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## Peripheral arterial disease, type 2 diabetes and postprandial lipidaemia: Is there a link?

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### Abstract

Peripheral arterial disease, manifested as intermittent claudication or critical ischaemia, or identified by an ankle/brachial index < 0.9, is present in at least one in every four patients with type 2 diabetes mellitus. Several reasons exist for peripheral arterial disease in diabetes. In addition to hyperglycaemia, smoking and hypertension, the dyslipidaemia that accompanies type 2 diabetes and is characterised by increased triglyceride levels and reduced high-density lipoprotein cholesterol concentrations also seems to contribute to this association. Recent years have witnessed an increased interest in postprandial lipidaemia, as a result of various prospective studies showing that non-fasting triglycerides predict the onset of arteriosclerotic cardiovascular disease better than fasting measurements do. Additionally, the use of certain specific postprandial particle markers, such as apolipoprotein B-48, makes it easier and more simple to approach the postprandial phenomenon. Despite this, only a few studies have evaluated the role of postprandial triglycerides in the development of peripheral arterial disease and type 2 diabetes. The purpose

of this review is to examine the epidemiology and risk factors of peripheral arterial disease in type 2 diabetes, focusing on the role of postprandial triglycerides and particles.

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**Key words:** Peripheral arterial disease; Type 2 diabetes; Postprandial lipidaemia; Apolipoprotein B-48; Ankle-brachial index; Non-fasting triglycerides

**Core tip:** Peripheral arterial disease is highly prevalent in type 2 diabetes; traditional risk factors contribute to the disease. Interestingly, postprandial lipidaemia is increased in both conditions. However, one study showed that only subjects with both type 2 diabetes and peripheral arterial disease had elevation of postprandial lipids; subjects with type 2 diabetes and a normal ankle-brachial index had a normal postprandial response. Because most of the triglycerides of chylomicrons are extracted in muscle and adipose cells in the legs, the authors speculate on whether arteriosclerosis in the legs may contribute to greater postprandial lipidaemia.

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### EPIDEMIOLOGY OF PERIPHERAL ARTERIAL DISEASE IN TYPE 2 DIABETES MELLITUS

Peripheral arterial disease (PAD) is produced by narrowing of the calibre of the medium-sized arteries and its widest

**Table 1** Prevalence of peripheral arterial disease in Spanish cohorts

Study	Number of subjects	Age (yr)	Study population	ABI < 0.9 (%)
HERMEX <sup>[17]</sup>	2833	51	General	All 3.7 Without diabetes 2.8 With Diabetes 6.2
ESTIME <sup>[6]</sup>	1324	68	General	All 8 Without diabetes 6.6 With diabetes 19
MERITO <sup>[19]</sup>	1519	66	Internal medicine outpatient clinic	SCORE ≥ 3 26.2 With Diabetes 26.1
VITAMIN <sup>[20]</sup>	493	68	Internal medicine outpatient clinic	Without DM2 21 With DM2 38
ARPTER <sup>[18]</sup>	3171	63	General	All 6.4 Without diabetes 5.4 With diabetes 12.6
REGICOR <sup>[21]</sup>	6262	56	General	All 4.5 Without diabetes 4 With diabetes 8.4
FUENCARRAL Health Center <sup>[22]</sup>	1360	70	Primary health care centre	Without diabetes 4.3 With diabetes 11.3
ALBACETE <sup>[23]</sup>	784	61	General	All 10.5 Without diabetes 9 With diabetes 19
RONDA PRIM Health Center <sup>[25]</sup>	289	65	Primary health centres	Diabetes 21.5
CIUDAD JARDIN Health Center <sup>[78]</sup>	456	61	Primary health centre	Diabetes 27
PADiD Study <sup>[24]</sup>	1462	78	Internal medicine outpatient clinics	Diabetes 60
MARINA BAIXA Hospital <sup>[89]</sup>	360	67	Internal medicine outpatient clinics	Diabetes 27

ABI: Ankle-brachial index.

definition encompasses all extracoronary and extracerebral vascular disease. However, the term PAD is usually restricted to involvement of the lower limbs, particularly in the iliac bifurcation, and the iliofemoral and popliteal arteries<sup>[1]</sup>. The main cause of arterial stenosis in developed countries is atherosclerosis.

