Original communication

Role of Lp(a) in patients with erectile dysfunction undergoing angioplasty for symptomatic pelvic artery disease

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Summary: *Background:* Atherosclerotic disease of erection-related arteries is a major reason for erectile dysfunction (ED). Lp (a) has been implied in the pathophysiology of atherosclerosis in the coronary and lower limb arteries. Here, we investigated if Lp(a) plays a specific role in ED due with symptomatic pelvic artery atherosclerosis. *Patients and methods:* Out of 276 consecutive patients treated for ED with angioplasties on proximal (69%) and distal (31%, distal to Alcock channel) erection-related arteries, 236 patients (age: 62±10 years) of which Lp(a) values were available were retrospectively analyzed. *Results:* The baseline International Index of Erectile Function-15 (IIEF-15) score was 29±15 and significantly increased to 43±20 (increase: 14±21) after treatment at average follow up of 286±201 days. In 25%, Lp(a) values were elevated to more than 30 mg/dL. Hypercholesterolemia, coronary, lower extremity peripheral, and polyvascular disease were more common in patients with Lp(a) ≥60 mg/dl. Anatomic arterial lesion distribution (proximal/distal), improvement in IIEF-15 and clinically driven re-intervention rate (overall 7%) did not differ between patients with <30, 30–59, and ≥60 mg/dL Lp(a). *Conclusions:* While angioplasty is an effective therapy for ED of arterial origin in patients with obstruction of erection-related arteries, Lp(a) does not seem to play a major role for clinical outcomes in these patients.

Keywords: Lipoprotein(a), erectile dysfunction, endovascular treatment, penile artery

Abbreviations

CAD: Coronary artery disease
CIA: Common iliac artery
cTLR: Clinically driven target lesion revascularisation
CVD: Cardiovascular disease
HDL: High density lipoprotein
IIA: Internal iliac artery
IIEF-15: International Index of Erectile Function-15
IPA: Internal pudendal artery
LDL: Low-density lipoprotein
PAD: Peripheral artery disease

Introduction

Over the last years, various studies have documented that erectile dysfunction (ED) is an increasing and common problem in cardiovascular medicine. The prevalence of ED may be as high as 30% in young men, while it may be as high as 86% in men older than 80 years [1, 2, 3]. It is estimated that about 322 million men will suffer from ED in the year 2025 [4].

ED is seen as a sentinel disease as it is often the first clinical manifestation of atherosclerosis [5, 6] and can be clinically evident years before any cardiovascular event [7, 8]. Several meta-analyses have indicated an increased risk of cardiovascular disease (CVD), stroke and all-cause mortality in men with ED [9, 10]. Thus, ED is considered an independent predictor for major cardiovascular events including myocardial infarction, cardiac arrest, fatal acute coronary syndrome and fatal stroke [11, 12]. In young patients, ED represents a surrogate marker for coronary artery disease (CAD) [13]. Indeed, a near 50-fold increase in CAD incidence was oberserved in men aged 40–49 with

ED vs. men without, indicating a potential prognostic utility of screening for CVD risk in younger men with ED [14]. If specific risk factors involved in ED exist is not known.

Striking similarities in the vascular pathophysiology are considered the evident link between ED and CVD. ED shares identical classical risk factors with CVD in other territories such as arterial hypertension, diabetes mellitus (DM), obesity, metabolic syndrome, dyslipidemia, lack of exercise and particulary cigarette smoking [15]. Interestingly, the specific role of novel risk factors such as Lipoprotein(a) [16] in the context of vascular ED is unknown. Lp(a) is an established independent causal risk factor not only for CVDs such as myocardial infarction [17] or ischemic stroke [18] but also for all-cause and cardiovascular mortality [19]. Elevated Lp(a) was found as a risk factor for peripheral artery disease (PAD) [20], with high Lp(a) levels associated with an increased risk of developing PAD [21] and more severe atherosclerosis [22] indicating a direct correlation between Lp(a) levels and the severity of PAD [23]. Furthermore, the prevalence of severe calcification of femoropopliteal lesions was higher in patients with high Lp(a) than compared to those with low Lp(a) [24]. In addition, Lp(a) was shown to be independently associated with an impaired outcome after surgical iliofemoral enarterectomy [25] and loss of primary patency after endovascular therapy for femoropopliteal PAD [26].

We hypothesized that Lp(a) may play a specific role in ED. The objectives of this study are to: (a) describe the distribution of Lp(a) across a large cohort of patients with ED undergoing endovascular treatment of pelvic artery obstructions, (b) determine the association between Lp(a) level and atherosclerotic lesion pattern and severity; (c) assess the impact of Lp(a) on clinical outcomes including symptomatic improvement, mortality and target lesion revascularisation.

Patients and methods

We retrospectively analyzed records of patients undergoing angioplasty for symptomatic atherosclerosis in erection related arteries with ED within a clinical registry approved by the local ethics committee (SwissPOWER registry, EKNZ 2018-00408).

Included patients did not respond sufficiently to conservative medical treatment with phosphodiesterase 5 inhibitors (PDE5i) or suffered from severe side effects of the latter. As the focus was on analyzing the data regarding the Lp(a) levels in patients with atherosclerotic ED, only 236 out of 276 consecutive patients undergoing angioplasties were included, as Lp(a) values at baseline were not available in all 276 patients.

Clinical investigation

All patients underwent detailed assessment, such as hormonal examination to exclude hypothalamic-pituitary and/or gonadal disorder, as well as thyroid dysfunction. Before they were urologically co-assessed and an urological pathology of ED excluded.

All patients initially underwent an intensive medical and sexual case history especially regarding comorbidities and cardiovascular risk factors.

