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Editorial

Non-esterified fatty acids: Another piece in the puzzle of PAD risk stratification?

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Low-density lipoprotein cholesterol (LDL-C) is without doubt the main target for peripheral artery disease (PAD) risk factor optimization within the lipid spectrum. Numerous randomized controlled trials have confirmed the strong causality of LDL-C lowering with reduction of fatal and non-fatal CV-events. The latest contributor to this overwhelming evidence, the FOURIER [1] study, showed even an absolute risk reduction of more than 2% in statin treated patients with further PCSK9 inhibition. This evidence reduced the LDL-C lowering target to values below 55 mg/dl in the current EAS/ESC dyslipidaemia guidelines [2]. In this cohort, patients with PAD profited the most, with an even higher absolute risk reduction of 3.5% [3]. LDL-C levels are even associated with primary prevention in PAD [4]. However, the highest associations in the primary prevention setting were with high-density lipoprotein cholesterol (HDL-C), triglycerides and their ratio, respectively [4]. Contrary to this finding, intervention by either HDL-C increasing [5] or triglyceride lowering [6] agents did not improve patient survival in randomized controlled trials. However, those neutral results should trigger studies to obtain a more detailed view of the complex lipid metabolism in PAD. Ahiawodzi et al. chose to investigate the relevance of non-esterified fatty acids (NEFA) in patients with PAD; the results are presented in the current issue of *Atherosclerosis* [7].

NEFAs predominantly enter the blood stream by hydrolysis from adipose tissue [8]. Circulating NEFA show a marked diurnal variation with a peak occurring in the middle of the night and a decline towards the morning in metabolically healthy individuals. Glucose intake during night time abolishes this nocturnal peak [9]. Metabolic disarray induced by unhealthy lifestyle choices thus results in higher circulating NEFA levels. Increased free fatty acids are known to link obesity with insulin resistance and type 2 diabetes mellitus [10]. In addition, elevated circulating NEFAs and higher blood pressure are interconnected [11]. Sleep restriction increases NEFA levels [12]. Simply put, unhealthy life style decreases metabolic flexibility, making elevated circulating NEFAs a driver of the pathological changes observed in insulin resistance (prediabetes), diabetes and atherosclerosis, thereby also providing a link of the latter three [13]. Thus, NEFAs can be seen as a marker for CVD genesis but also progression.

Ahiawodzi et al. demonstrate associations of NEFAs with PAD and ankle-brachial index (ABI) after a long-term follow-up in a large population-based cohort of more than 4575 participants [7]. NEFAs were measured at the first visit between 1992 and 1993 and assessment for incidental PAD was performed annually until 2015. Furthermore, ABI was measured at the first visit and then at visit 9 between 1998 and 1999. In a sense contrary, NEFAs were only associated with incidental PAD but not with ABI decline. The authors present possible explanations for this situation, which partly display some of their limitations. ABI was measured after six years, whereas incidental PAD was assessed for nearly 20 years. The cohort of participants with ABI measurement was only half as large with 2251. Interestingly, in a subgroup analysis NEFAs were not associated with incidental PAD until visit 9 (between 1998–99), which indicate that this effect occurs only after prolonged exposition to higher NEFA levels. What can thus be derived from those first of a kind result for NEFAs in PAD?

First, several limitations have to be addressed. Patient records of participants were searched for PAD ICD-codes or assessment was performed with phone calls. Both leads to inconsistency and selection biases. An ABI measurement to a later time point of this study is missing as several participants did not receive a measurement per se. No longitudinal NEFA measurements were performed, and patient cohorts were included nearly 30 years ago. As NEFAs appear to have a high volatility due to the portrayed mechanisms, changes over time would be of major interest. In addition, standard of care dramatically changed during this time. However, this can also be regarded as a strength, as only a negligible proportion received up-to-date standard of care medication, such as modern antidiabetic agents or statins, at inclusion. Thus, possible effects of those agents on outcome but more important on lipid metabolism and insulin sensitivity and thereby possible also on NEFAs are not as present as in contemporary cohorts.

In conclusion, the results of the presented study show a potential novel target for PAD risk factor optimization in primary prevention and underlines the importance to look beyond LDL-C. However, due to the discussed limitations, future prospective studies are needed to address these issues.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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