The prevalence of PAD in Europe and the United States is estimated to be 27 million persons<sup>[2]</sup>. The prevalence of PAD increases progressively with age, with most cases starting after the age of 40 years. It is well known that only a very few PAD patients actually have symptoms, around 10%-20%<sup>[3]</sup>. The use of a standardized questionnaire in the physician's office can increase the detection of claudicant patients<sup>[4,5]</sup>. Most patients with PAD are identified from non-invasive tests, such as the ankle-brachial index (ABI). Using this widely extended technique in Spain led to the identification of PAD in 8% of individuals aged 55-85 years<sup>[6]</sup>. In addition to age, the other cardiovascular risk factors also increase the likelihood of developing PAD. Thus, in persons with a low cardiovascular risk the prevalence of PAD is almost inconsiderable<sup>[7]</sup>, whereas it can reach 27% in persons with type 2 diabetes<sup>[8]</sup>.

The prognosis for patients with PAD, both symptomatic and asymptomatic, is poor<sup>[9]</sup>. Overall mortality is increased and the risk of death is even greater than that in patients who have angina or acute myocardial infarction<sup>[10-13]</sup>. Data from Spain confirm these findings. An analysis of the FRENA, REACH and AIRVAG registries showed that patients with PAD have a greater frequency of symptomatic multivessel disease and a worse one-year

prognosis than patients with single-vessel involvement or cerebrovascular disease<sup>[14]</sup>.

### Diabetes and PAD

Diabetes, together with smoking, is the main risk factor for PAD<sup>[15]</sup>. Of patients who attended an angiology office in Spain due to intermittent claudication and who underwent arterial surgery or had an ABI ≤ 0.9, 67% had diabetes mellitus<sup>[16]</sup>. Population-based studies in Spain, undertaken in either the general population or at various levels of care, showed that the presence of diabetes mellitus doubled or even tripled the possibility of having PAD (Table 1)<sup>[6,17-23]</sup>. The prevalence of an ABI < 0.9 in series of Spanish patients with diabetes ranges from 21% to 60% (Table 1)<sup>[8,24,25]</sup>. In the autonomous communities of Andalusia and the Canary Islands, 72% of all lower-limb amputations between 1996 and 2006 involved patients with diabetes<sup>[23,26,27]</sup>. In patients with diabetes, for every 1% increase in haemoglobin A1c there is a corresponding 26% increased risk of PAD<sup>[28]</sup>. The presence of PAD also increases the risk of death in patients with diabetes mellitus<sup>[29,30]</sup>. The prognosis for PAD is worse in patients with diabetes than those without diabetes<sup>[31]</sup>.

### Diagnosis of PAD in diabetes

The diagnosis of PAD usually depends on the sum of the symptoms, particularly intermittent claudication, plus the physical examination, especially the lack of pulses and the trophic disorders leading to critical limb ischaemia and distal necrosis<sup>[32]</sup>. However, patients, particularly diabetic patients, commonly have other processes at

the same time that can alter the traditional symptoms of PAD, making them much less specific<sup>[33]</sup>. Accordingly, the measurement of the ratio of the systolic blood pressures in the ankle and the arm, the ABI, has been recommended as the screening method for asymptomatic PAD and as a form of confirmation in symptomatic PAD<sup>[2,34,35]</sup>. A finding in one limb of an ABI < 0.9 with the measurement taken at rest under standard conditions is considered diagnostic of PAD, with an ABI between 0.9 and 1.0 considered borderline<sup>[36]</sup>.

One limitation of the ABI, especially relevant in patients with diabetes, is arterial media calcification, which can lead to non-compressible arteries (ABI > 1.4) or false normal values. A recent study showed that individuals with an ABI > 1.4 have a worse prognosis than those with a normal ABI and even those with an ABI < 0.9. The prevalence of diabetes in the group with an ABI > 1.4 was 58%, compared with 18% and 48% in those with a normal ABI or those with an ABI < 0.9<sup>[37]</sup>. It has long been known that the sensitivity of the ABI to correctly diagnose PAD is considerably reduced in the presence of arterial media calcification and that, clinically, this calcification is associated with the presence of peripheral neuropathy<sup>[38,39]</sup>. Accordingly, in the presence of peripheral neuropathy it is recommended to use an alternative method, such as flow wave analysis using Doppler colour ultrasound<sup>[40,41]</sup>. In our experience this limitation is not negligible. In a series of 456 patients with type 2 diabetes, 35 were found to have intermittent claudication (7.6%); only 22 of these had an ABI < 0.9. Of the other 13, 12 underwent colour Doppler ultrasound and in 3 (25%) we obtained a monophasic wave, diagnostic of PAD. Thus, a normal ABI does not rule out PAD in patients with type 2 diabetes, and these patients should therefore undergo complementary tests if they have symptoms suggestive of PAD<sup>[8]</sup>.