The International Index of Erectile Function-15 (IIEF-15) questionnaire was used to quantify treatment-related changes in patients with erectile dysfunction [27]. The self-administered IIEF addresses the relevant domains of male sexual function (that is, erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction), is psychometrically sound, and has been linguistically validated in ten languages. It was completed by the patients before endovascular revascularization and in the context of the follow up assessment. The minimal achievable score was five, the highest 75. Under a score of ten, severe ED was high likely, over 26 it was more improbable.

As part of the diagnostic work-up, vascular duplex ultrasound examination was performed in all patients. To examine the arterial part of the erection related vascular system a pharmacological erection was induced by intracavernosal administration of 10 µg of prostaglandin E1 (Alprostadil) injected into the corpus cavernosum from lateral. When maximum possible erection was achieved, peak systolic velocity (PSV) and end diastolic velocity (EDV) were measured. PSV<0.3 m/s defined pathological arterial flow [28, 29, 30, 31], indicative of an atherosclerotic cause for the ED. To rule out venous leakage as a cause of vascular ED, end-diastolic velocity had to be <0.05 m/s [32].

To substantiate the results and gather information regarding localization and severity of the lesions computed tomography angiography (CTA) of the iliac and pudendal arteries was performed.

More data was collected regarding patient comorbidities and angiographic characteristics of the lesions in erection related arteries. The lipid profile included total cholesterol, low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and Lp(a). Queried comorbidities were diabetes mellitus, hypercholesterolemia, arterial hypertension, terminal renal insufficiency (dialysis) and vascular diseases including CAD, lower extremity PAD and cerebrovascular disease. Moreover, the patients were questioned about their current and previous smoking status.

The cohort was subdivided in three groups depending on their Lp(a)-levels: normal (<30 mg/dL), moderately increased (30–59 mg/dL) and high (≥60 mg/dL) Lp(a). The above-described data was assigned to these groups and compared regarding the severity of symptoms, the improvement of the symptoms after angioplasty, the location of the most proximal lesion and number of lesions, the separate parts of the lipid profile, the comorbidities, risk factors and clinical necessity of a repeat procedure.

Endovascular therapy

The indication for endovascular therapy was set when patients still suffered from ED after uneffective medical therapy with PDE5i and/or intracavernosal prostaglandin

or had severe side effects/contraindications regarding that medication. In addition a vascular cause had been established by means of duplex ultrasound and non-vascular causes like psychogenic causes, pelvic trauma/radiation had been ruled out.

Endovascular therapy was performed as previously described [33]. Before endovascular revascularization was carried out, patients were further assessed by selected angiographic imaging by placing a diagnostic catheter at the origin of the internal iliac artery via cannulation of the usually right common femoral artery. By administration of contrast material, the degree of the arterial obstruction could be assessed, a lumen compromise >50% hereby confirmed the diagnosis of atherogenic ED and indicated endovascular revascularization. By this means, the exact location of the lesion(s) could be documented and categorized into proximal (common iliac artery (CIA), internal iliac artery (IIA), proximal internal pudendal artery (IPA)) and distal (distal internal pudendal artery (IPA), common penile artery, dorsal penis artery, cavernous artery/deep penis artery) lesions.

When atherosclerotic lesions were confirmed on intra-arterial angiographic imaging, endovascular therapy was performed subsequently. Heparin (5,000 units) was administered and the lesion was crossed with a 0.014″ guidewire.

The reference vessel diameter (RVD) of the lesion was visually estimated, in case of a RVD $\leq$1.5 mm, angioplasty with a drug-coated balloon was conducted without inserting a stent. In case of RVD $\geq$1.5 mm a drug-eluting stent (DES) was implanted (Angiolite [iVascular, Barcelona, Spain]). In case the lesion was not primarily crossable with the DES, a predilation with an appropriate balloon has been carried out.

Revascularization of bilateral lesions was conducted in one stage at the operator's discretion. All patients were treated by the same operator, who had more than seven years of experience in the area of endovascular treatment of ED.

After endovascular therapy, patients received a dual platelet inhibition with acetylsalicylic acid 100 mg/d and clopidogrel 75 mg/d for 6 months. Tadalafil 5 mg/d was prescribed for 3 weeks.

Statistics

Data are presented as mean±standard deviation. Mean values were compared by independent t-test or one way-ANOVA for continuous parameters and Mann-Whitney U or Kruskal-Wallis test for categorical variables. Outcome data were compared with Kaplan-Meier survival analysis and log-rank test. P-values of less than 0.05 were regarded as statistically significant. Analyses were performed with SPSS 28 (IBM). Lp(a) values of less than 10 mg/dL were treated as zero.

Results

Baseline characteristics

Out of 276 consecutive male patients receiving endovascular therapy of erection-related arteries for ED, we analyzed 236 patients of which Lp(a) values were available. In 78 of the patients (33%) the procedure was performed in two sessions (staged procedure). The mean age was 62±10 years. Overall, 203 patients attended their follow-up appointments on average 286±201 (SD) days after the procedure. All patients were alive at the end of the FU period.

Table I summarizes the patient's baseline characteristics.

The patients were divided into three groups according to the level of Lp(a) concentration in plasma at the time of baseline exams as described above. In 25% of the patients (n=59) Lp(a) values were elevated above the normal limit of 30 mg/dL. Out of those, 8% (n=18) were in the moderate group (30–59 mg/dL), 17% (n=41) had high Lp(a) levels $\geq$60 mg/dL. There was no significant difference in terms of age, total cholesterol, LDL and HDL between the three groups. A significantly higher proportion of people with elevated Lp(a) had a diagnosis of hypercholesterolaemia, CAD, PAD and polyvascular disease and were on statin medication. Within the group of patients with CAD, 43% had elevated Lp(a) >30 mg/dl (no CAD: 22%) and in PAD 44% were elevated (no PAD: 23%). On average, patients with CAD had Lp(a) values of 43±61 mg/dl [mean±SD] (no CAD: 22±36 mg/dl, *p=0.004*) and PAD 39±46 mg/dl (not PAD 40±46 mg/dl, *p=0.061*). There was no statistically significant difference in terms of Lp(a) between patients with isolated CAD and PAD.

