Arh. farm. 2022; 72: 184 – 192 *Review article/Pregledni rad*

Biomarkers of dyslipidemia in patients with diabetic foot

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Abstract

Diabetic foot (DF) is one of the most severe complications of diabetes that significantly reduces the quality of life and survival of patients. Besides firmly established risk factors, novel data indicate that alterations in lipid metabolism might also be implicated in the development and progression of DF. Diabetic dyslipidemia is characterized by the atherogenic triad, consisting of increased triglycerides (TG), decreased high-density lipoprotein cholesterol (HDL-C) levels and the presence of small, dense low-density lipoprotein (LDL) particles. Accumulating evidence suggests that profound hypertriglyceridemia and HDL-C reduction are common findings in patients with diabetic neuropathy and significantly contribute to an increased risk for DF, amputation and mortality. Small, dense LDL particles play an important role in the development of cardiovascular complications of diabetes, but their clinical importance in patients with DF remains to be established. In this paper, we will discuss the significance of standard and novel lipid biomarker determination in the assessment of the risk for the development and progression of DF.

Keywords: lipid profile, small dense LDL, HDL functionality, diabetes

https://doi.org/10.5937/arhfarm72-36296

Introduction

Diabetes mellitus (DM) is a complex metabolic disorder characterized by persistent hyperglycemia (1). As a consequence of inadequate insulin secretion and/or insulin resistance, patients with DM have multiple metabolic alterations, including dyslipidemia (2). Experimental studies have demonstrated that persisting hyperglycemia initiates the development and progression of chronic microvascular and macrovascular complications, with detrimental effects on multiple tissues. Furthermore, the results of large, prospective studies Diabetes Control and Complications Trial (DCCT) and Prospective Diabetes Study (UKPDS) confirmed a strong positive association between hyperglycemia and development of chronic complications. Both studies unequivocally established hyperglycemia as the most important contributor to end-organ damage in patients with DM (3,4).

Diabetic neuropathy (DN) is a common chronic complication of diabetes, manifested as peripheral nerve dysfunction in the absence of other causes (5). Since the pathophysiology of DN is similar to other microvascular complications, the risk of developing DN is proportional to the degree of hyperglycemia. Mutual effects of DN and peripheral ischemia are the main underlying mechanisms which are responsible for the development of diabetic foot (DF), as one of the most severe diabetic complications (6). Patients with DF have a dramatically deteriorated quality of life and significantly increased risk of amputations and cardiovascular mortality (5). Moreover, DF ulcerations and subsequent amputations have a strong impact on the healthcare system. For instance, the annual costs of DF management in England reach 962 million dollars, which is almost 1% of the National Health Service budget (7). The presence of DF prolongs hospital stay by about 8 days. It is estimated that the reduction of DF prevalence by a third would decrease total costs of DF management almost four times (7). Diabetic dyslipidemia is the most frequent disorder of lipoprotein metabolism in patients with DM. It is manifested by elevated triglycerides (TG), reduced high-density lipoprotein cholesterol (HDL-C) levels and the presence of small, dense low-density lipoprotein (sdLDL) particles (2). In patients with optimal metabolic control of DN concentration of LDL-cholesterol (LDL-C) may not be elevated, but considerable qualitative changes of LDL particles remain evident. Nowadays, it is firmly established that sdLDL is one of the main risk factors for the onset of cardiovascular disease (CVD) in patients with DM (8).

The development of DF and atherosclerosis share several common risk factors and mechanisms; hence, it is reasonable to assume a potential role of dyslipidemia in both processes. However, unlike studies on cardiovascular complications of DM, data on lipid biomarkers in patients with DF are scarce. In this paper, we will discuss alterations of lipid profile and the usefulness of standard and novel lipid biomarker determination in the assessment of the risk for DF development.

Atherogenic lipoproteins

To date, several observational studies suggested that certain lipid biomarkers may be associated with DN, particularly serum TG level. Namely, in DM patients, the lack of insulin action causes profound changes in the metabolism of TG-rich lipoproteins (9). The activation of hormone-sensitive lipase leads to increased lipolysis of TG in adipose tissue, while consequently increased free fatty acid flux to the liver enhances the production of very low-density lipoproteins (VLDL). In addition, due to the reduced activity of lipoprotein lipase, catabolism of chylomicrons and VLDL particles in plasma is delayed (9).

A recent meta-analysis of 35 studies showed that DN patients have significantly higher TG concentrations than healthy subjects (10). The authors reported that patients with the highest serum TG levels have an increased risk for DN development (10). It has also been documented that hypertriglyceridemia contributes to the progression of DN (11). Finally, prospective data from the DISTANCE study showed that elevated TG levels were associated with the risk of amputation in patients with DF (12).