The resting ABI should be used as the diagnostic technique for PAD when lower limb arteriosclerosis is suspected. This should be done in persons with one or more of the following: symptoms in the lower limbs after exercise, wounds with delayed healing, and individuals older than 65 years of age or older than 50 years with a history of smoking or diabetes<sup>[34]</sup>. Given the high prevalence of PAD in patients with diabetes, the ADA recommends screening with the ABI in patients with diabetes who are older than 50 years and who have another risk factor (smoking, hypertension, hyperlipidaemia, or diabetes for more than 10 years)<sup>[42]</sup>.

## LIPIDS, POSTPRANDIAL LIPIDAEMIA AND PAD

### Fasting lipids in PAD

Lipid abnormalities in PAD have received less attention than in other areas, as for example, in coronary anomalies. Very few prospective studies have focused on the relation between triglycerides and peripheral vascular disease. The most common feature of PAD is raised levels

of triglycerides and lower levels of high-density lipoprotein (HDL) cholesterol as compared with age- and sex-matched controls without vascular disease, with similar levels of cholesterol and low-density lipoprotein (LDL) cholesterol<sup>[43-47]</sup>. The frequency of a cluster of lipid abnormalities of the type of raised triglycerides and small and dense LDL and reduced HDL was 20% in persons with PAD *vs* 0% in the control group<sup>[48]</sup>. Several studies have also shown that triglyceride levels are a predictive factor for PAD<sup>[49-51]</sup>, though not all<sup>[52]</sup>.

### Postprandial lipidaemia: Atherogenic mechanism

Unlike the carbohydrates, which normally only show transitory increases after a meal, the circulating triglycerides show a pronounced increase (postprandial lipidaemia) one hour after the intake of a fat-rich meal (around 30-60 g), and can remain high for 5-8 h after the meal. As most persons regularly consume fatty meals every 4-5 h, the usual state in humans insofar as their triglyceride metabolism is concerned is clearly a continuous postprandial lipidaemic state<sup>[53,54]</sup>.

The large triglyceride-transporting particles, the chylomicrons and the very low-density lipoprotein (VLDL), are too large to cross the endothelium and they therefore don't contribute to the atherosclerosis, but the same does not occur with the chylomicron remnants and the intermediate-density lipoprotein (IDL), which are much smaller particles<sup>[55]</sup>. Evidence exists that the cholesterol in the postprandial particles, originating in the intestine, contribute to the phenomenon of atherosclerosis, both in animals and in humans<sup>[56-59]</sup>.

### Postprandial lipidaemia and cardiovascular disease: Case-control vs prospective studies

Since the seminal work of Zilvermit, many case-control studies have found an association between the magnitude of the postprandial lipidaemia and the presence and severity of coronary artery disease<sup>[60,61]</sup>; these studies have been reviewed by Lopez-Miranda *et al.*<sup>[62]</sup>. Prospective studies, however, are few and controversial. Reyes-Soffer *et al.*<sup>[63]</sup> followed 69 patients with type 2 diabetes who were free of coronary disease for a mean of 8.7 years; 33 patients remained disease-free. No differences were found in the postprandial parameters at the initial visit between the groups, and the authors concluded that the postprandial triglycerides do not predict the onset of coronary disease in individuals with diabetes. A more recent study involving 514 survivors of an acute coronary syndrome found that the postprandial triglycerides after the oral intake of 75 g of fat predicted the appearance of new events at 18 mo. In the subgroup of patients without diabetes or oral glucose intolerance the relative increase in postprandial triglycerides was an independent predictor of events<sup>[64]</sup>.

### Non-fasting triglycerides

Interest in studying postprandial lipidaemia has increased over recent years as a result of studies showing that serum triglyceride levels measured in a non-fasting state have

proved to be better predictors for the risk of vascular disease than fasting triglyceride concentrations, *i.e.*, when they are quantified after 8-10 h of fasting<sup>[65-68]</sup>. Two meta-analyses also support the association between fasting and postprandial triglycerides and the vascular risk<sup>[69,70]</sup>. One of the problems encountered when introducing postprandial triglyceride measurements in the clinical setting is the absence of specific recommendations in the clinical practice guidelines and thus the identification of a threshold level above which postprandial hypertriglyceridaemia is recognised. To date, only the American Association of Clinical Endocrinologists has considered the possibility of evaluating the non-fasting triglyceride concentration<sup>[71]</sup>. Based on evidence from the above mentioned population-based studies, an expert group estimated non-fasting triglyceride levels < 180 mg/dL as desirable<sup>[72]</sup>. This means that 38% of the men and 20% of the women in the Copenhagen study who had figures above these levels have postprandial hypertriglyceridaemia<sup>[73]</sup>.

