

We investigated 39 patients with erectile dysfunction according to a standard diagnostic algorithm. A detailed history was taken including smoking habits, alcohol consumption, the presence of chronic diseases and drug usage. Complete physical examination was performed. Laboratory tests consisted of Lp (a), total cholesterol (TC), triglyceride (TG), and high density lipoprotein (HDL) determinations in both peripheral and cavernosal blood samples.

Human Lp (a) forms a precipitate with a specific anti Lp (a) antiserum [(rabbit) (Roche Diagnostic System, Basel)] that is determined turbidimetrically at 340 nm with the Cobas Mira S autoanalyzer. The serum samples were worked freshly or stored for a maximum of 1 day at +2 °C [9].

Total cholesterol and triglyceride levels were measured using Cobas Mira S autoanalyzer with the Roche kits (Roche Diagnostic Systems, Basel). Serum HDL concentrations were measured using the same autoanalyzer after very low-density lipoprotein, and LDL were precipitated with sodium phosphotungstate in the presence of magnesium chloride.

To demonstrate the vascular aetiology colour Doppler ultrasonic flowmetry, dynamic infusion cavernosometry (DIC) were done and the pressure difference between the brachial arterial systolic pressure (BASP) and cavernosal arterial systolic pressure (CASP) (PDBC) was measured.

Colour Doppler ultrasonic flowmetry was performed using a 5 MHz Toshiba SAL 270-A linear scanner (Toshiba Corp., Japan). With the patient supine the duplex probe was placed on the ventral side at the base of the penis, and a baseline image of the penis was obtained in the longitudinal and transverse planes, including measurements of the blood flow in the cavernous arteries. A dose of 60 mg papaverine was injected intracavernously using a 27 gauge needle. Measurements of blood flow in the cavernous arteries were repeated approximately 2, 5, 10 and 20 minutes after the injection, and peak, end diastolic velocities and diameters of the cavernous arteries were determined. Peak systolic velocity greater than 25 cm per second, end diastolic flow velocity less

than 4.5 cm per second and a mean increase of 70% in the diameter of the cavernous arteries after papaverine injection were accepted as normal penile arterial flow. If after an intracavernous injection of 60 mg papaverine a full erection had not been achieved despite a blood velocity of 30 cm/s with an end diastolic value of more than 5 cm/s and detection of leakage >20 ml/min in the deep dorsal vein, then the dynamic infusion cavernosometry was performed using IVAC 770 infusion pump (IVAC Corp., San Diego, CA, USA). Papaverine was injected into the corpus cavernosum and 10 minutes later, if the infusion rate needed to maintain the intracavernous pressure at 90 cm H_2O was >30 ml/min, leakage was suspected. The intracavernous pressure was then raised to 150 cm H_2O and the infusion stopped for 30 s. If the fall in intracavernous pressure was >50 cm H_2O and the measured intracavernous pressure after 5 min was <50 cm H_2O, leakage was confirmed [10].

BASP and the right and left CASP were recorded while DIC was performed. Gradients were then calculated between the brachial and cavernosal arterial systolic pressures (brachial minus cavernosal arterial systolic pressures). Normal values for BASP–CASP were accepted as 35 mm Hg or less [11, 12].

After complete evaluation of the patients, the subjects were divided into 2 groups. Group 1: VED group having venous leakage or arterial pathology detected by colour Doppler ultrasonic flowmetry or DIC. Group 2: NVED group having no pathology detected by colour Doppler ultrasonic flowmetry or DIC. Biochemicl values were compared in both groups.

Statistical analysis was carried out by using SPSS software (Release 5.0). For statistical comparison of sample percentages among the two groups the chi-square test was used. Differences between the groups were determined by means of *t*-tests for independent samples. Sensitivity and specificity of plasma level of Lp (a) were estimated.

Results

Patient characteristics are given in Table 1. There were no significant differences in age, duration of symptoms, smoking habits and presence of chronic diseases between the VED and NVED groups (Table 1). Chronic illness included hypertension in 2 patients, diabetes mellitus in 1, chronic renal failure in 1 patient with VED and rheumatoid arthritis in 1 patient with NVED.

In the VED group venous leakage was found in 16 (73%), pure arterial pathology in 4 (17%) and mixed arterial and venous pathology in 2 patients (10%).