Distribution of arterial lesions

Figure 1 and Table II show the distribution of (most proximal) treated lesions according to Lp(a) category. The majority of treated lesions were proximal to the Alcock canal (n=163, 69%). The most common lesions treated were in the internal pudendal artery (55%), followed by the internal iliac artery (13%) and common penile artery (12%).

There was no obvious pattern of distribution related to Lp(a) levels. Between the Lp(a) categories there was no significant difference in terms of distribution (proximal vs. distal to Alcock canal) (*p=0.073*).

In the majority of cases (n=150, 55%) only one lesion was treated and in fewer patients two (32%), three (8%), four (4%) or five (0.4%) lesions were treated. The total number of lesions requiring angioplasty did not significantly differ between Lp(a) categories (1.6±0.8, *p=0.080*).

Clinical success of procedures

At baseline, the clinical erectile function score (IIEF-15) was 29±15. After the endovascular treatment it significantly increased to 43±20 (increase: 14±21) (*p<0.001*) at an average follow up of 286±201 days. The IIEF-15 score at baseline, after treatment or the change did not differ between Lp(a) categories (*p=0.265, p=0.274, p=0.679*). The change in IEFF-15 also did not differ when proximal or distal lesions were treated (proximal lesions: increase 14.3±21.3; distal lesions: increase 12.7±21.3; *p=0.631*) and there was

Table I. Baseline characteristics

	All	Lp(a) <30 mg/dL	Lp(a) 30–59 mg/dL	Lp(a) ≥60 mg/dL	*p-value*
n (%)	236 (100)	177 (75)	18 (8)	41 (17)	
Age (years)	62±10	62±9	57±9	62±11	*0.114*
Baseline IIEF-15 score	29±15	30±15	32±14	26±14	*0.192*
FU IIEF-15 score	43±20*	44±19*	36±21*	41±18*	*0.309*
Change in IIEF score	14±21	14±21	10±21	16±22	*0.686*
Total cholesterol (mmol/L)	5.0±1.2	5.1±1.1	4.7±1.0	5.0±1.3	*0.546*
LDL (mmol/L)	3.3±1.0	3.3.±1.0	3.2±1.0	3.4±1.1	*0.770*
HDL (mmol/L)	1.3±0.4	1.3±0.4	1.2±0.3	1.3±0.4	*0.206*
Lp(a) (mg/L)	278±543	60±83	441±102	1,121±841	*<0.001*
Proximal disease n (%)	153 (69)	117 (66)	14 (78)	27 (78)	*0.234*
Distal disease n (%)	83 (31)	65 (34)	4 (22)	14 (22)	
Number of lesions (n)	2.0±1.2	2.0±1.1	2.1±1.5	2.3±1.1	*0.184*
Diabetes mellitus n (%)	49 (18)	31 (18)	5 (28)	9 (21)	*0.540*
Dialysis (n)	0	0	0	0	
Hypercholesterolaemia n (%)	114 (41)	70 (40)	7 (39)	26 (62)	*0.034*
Hypertension n (%)	140 (51)	88 (55)	9 (50)	21 (50)	*0.999*
Current smoker n (%)	78 (28)	44 (25)	11 (61)	9 (21)	*0.125*
Ex smoker n (%)	80 (29)	47 (27)	5 (28)	13 (31)	
Statin n (%)	115 (42)	69 (39)	9 (50)	25 (61)	*0.033*
Aspirin n (%)	154 (56)	94 (54)	10 (56)	24 (59)	*0.816*
Clopidogrel n (%)	29 (11)	18 (10)	1 (6)	3 (7)	*0.724*
Oral anticoagulation n (%)	29 (11)	13 (7)	2 (11)	5 (12)	*0.555*
Blood pressure lowering medication n (%)	132 (48)	83 (47)	7 (39)	21 (51)	*0.682*
CAD n (%)	49 (18)	21 (12)	2 (11)	14 (33)	*0.003*
PAD n (%)	31 (11)	15 (9)	3 (17)	9 (21)	*0.050*
CVD n (%)	4 (1)	3 (2)	0	1 (2)	*0.808*
Number of vascular beds (CVD/PAD/CAD)	0.3±0.6	0.2±0.5	0.3±0.6	0.6±0.8	*0.001*

Notes. Values are mean and standard deviation. P values are from one way ANOVA or Kruskal-Wallis test. *p<0.05 vs. baseline.