### **Suggestion for the measurement of postprandial lipidaemia**

The study of postprandial (hyper)lipidaemia has several inconveniences. The most important at present is the poor clinical yield and the great complexity of the fat test; its prolonged time is uncomfortable for both the patient and the medical personnel, not to mention the lack of standardization for the test. A few years ago, using data from a meta-analysis of 113 studies in healthy subjects by Mihás *et al.*<sup>[74]</sup>, an expert group attempted to standardize the test and recommended a fat tolerance test meal consisting of 75 g fat, 25 g carbohydrates and 10 g protein. Furthermore, the fatty test meal should contain mixtures of saturated and unsaturated fatty acids in a digestible form and be easy to prepare. The candidates for the test should have fasting triglycerides of 90-180 mg/dL and the test can be shortened with the measurement of the serum triglycerides at 4 h, with no need to reach a complete postprandial curve of 8 or 12 h<sup>[72]</sup>.

## **POSTPRANDIAL LIPIDAEMIA AND PAD IN TYPE 2 DIABETES**

Little attention has been given to the study of postprandial lipidaemia in patients with PAD. Only the elegant paper by Lupattelli *et al.*<sup>[75]</sup> showed that the magnitude of postprandial lipidaemia, expressed as “the area under the incremental curve for triglycerides,” was higher in 16 non-diabetic normolipidaemic claudicant patients with PAD than in 10 normolipidaemic control subjects, suggesting the relevance of postprandial lipoprotein metabolism in the pathogenesis of peripheral atherosclerosis. However, although normolipidaemic, the patients in Lupattelli's study had slightly higher fasting triglycerides than their controls.

In recent years our group has studied the relation between lipids and postprandial particles, PAD and type 2 diabetes mellitus. Firstly, the postprandial triglycerides

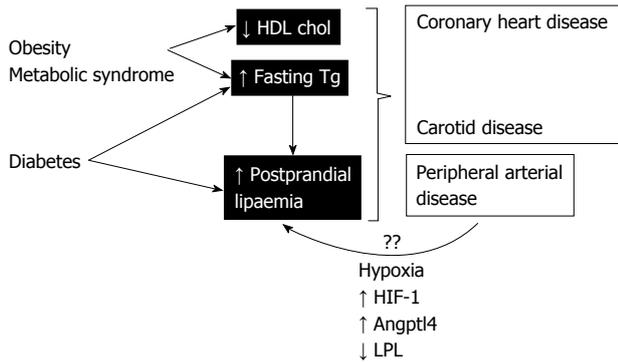
were more strongly associated with PAD in individuals with type 2 diabetes mellitus than were the fasting triglycerides. A group of 119 patients with type 2 diabetes mellitus treated with just diet and/or oral glucose lowering agents, with no lipid-lowering treatment, were analyzed at fasting and 4 h after a mixed breakfast containing 50 g of fat and 40 g of carbohydrates. Although the patients with cardiovascular disease, most of them with asymptomatic PAD and identified by an ABI < 0.9, had lower fasting HDL cholesterol levels and higher triglyceride levels, only the triglycerides at 4 h post-breakfast were associated in the multivariate analysis with cardiovascular disease, together with the duration of the disease and smoking<sup>[76]</sup>.

The postprandial triglycerides include not only those contained in chylomicron particles and their remnants, but also those contained in VLDL and IDL. In an attempt to further understand the role of postprandial fat in PAD, we undertook a second experiment to analyze the serum concentration of apolipoprotein B48, a protein that is only associated with chylomicrons and their remnants and is not interchanged with any other circulating particle. This second study involved 101 patients with type 2 diabetes mellitus and 73 controls without diabetes, both groups with no known cardiovascular disease. Asymptomatic vascular disease was identified from the ABI and as a marker of postprandial particles we used the apolipoprotein B48, measured with a commercial enzyme-linked immunosorbent assay. Of the patients with type 2 diabetes mellitus, 21 had PAD as defined by an ABI < 0.9, though no control had PAD. The levels of triglycerides and apolipoprotein B48, both fasting and postprandial, were significantly higher in the group of diabetic patients with PAD than in those without PAD and the controls. Curiously, no differences were found between the controls and the patients with type 2 diabetes mellitus without PAD. Of all the lipid and non-lipid parameters studied, only apolipoprotein B48 and smoking were associated with the presence of PAD in a binary logistic regression analysis. Likewise, the presence of PAD was an independent predictor of the levels of apolipoprotein B48, both fasting and 4 h after a mixed breakfast<sup>[77]</sup>.