Peripheral blood levels of apolipoprotein-(a) ranged from 30 to 78 mg/dl (mean 53.6±14.3) and from 12 to 41 mg/dl (mean 25.9±8.7) in the VED and NVED groups, respectively ($p=0.000$) (Fig. 1). Cavernosal blood levels of apolipoprotein-(a) were 32 to 71 mg/dl (mean 51.6±12.3) and 13 to 47 mg/dl (mean 25.9±10.4), respectively, in the same patient group ($p=0.000$). There were no differences between peripheral and cavernosal blood levels of apolipoprotein-(a) within the same groups ($p>0.05$).

Table 1
Patient characteristics of vasculogenic and nonvasculogenic erectile dysfunction groups

	Vasculogenic group	Nonvasculogenic group	p value
Patients (n)	22	17	–
Mean age±SD (years)	47.8±12.4	43.1±9	0.177
Duration of symptoms (months)	13.8±20.9	18.9±21.5	0.461
Smoking habits (n/percentage)	12/57	9/53	0.822
Presence of chronic diseases (n/percentage)	4/19	1/6	0.261

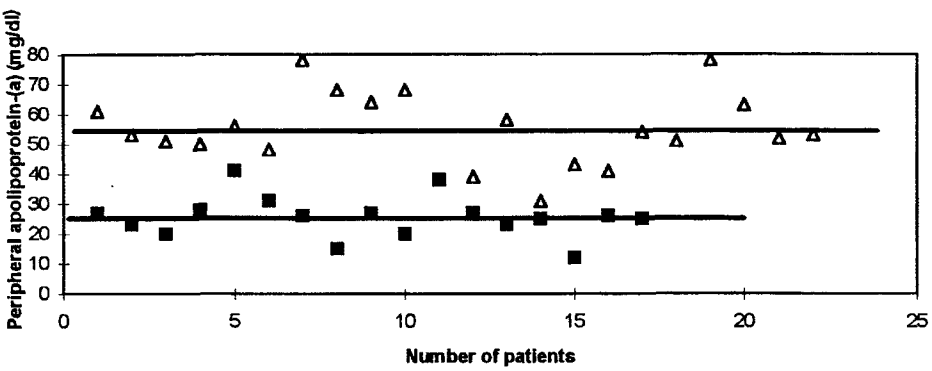

Fig. 1. Peripheral blood levels of apolipoprotein-(a) in patients with vasculogenic and nonvasculogenic erectile dysfunction

TC levels were higher in both peripheral and cavernosal samples of the VED group than in the NVED group ($p=0.000$), with no differences between peripheral and cavernosal blood levels within the same groups ($p>0.05$). There were no significant changes in TG and HDL levels in either group ($p>0.05$).

Discussion

Normal erectile function requires intact vasculogenic, neurogenic and psychogenic factors. Despite the body of literature that has accumulated regarding vascular function and impotence [3, 4, 13, 14], the causes of the development of erectile dysfunction are incompletely understood.

Significant arterial insufficiency was defined as a PDBC of more than 35 mm Hg [11, 12]. This technique discriminates intracorporeal (cavernosal) from extracorporeal (dorsal) arteries, as only those vessels lying within the tunica albuginea will be occluded following a suprasystolic elevation of the corporeal body pressure. It has been reported that a PDBC greater than 35 mm Hg had a sensitivity of 77% in predicting the presence of haemodynamically significant lesions at subsequent selective internal pudendal pharmacoangiography, and also that the PDBC was significantly more sensitive than either the penile brachial index or flow velocity of the cavernosal artery in predicting the presence of haemodynamically significant lesions at subsequent arteriography [12].

Raised Lp (a) levels are associated with an increased risk of atherosclerosis. The epidemiological relationship between high Lp (a) levels and atherosclerosis has been clearly demonstrated in recent publications [15]. Differences in disease progression among patients seem to be related to the presence or absence of Lp (a). For example, heterozygotes with familial hypercholesterolaemia with coronary heart disease often have higher plasma Lp (a) levels than those without associated coronary heart disease. The mechanism of the atherogenicity of Lp (a) is unclear, but some of the following characteristics may be relevant. Lp (a) strongly interacts with cellular matrix proteins such as fibronectin and proteoglycans. These complexes are avidly taken up by monocytes, macrophages and smooth muscle cells, transforming them into foam cells. A difference in affinity of LDL receptor to LDL and Lp (a), being lower for the latter one, may favour the uptake of Lp (a) by macrophages. As a consequence fatty streak development is favoured. Lp (a) may compete with fibrinolysis, increasing the predisposition to atherosclerosis and thrombosis [1, 9, 15]. The mean plasma Lp (a) level for the Turkish population was 21±17 mg/dl [16]. In vascular erectile dysfunction, impairment may occur in either arteries or cavernosal tissue and changes were detected in venous peripheral and cavernosal blood as increased Lp (a) levels. In this case, Lp (a) can bind to fibrin by supply of cholesterol thus supporting vascular or cavernosal pathology. A decrease in blood flow will result from arterial lumen pathology or there will not be sufficient relaxation in cavernosal tissue due to accumulation of fibrin which will lead to restriction mechanism of the corpus cavernosum causing venous impotence. We investigated the ways of diagnosing vascular aetiology by determining blood lipids, especially Lp (a), in patients with erectile dysfunction. The data suggest a correlation between the high plasma level of Lp (a) and vasculogenic erectile dysfunction. The detection of more than 31 mg/dl in Lp (a) level solely shows the vascular origin with a sensitivity and specificity of 95 and 82.3%, respectively.