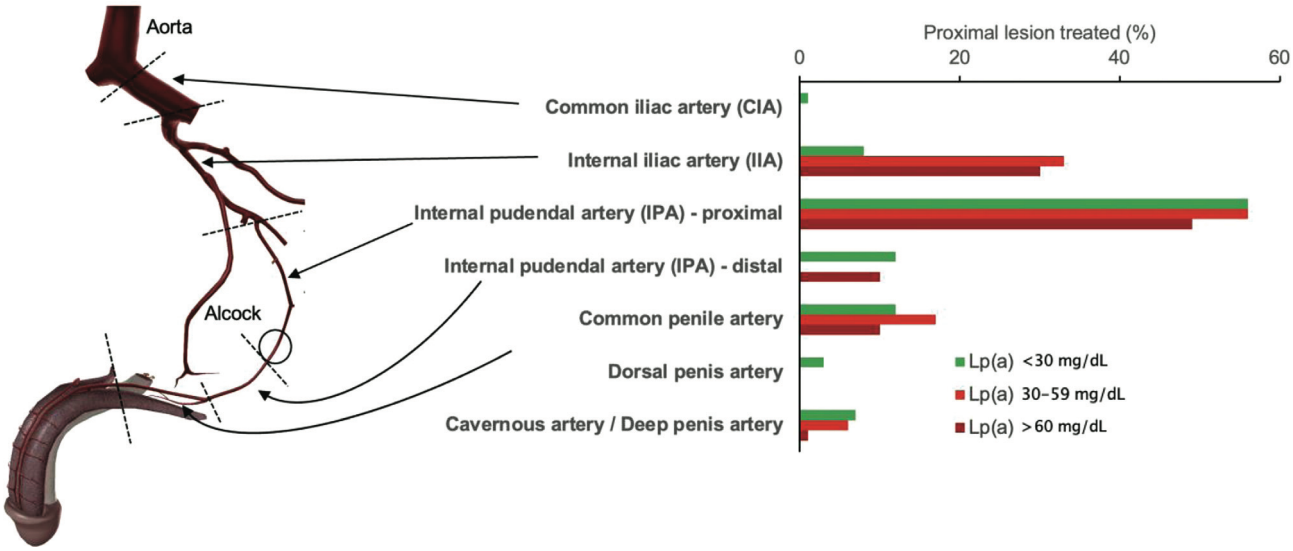

Figure 1. Distribution of most proximal lesion treated according to Lp(a) values.

no significant difference when multiple lesions were treated (*p=0.606*).

Overall, 68.6% of the treated patients clinically improved after the procedure as indicated by an increase in the IIEF-15.

Re-intervention

In a few patients (n=6, 2.5%) symptoms persisted or re-occurred requiring unplanned clinically driven target lesion revascularisations that were performed at a mean of 776

Table II. Anatomic distribution according to most proximal lesion

	All	Lp(a) <30 mg/dL	Lp(a) 30–59 mg/dL	Lp(a) ≥60 mg/dL
Proximal				
Common iliac artery (CIA)	2 (1%)	2 (1%)		
Internal iliac artery (IIA)	31 (13%)	15 (8%)	4 (22%)	12 (30%)
Internal pudendal artery (IPA) – proximal	130 (55%)	100 (56%)	10 (56%)	20 (49%)
Distal				
Internal pudendal artery (IPA) – distal	25 (11%)	21 (12%)		4 (10%)
Common penile artery	28 (12%)	21 (12%)	3 (17%)	4 (10%)
Dorsal penis artery	6 (3%)	6 (3%)		
Cavernous artery/Deep penis artery	14 (6%)	12 (7%)	1 (6%)	1 (2%)

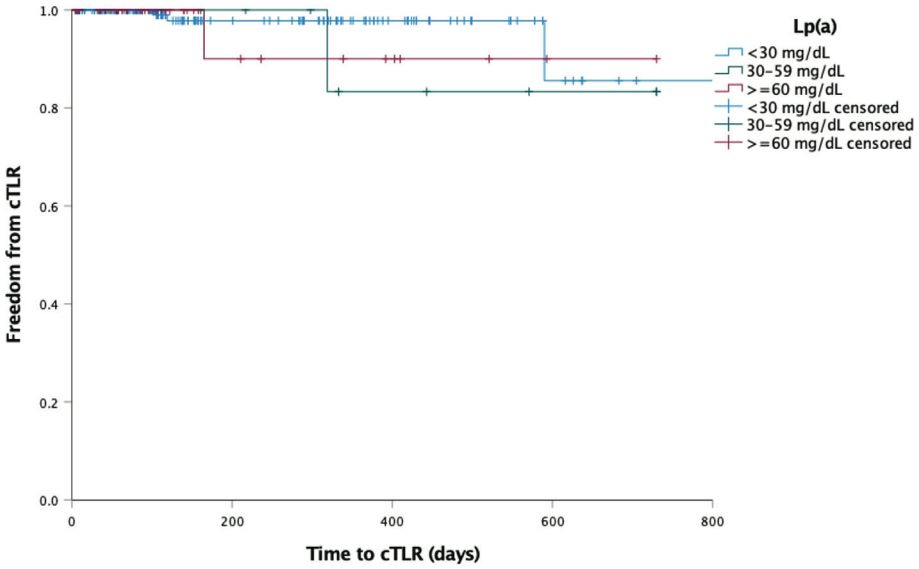

Figure 2. Freedom from clinically driven target lesion revascularization (cTLR) did not differ between Lp(a) categories. Log-Rank Mantel Cox *p=0.865.*

days (95% CI: 728 days, 823 days). There was no difference between the Lp(a) categories (*p=0.705*, log Rank [Mantel Cox], Figure 2) and between proximal or distal lesions (*p=0.691,* Figure 3).

Discussion

Our data show the prevalence of elevated Lp(a) in patients with ED of arterial cause, that were treated for stenosis in erection related arteries. The patients with high Lp(a) values were significantly more affected by CAD, PAD, and polyvascular disease.

While endovascular treatment significantly clinically improved erectile dysfunction, our data demonstrate that Lp(a) does not play a relevant role in regards to clinical severity of ED, anatomic arterial lesion distribution in erection-related arteries and clinical outcome after endovascular treatment. This study adds to this growing body of evidence and sheds further light on the understanding of specific risk factors involved in ED.