As the patients with type 2 diabetes mellitus in the previous studies did not receive any insulin or lipid-lowering therapy, we decided to confirm the findings in a larger population with type 2 diabetes mellitus without these exclusion criteria. Again, using an ABI < 0.9 as a marker of PAD, we found in 456 patients with type 2 diabetes mellitus that fasting apolipoprotein B48 was a marker of PAD, independently of the other lipid factors, statin treatment or insulin therapy<sup>[78]</sup>. Identical results have also been reported by another group<sup>[79]</sup>.

### **May PAD delay postprandial lipid catabolism?**

Taken together, these studies confirm an association between postprandial particles, measured as triglycerides 4 h after breakfast or as fasting and postprandial apolipoprotein B48, and PAD. In the above-mentioned studies, a diabetic status in itself was not associated with a greater



**Figure 1** Proposed mechanism linking peripheral arterial disease and worsening postprandial lipaemia. HIF-1: Hypoxia-induced factor 1; Angptl4: Angiotensin-like protein 4; LPL: Lipoprotein Lipase; HDL: high density lipoproteins.

concentration of postprandial triglycerides or apolipoprotein B48 if there was no PAD. As mentioned earlier, the case-control studies show an association between postprandial lipidaemia and cardiovascular disease, particularly coronary disease.

An explication for this association was provided by Lupattelli *et al*<sup>[75]</sup>. Somehow, and following the hypothesis of Zilvermit<sup>[80]</sup>, the exposure of the endothelium to greater concentrations of postprandial particles favours the appearance of arteriosclerotic lesions, in our case in the lower limbs. Though this hypothesis is the most plausible, no causality can be deduced from the association studies. Accordingly, it is worth speculating about whether arteriosclerotic disease in the legs could alter chylomicron metabolism, slowing it. With this in mind, consideration should be given to the study by Horton *et al*<sup>[81]</sup>, who showed that men have higher triglyceride concentrations than women because women possess a greater extractive capacity of triglycerides in adipose and muscle tissues in the lower limbs when they undergo a fatty breakfast. For some reason the catabolism of the chylomicrons in the legs is not negligible and an alteration in the circulation in the legs may worsen or slow this metabolism.

The kinetics of lipoproteins are marked by (1) their intestinal production; (2) hydrolysis of their triglycerides by the action of lipoprotein-lipase anchored in the endothelium (but synthesised in adipose and muscle tissue cells); and (3) removal of chylomicron remnants by hepatic receptors. These steps are all modulated by the levels and genetic variants of the apolipoproteins like C-II, C-III, E, A-5<sup>[82,83]</sup>. As persons with arteriosclerosis, particularly those with PAD, have a marked endothelial dysfunction<sup>[84]</sup>, it is possible to speculate that the action of an enzyme anchored to the endothelium, as is the case of lipoprotein lipase (LPL), is reduced. Given the great extension of the endothelial surface in the legs (in comparison with coronary arteriosclerosis), established PAD might affect postprandial lipidaemia more intensely than coronary disease.

If this hypothesis were true, what would its mechanism of production be? The consequence of arteriosclerosis is tissue ischaemia. This is usually manifested as intermittent claudication, though the tissues may experience

hypoxia in earlier stages. Tissue hypoxia leads to changes in the endothelial cells (where the LPL are anchored) or in the production of LPL (or its associated proteins) by adipose or muscle cells<sup>[85]</sup>. Cells submitted to hypoxia upregulate the expression of hypoxia-inducible factor 1, a transcription factor that induces changes in innumerable target genes that were reviewed some time ago<sup>[86]</sup>. Of note among these changes is the raised expression of angiotensin-like 4 protein (Angptl4) and vascular endothelial growth factor (VEGF). VEGF intervenes in the processes of angiogenesis, much related with chronic ischaemia of the lower limbs and the formation of collateral vessels. Angptl4 is a potent inhibitor of LPL, the enzyme that intervenes critically in the first step of the catabolism of triglyceride-rich particles<sup>[87]</sup>. A recent experimental animal study showed that mice submitted to cyclic hypoxia experienced inhibition of the catabolism of triglyceride-rich lipoproteins as a consequence of a drastic reduction in adipose tissue LPL activity, coupled with a notable increase in Angptl4<sup>[88]</sup> (Figure 1).

Taken together, these data suggest that postprandial hyperlipidaemia, a recognised vascular risk factor associated with obesity, the metabolic syndrome and type 2 diabetes, could be aggravated by PAD, further exposing other arterial territories to greater concentrations of postprandial atherogenic particles. Finally, if the hypoxia were an underlying mechanism, it could be improved by percutaneous or surgical revascularization.

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