Some previous studies showed that smoking, hypertension, diabetes mellitus, and hyperlipidaemia may be risk factors for erectile dysfunction [3, 4, 14]. It has been shown that a high level of TC and a low level of HDL were important risk factors for erectile dysfunction and may result in arteriosclerosis and induce erectile dysfunction by arterial insufficiency [17, 18]. In addition, a high level of TC or low level of HDL could also result in degeneration of cavernous smooth muscle and inability to expand the cavernosal trabeculae against the

tunica albuginea and compress the subtunical venules, thereby inducing erectile dysfunction by excessive blood outflow [8, 14, 18, 19].

Physical loss of endothelial cells and changes in the endothelial cell organelles such as swollen mitochondria, distended vesicles, and degenerating nuclei, focal areas of endothelial disruption with protruding, vacuolated endothelial cells containing increased numbers of cytoplasmic organelles have been reported in hypercholesterolaemia. It has been shown that ultrastructural evidence of an early atherosclerotic-like process in the endothelium and smooth muscle of the corpus cavernosum was accompanied by vasomotor changes [6]. Such alterations can lead to impaired ability of the endothelium to synthesize nitric oxide (NO). Another possibility is that Lp (a) and hypercholesterolaemia could impair diffusion and enhance degradation of NO during transit from endothelial cells to underlying smooth muscle. Hypercholesterolaemia has been found to be associated with altered synthesis of collagen in vascular tissue and increased cross-linking of collagen fibres and to result in loss of compliance of the arterial wall [14]. It was demonstrated that hypercholesterolaemia impaired the endothelium-mediated relaxation of the rabbit corpus cavernosum smooth muscle [5].

A decrease in the smooth muscle fibres was shown in patients with corporeal venoocclusive dysfunction and arterial lesions using computerized digital image analysis of corpus cavernosum biopsies [19]. It has been shown that erectile dysfunction and decreased papaverine efficacy in rabbits may be secondary to hypercholesterolaemia [6]. It has been demonstrated that cholesterol, triglycerides and free fatty acids were elevated in cavernous tissue of rabbits fed a high lipid diet when compared with the control group [8]. Pickard et al. [20] found impaired smooth muscle contractility and nerve-evoked relaxation in tissue of patients with vasculogenic impotence.

In the present study, our findings also suggest that high peripheral and cavernosal plasma levels of Lp (a) and cholesterol may accumulate in the corpus cavernosum, destroy the smooth muscle fibres of the cavernosum and may lead to a decrease in their number, impairing cavernosal relaxation in response to papaverine. In addition, a high plasma level of Lp (a) could also result in degeneration of cavernous smooth muscle and inability to expand the cavernosal trabeculae against the tunica albuginea and compress the subtunical venules, thereby inducing erectile dysfunction as shown previously in patients with high level of TC and low level of HDL [8, 14, 18, 19].

In conclusion, our preliminary results suggest that simply the finding of high peripheral blood apolipoprotein-(a) may replace other invasive diagnostic parameters obtained by intracavernous pharmacological test, DIC, PDBC measurements to indicate a vascular aetiology in erectile dysfunction. Due to its simplicity, it may also help to decrease the number of invasive diagnostic tests in many cases of vasculogenic erectile dysfunction. Further studies on larger patient populations are required to improve the interpretation of serum apolipoprotein-(a) levels in vasculogenic erectile dysfunction in order to establish the possible usefulness of the plasma apolipoprotein-(a) level as an indicator of vasculogenic erectile dysfunction.

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