Lp(a) may be the strongest genetic risk factor for cardiovascular disease identified so far [34, 35]. Many large population studies have shown a strong independent and causal relationship between high Lp(a) levels not only with heart disease [36, 37, 38, 39, 40, 41, 42], but also with all-cause and cardiovascular mortality [19]. It has long been shown and more recently genetically confirmed that patients with premature vascular disease like PAD have over proportionately often elevated plasma levels of Lp(a) [39, 43]. Apart from male gender, smoking, hypertension or a positive family history, elevated Lp(a) levels are the most important CV risk factors in patients with premature CV disease [44] and associated with a high lifetime risk of cardiovascular disease similar to those with heterozygous familial hypercholesterolaemia [45]. Lp(a) is thought to increase the risk of cardiovascular disease by two different pathways. Firstly by causing atherosclerosis increaseing the size of atheroma in artery walls, causing inflammation, instability and growth of smooth muscle cells. Secondly Lp (a) also triggers blockage of arteries by interfering with clotting mechanisms and therefore promotes clot development on the inner surface of blood vessels [46]. We show here for the first time that 25% of patients with symptomatic ED exhibited elevated Lp(a) values of >30 mg/dL. It is quite difficult to put this in perspective with epidemiological data on Lp(a) in the general population. Most of the surveys

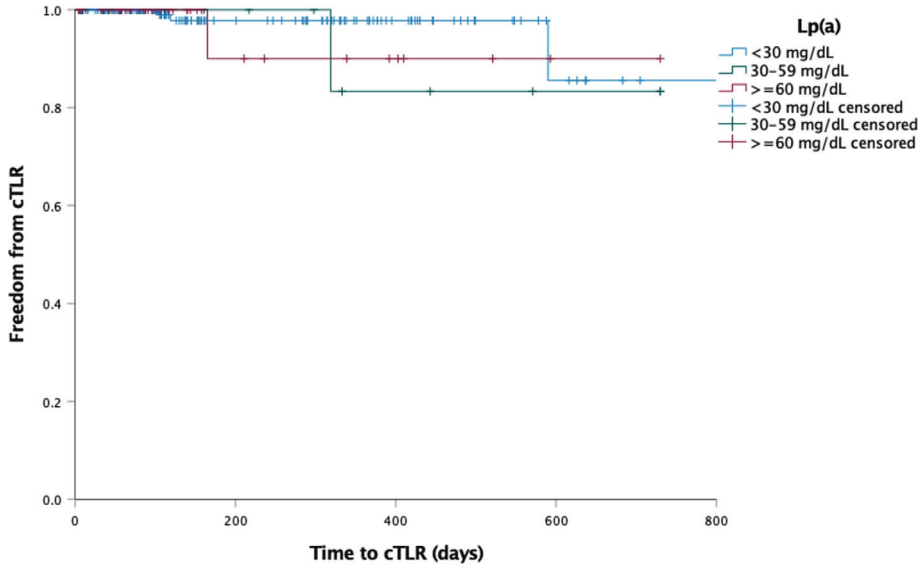

Figure 3. Freedom from clinically driven target lesion revascularization (cTLR) according to proximal vs distal lesion localization (Log-Rank Mantel Cox [*p=0.691*]).

refer to one study, the Copenhagen General Population Study, which used a cut off of 50 mg/dL. This study showed that Lp(a) values were increased in 20% of the general population and 36% in patients with CAD [42, 47]. Researchers that used a 30 mg/dL cut off found elevated Lp(a) levels in 25% of their control groups [48, 49]. In the current study 43% and 44% of patients with CAD and PAD had Lp(a) levels >30 mg/dL and 22–23% in patients without CAD and PAD. Taken together our data align with epidemiological data on control and vascular disease patients but do not support that an increased prevalence of elevated Lp(a) exists in ED patients. Our data confirm previous findings that the majority of arterial obstructions are located in the proximal segments including the pudendal artery (69%) and less frequent in the more distally located penile arteries (31%) [50]. However, neither the distribution of lesions nor the severity of ED in terms of IEFF-15 score differed between patients with and without elevated Lp(a). This may indicate that the pelvic arteries are rather not specifically prone to effects of Lp(a). However, in the groups with elevated Lp(a) the proportion of CAD, PAD and polyvascular disease were significantly higher. This would be expected from previous research. It is known that ED and CVD share common classical risk factors such as the ones mentioned above, as well as obesity, diabetes, metabolic syndrome and lack of exercise [51, 52]. Researchers have used CVD risk factors or protective factors to study its relationship with ED, and have confirmed that ED prevalence was positively associated with diabetes, obesity, hypertension, heart disease, and psychological stress in middle and old aged men [10]. An association between ED and hyperlipidemia has been established with high concentrations of LDL and low levels of HDL being strong risk factors for penile atherosclerosis [53]. In our current patient cohort, cardiovascular risk factors like hypercholesterolaemia (41%), hypertension (51%) and smoking (28%) were quite frequent. 18% and 11% were previously diagnosed with cardiovascular diseases CAD and PAD. Previous studies showed a high incidence of hypertension in ED patients (41–42%) vs. 19% in men without ED [54, 55]. Around 20% were affected by diabetes [55, 56], approximately 23% (vs. 17% in the control group) were smokers [57]. Our data confirm these findings and partly even exceed them as outlined above. Taken together, ED is a sentinel disease [5, 6] and men presenting with ED should be considered for CVD risk assessment [58] including Lp(a) as this should be considered at least once in each adult person's lifetime to identify those with very high Lp(a) levels and for the purpose of reclassification [45].

Endovascular treatment can significantly improve symptoms of ED. Over the last decade various studies investigated the efficiency of endovascular ED treatment. In 2014–2018 analysis of the PERFECT registry, PERFECT studies-1 and -2 found clinical success rates of 62%, 60% and 50% [59, 60, 61] after endovascular treatment. A recent meta-analysis of 162 patients confirmed these results by establishing a clinical improvement of 63% of the cohort [62]. In our current study, the proportion of patients that exhibited clinical improvement of ED was 69% supporting the clinical utility of endovascular revascularization in ED. Furthermore, while other trials used the IIEF-5 score, we used the IIEF-15 questionnaire to examine the clinical expression of ED. That questionnaire contains ten more questions regarding quality, frequency and confidence regarding the erection, which makes it more precise and might even increase the value of our proven efficiency rate.

In the present study, only a small number of clinically driven target lesion revascularizations (cTLR) were required (2.5%). Lp(a) did not affect the rate of reinterventions. Currently there are no comparable data regarding cTLR in ED patients with a focus on Lp(a) levels. In contrast, Lp(a) and cTLR/in-stent restenosis became a subject of interest in endovascular treatment of other

cardiovascular diseases in particular coronary interventions. The results are controversial. While some studies could not find a significant relation between high Lp(a) levels and restenosis [63, 64] others indicated Lp(a) as an independent predictor for these [65]. A recent meta-analysis found that elevated plasma Lp(a) seems to be associated with in-stent restenosis, but apparently highly dependent on the patient's ethnicity, which in this case was mostly Asian [66] which is not comparable to our data in a Caucasian population.

Limitations

Several limitations of the current study need to be taken into account when interpreting the results. These are mostly related to the retrospective analysis of routine data, relatively small samples size and number of cTLR. All patients were scheduled for a follow-up appointment after the endovascular procedure to evaluate the clinical success. The observed time between procedure and clinic appointment was very heterogeneous (mean time±SD: 286±201 days). If the procedure was technically successful, and symptoms had improved the patients were usually discharged from the clinic after this appointment and instructed to come back if symptoms re-occurred or worsened. The number of patients and cTLR recorded was low (n=6) and 40 patients needed to be excluded because Lp(a) baseline values were not available. We cannot rule out that patients might have been missed because they did not come in to report worsening symptoms or went to another physician to seek treatment. However comparable studies investigating the role of Lp(a) in other vascular regions had similar or much smaller numbers of patients and yet were able to show a clear association between Lp (a) levels and lesion and restenosis severity [24, 26].

Conclusions

Our data in patients with severe ED confirm that elevated Lp(a) levels are associated with hypercholesterolemia, CAD, PAD and polyvascular disease. While endovascular treatment of erection-related arteries is a safe and effective mean to improve ED, there was no association between elevated Lp(a), clinical severity, arterial lesion distribution or cTLR. Thus, Lp(a) might not play a major specific role in atherosclerotic disease and endovascular treatment of erection related pelvic arteries. However, patients with ED should be screened for CVD risk factors and this may be a good time to evaluate Lp(a) levels as part of the assessment. Our findings provide further evidence that the human vasculature is very heterogeneous and that the impact of different risk factors on atherosclerotic disease progression varies greatly between regions as already demonstrated in the Scottish heart Health Cohort for CHD and PAD [67].

References

1. Nguyen HMT, Gabrielson AT, Hellstrom WJG. Erectile dysfunction in young men – a review of the prevalence and risk factors. Sex Med Rev. 2017;5(4):508–20.
2. Prins J, Blanker MH, Bohnen AM, Thomas S, Bosch JL. Prevalence of erectile dysfunction: a systematic review of population-based studies. Int J Impot Res. 2002;14(6):422–32.
3. Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. J Urol. 2000;163(2):460–3.
4. Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int. 1999;84(1):50–6.
5. Uddin SMI, Mirbolouk M, Dardari Z, Feldman DI, Cainzos-Achirica M, DeFilippis AP, et al. Erectile dysfunction as an independent predictor of future cardiovascular events: the multi-ethnic study of atherosclerosis. Circulation. 2018;138(5):540–2.
6. Corona G, Rastrelli G, Isidori AM, Pivonello R, Bettocchi C, Reisman Y, et al. Erectile dysfunction and cardiovascular risk: a review of current findings. Expert Rev Cardiovasc Ther. 2020;18(3):155–64.
7. Vlachopoulos C, Jackson G, Stefanadis C, Montorsi P. Erectile dysfunction in the cardiovascular patient. Eur Heart J. 2013;34(27):2034–46.
8. Scranton RE, Goldstein I, Stecher VJ. Erectile dysfunction diagnosis and treatment as a means to improve medication adherence and optimize comorbidity management. J Sex Med. 2013;10(2):551–61.
9. Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol. 2011;58(13):1378–85.
10. Vlachopoulos C, Rokkas K, Ioakeimidis N, Aggeli C, Michaelides A, Roussakis G, et al. Prevalence of asymptomatic coronary artery disease in men with vasculogenic erectile dysfunction: a prospective angiographic study. Eur Urol. 2005;48(6):996–1002. Discussion 1002–3.
11. Yannas D, Frizza F, Vignozzi L, Corona G, Maggi M, Rastrelli G. Erectile dysfunction is a hallmark of cardiovascular disease: unavoidable matter of fact or opportunity to improve men's health? J Clin Med 2021;10(10):2221.
12. Mostafaei H, Mori K, Hajebrahimi S, Abufaraj M, Karakiewicz PI, Shariat SF. Association of erectile dysfunction and cardiovascular disease: an umbrella review of systematic reviews and meta-analyses. BJU Int. 2021;128(1):3–11.
13. Dattatrya KY, Vedpalsingh TH, Gorakhnath WV, Kiran PS. Can erectile dysfunction in young patients serve as a surrogate marker for coronary artery disease? J Clin Diagn Res 2015; 9(11):PC01–3.
14. Inman BA, Sauver JL, Jacobson DJ, McGree ME, Nehra A, Lieber MM, et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clin Proc. 2009;84(2):108–13.
15. Osondu CU, Vo B, Oni ET, Blaha MJ, Veledar E, Feldman T, et al. The relationship of erectile dysfunction and subclinical cardiovascular disease: a systematic review and meta-analysis. Vasc Med. 2018;23(1):9–20.
16. Klarin D, Lynch J, Aragam K, Chaffin M, Assimes TL, Huang J, et al. Genome-wide association study of peripheral artery disease in the Million Veteran Program. Nat Med. 2019;25(8): 1274–9.
17. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009;301(22):2331–9.
18. Langsted A, Nordestgaard BG, Kamstrup PR. Elevated lipoprotein(a) and risk of ischemic stroke. J Am Coll Cardiol. 2019;74(1):54–66.
19. Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein (a) and high risk of mortality. Eur Heart J. 2019;40(33):2760–70.

20. Kosmas CE, Silverio D, Sourlas A, Peralta R, Montan PD, Guzman E, et al. Role of lipoprotein (a) in peripheral arterial disease. Ann Transl Med. 2019;7(Suppl 6):S242.
21. Cheng SW, Ting AC, Wong J. Lipoprotein (a) and its relationship to risk factors and severity of atherosclerotic peripheral vascular disease. Eur J Vasc Endovasc Surg. 1997;14(1):17–23.
22. Tmoyan NA, Ezhov MV, Afanasieva OI, Klesareva EA, Razova OA, Kukharchuk VV, et al. The association of lipoprotein(a) and apolipoprotein(a) phenotypes with peripheral artery disease. Ter Arkh. 2018;90(9):31–6.
23. Aboyans V, Criqui MH, Denenberg JO, Knoke JD, Ridker PM, Fronek A. Risk factors for progression of peripheral arterial disease in large and small vessels. Circulation. 2006;113(22): 2623–9.
24. Yanaka K, Akahori H, Imanaka T, Miki K, Yoshihara N, Kimura T, et al. Relationship between lipoprotein(a) and angiographic severity of femoropopliteal lesions. J Atheroscler Thromb. 2021;28(5):555–61.
25. Verwer MC, Waissi F, Mekke JM, Dekker M, Stroes ESG, de Borst GJ, et al. High lipoprotein(a) is associated with major adverse limb events after femoral artery endarterectomy. Atherosclerosis. 2022;349:196–203.
26. Yanaka K, Akahori H, Imanaka T, Miki K, Yoshihara N, Kimura T, et al. Impact of lipoprotein(a) levels on primary patency after endovascular therapy for femoropopliteal lesions. Heart Vessels. 2023;38(2):171–6.
27. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49(6):822–30.
28. Soylu A, Sarier M, Kutlu R. Diagnostic value of penile color doppler ultrasonography in patients with veno-occlusive erectile dysfunction. Niger J Clin Pract. 2021;24(4):551–4.
29. Sikka SC, Hellstrom WJ, Brock G, Morales AM. Standardization of vascular assessment of erectile dysfunction: standard operating procedures for duplex ultrasound. J Sex Med. 2013;10(1):120–9.
30. Benson CB, Aruny JE, Vickers MA Jr. Correlation of duplex sonography with arteriography in patients with erectile dysfunction. AJR Am J Roentgenol. 1993;160(1):71–3.
31. Aversa A, Crafa A, Greco EA, Chiefari E, Brunetti A, La Vignera S. The penile duplex ultrasound: how and when to perform it? Andrology 2021;9(5):1457–66.
32. Rogers JH, Goldstein I, Kandzari DE, Kohler TS, Stinis CT, Wagner PJ, et al. Zotarolimus-eluting peripheral stents for the treatment of erectile dysfunction in subjects with suboptimal response to phosphodiesterase-5 inhibitors. J Am Coll Cardiol. 2012;60(25):2618–27.
33. Diehm N, Marggi S, Ueki Y, Schumacher D, Keo HH, Regli C, et al. Endovascular therapy for erectile dysfunction – who benefits most? Insights from a single-center experience. J Endovasc Ther. 2019;26(2):181–90.
34. Kronenberg F. Human genetics and the causal role of lipoprotein(a) for various diseases. Cardiovasc Drugs Ther. 2016;30(1):87–100.
35. Jang AY, Han SH, Sohn IS, Oh PC, Koh KK. Lipoprotein(a) and cardiovascular diseases. Circ J. 2020;84(6):867–74.
36. Willeit P, Ridker PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. Lancet. 2018;392(10155):1311–20.
37. Reyes-Soffer G, Ginsberg HN, Berglund L, Duell PB, Heffron SP, Kamstrup PR, et al., Lipoprotein(a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2022;42(1):e48–e60.
38. Patel AP, Wang M, Pirruccello JP, Ellinor PT, Ng K, Kathiresan S, et al. Lp(a) (lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. Arterioscler Thromb Vasc Biol. 2021;41(1):465–74.
39. Melita H, Manolis AA, Manolis TA, Manolis AS. Lipoprotein(a) and cardiovascular disease: a missing link for premature atherosclerotic heart disease and/or residual risk. J Cardiovasc Pharmacol. 2022;79(1):e18–e35.
40. Nordestgaard BG, Chapman MJ, Ray K, Boren J, Andreotti F, Watts GF, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010;31(23):2844–53.
41. Waldeyer C, Makarova N, Zeller T, Schnabel RB, Brunner FJ, Jorgensen T, et al. Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. Eur Heart J. 2017;38(32):2490–8.
42. Oo HP, Giovannucci J, O'Brien RC, Hare DL. The prevalence of elevated lipoprotein(a) in patients presenting with coronary artery disease. Heart Lung Circ. 2020;29(11):1682–7.
43. Valentine RJ, Grayburn PA, Vega GL, Grundy SM. Lp(a) lipoprotein is an independent, discriminating risk factor for premature peripheral atherosclerosis among white men. Arch Intern Med. 1994;154(7):801–6.
44. Schatz U, Fischer S, Muller G, Tselmin S, Birkenfeld AL, Julius U, et al. Cardiovascular risk factors in patients with premature cardiovascular events attending the University of Dresden Lipid Clinic. Atheroscler Suppl. 2019;40:94–9.
45. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88.
46. Kamstrup PR. Lipoprotein(a) and cardiovascular disease. Clin Chem. 2021;67(1):154–66.
47. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. Circulation. 2008;117(2):176–84.
48. Kronenberg F, Utermann G. Lipoprotein(a): resurrected by genetics. J Intern Med. 2013;273(1):6–30.
49. Vormittag R, Vukovich T, Stain M, Lehr S, Minar E, Pabinger I. Lipoprotein (a) in patients with spontaneous venous thromboembolism. Thromb Res. 2007;120(1):15–20.
50. Wang T-D, Lee W-J, Chen W-J, Chen M-F, TCT-529 comprehensive assessment of prevalence and distribution of obstructive pelvic arterial lesions by computed tomographic angiography in patients with erectile dysfunction. J Am Coll Cardiol. 2013;62(18 Suppl 1):B160.
51. Leye MM, Faye A, Ka O, Seck I, Tal Dia A. Cardiovascular risk factors associated with erectile dysfunction in the region of Dakar, Senegal. Rev Epidemiol Sante Publique. 2016;64(3):195–200.
52. Salonia A, Bettocchi C, Capogrosso P, Carvalho J, Corona G, Hatzichristodoulou G, et al. EAU guidelines on sexual and reproductive health. European Association of Urology; 2023. Available from: https://uroweb.org/guidelines/sexual-and-reproductive-health/chapter/citation-information
53. Vrentzos GE, Paraskevas KI, Mikhailidis DP. Dyslipidemia as a risk factor for erectile dysfunction. Curr Med Chem. 2007; 14(16):1765–70.
54. Sun P, Swindle R. Are men with erectile dysfunction more likely to have hypertension than men without erectile dysfunction? A naturalistic national cohort study. J Urol. 2005;174(1):244–8.
55. Seftel AD, Sun P, Swindle R. The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. J Urol. 2004;171(6 Pt 1):2341–5.
56. Mazzilli R, Elia J, Delfino M, Benedetti F, Scordovillo G, Mazzilli F. Prevalence of diabetes mellitus (DM) in a population of men affected by erectile dysfunction (ED). Clin Ter. 2015;166(5):e317–20.
57. Ramirez R, Pedro-Botet J, Garcia M, Corbella E, Merino J, Zambon D, et al. Erectile dysfunction and cardiovascular risk factors in a Mediterranean diet cohort. Intern Med J. 2016; 46(1):52–6.
58. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–337.

59. Wang TD, Lee WJ, Yang SC, Lin PC, Tai HC, Hsieh JT, et al. Safety and six-month durability of angioplasty for isolated penile artery stenoses in patients with erectile dysfunction: a first-in-man study. EuroIntervention. 2014;10(1):147–56.
60. Wang TD, Lee WJ, Yang SC, Lin PC, Tai HC, Liu SP, et al. Clinical and imaging outcomes up to 1 year following balloon angioplasty for isolated penile artery stenoses in patients with erectile dysfunction: the PERFECT-2 study. J Endovasc Ther. 2016;23(6):867–77.
61. Wang XY, Huang W, Zhang Y. Relation between hypertension and erectile dysfunction: a meta-analysisof cross-section studies. Int J Impot Res. 2018;30(3):141–6.
62. Doppalapudi SK, Wajswol E, Shukla PA, Kolber MK, Singh MK, Kumar A, et al. Endovascular therapy for vasculogenic erectile dysfunction: a systematic review and meta-analysis of arterial and venous therapies. J Vasc Interv Radiol. 2019;30(8): 1251–8e2.
63. Gazzaruso C, Garzaniti A, Falcone C, Puija A, Geroldi D, Giordanetti S, et al. Lipoprotein(a), apolipoprotein(a) polymorphism and restenosis after intracoronary stent placement in type 2 diabetic patients. J Diabetes Complications. 2003; 17(3):135–40.
64. Morita Y, Himeno H, Yakuwa H, Usui T. Serum lipoprotein(a) level and clinical coronary stenosis progression in patients with myocardial infarction: re-revascularization rate is high in patients with high-Lp(a). Circ J. 2006;70(2):156–62.
65. Kamitani T, Taniguchi T, Miyai N, Kawasaki T, Kawasaki S, Sugihara H. Association between plasma lipoprotein(a) concentration and restenosis after stent implantation. Circ J. 2005;69(6):644–9.
66. Qin SY, Liu J, Jiang HX, Hu BL, Zhou Y, Olkkonen VM. Association between baseline lipoprotein (a) levels and restenosis after coronary stenting: meta-analysis of 9 cohort studies. Atherosclerosis. 2013;227(2):360–6.
67. Tunstall-Pedoe H, Peters SAE, Woodward M, Struthers AD, Belch JJF. Twenty-year predictors of peripheral arterial disease compared with coronary heart disease in the Scottish Heart Health Extended Cohort (SHHEC). J Am Heart Assoc. 2017;6(9):e005967.

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