Further unfavorable effects of hypertriglyceridemia are reflected by an intensive exchange of TG and cholesterol-esters (CE) between VLDL and LDL particles, mediated by cholesterol-ester transfer protein (CETP). Following TG-enrichment of LDLs, the activity of hepatic lipase converts them into smaller and denser particles (13). As it was already mentioned, patients with DM are particularly prone to developing atherogenic lipoprotein phenotype, characterized by increased TG and low HDL-C levels and sdLDL particles. Small, dense LDL particles have the highest atherogenic potential, since they have longer plasma retention time, penetrate in vascular intima more readily and are more susceptible to glycation and oxidation (8). Several previous studies demonstrated increased levels of plasma prooxidants and biomarkers of lipid peroxidation in patient with DF (14,15), so it is reasonable to assume accelerated generation of oxidized LDL particles (oxLDL), as well. Of note, oxLDL particles are directly implicated in atherosclerotic plaque formation and progression, by increased accumulation in macrophages and ability to promote the generation of reactive oxygen species, proinflammatory mediators and procoagulant factors (16,17). Since neurons can also uptake oxLDL particles, further activation of intracellular signalling pathways could be responsible for enhanced oxidative stress, inflammation and tissue injury (18).

So far, it is unknown whether the preponderance of sdLDL particles is associated with the incidence and severity of DN. Nevertheless, sdLDLs are reportedly related to the development of other microvascular complications, such as diabetic nephropathy (19) and diabetic retinopathy (20). Therefore, future studies aiming to address the role of sdLDL in the development of DF are required. Regarding oxLDL particles, in a study of young type 1 DM patients, it was shown that the levels of anti-oxLDL antibodies were similar between the patients with and without subclinical diabetic complications, including DN (21). Similarly, Rosales-Hernandez et al. (22) found no significant differences in oxLDL levels between type 2 DM patients with and without DN. On the other hand, a recent

study showed increased oxLDL in patients with DF, as compared to controls (23). Moreover, the levels of oxLDL were higher in those who underwent amputation (23). However, the number of patients included in the above-mentioned studies was relatively small, so additional studies are needed to expand these preliminary observations.

At this point, it should also be stressed that serum LDL-C level is not associated with DN development. To be precise, in a recent meta-analysis of 39 studies no significant differences in serum LDL-C levels between DN patients and controls were confirmed (10). The available data on LDL-C in patients with DF are limited and inconclusive; some authors found increased (24), while others reported reduced LDL-C levels in DF patients (23).

Lastly, the data from earlier studies suggest that increased Lp(a) level should also be considered as a risk factor for the development of DF (25,26). Actually, the proposed role of elevated Lp(a) is based on its procoagulant properties and therefore related to an increased potential for thrombus formation in the microvasculature and consequent progression to limb ischemia and gangrene (25). Taken together, the data presented herein clearly support the importance of advanced lipid testing in assessing the risk for the development of DF.

HDL structure and functionality

In addition to decreased cholesterol content, HDL particles in patients with DM also undergo significant qualitative changes (8). Structural alterations of HDL particles in diabetes are mediated by a decreased production of apolipoprotein A-I (apoA-I), the main protein component of HDL, and hypertriglyceridemia, the dominant disorder of lipid metabolism in the absence of insulin action. As it was already explained, hypertriglyceridemia induces the process of reciprocal exchange of CE and TG esters between VLDL and HDL particles, and such structural modifications favor the formation of small, dense HDL particles (13). In addition, chronic hyperglycemia intensifies the glycation and oxidation of apoA-I, while proinflammatory environment, usually presented in patients with DM, promotes the accumulation of acute phase proteins within HDL (27). Such a profound deterioration of structural integrity ultimately leads to HDL's dysfunction, as it has been commonly seen in both cardiometabolic and malignant diseases (8,28).

The results of meta-analysis of 34 studies showed that serum HDL-C levels in type 1 DM patients with DN were lower than those in control group, whereas type 2 DM patients had HDL-C levels comparable with controls (10). Still, there is a mounting body of evidence suggesting that decreased serum HDL-C level is an important risk factor for the development of DF. In particular, several studies clearly demonstrated that patients with DF had lower HDL-C levels than healthy controls (23,24), but also than diabetic patients who had not developed this complication (29). Moreover, in a prospective study by Ikura et al. (30), low HDL-C level in patients with DF was independently associated with amputation and shorter survival.

The possible contribution of HDL particles to DF development and progression should be further addressed with respect to its dysfunction. The term HDL functionality refers to different protective properties of HDL particles within the maintenance of vascular homeostasis. In brief, HDL promotes cholesterol efflux from the cells and its transport to the liver, but also possesses antioxidative, anti-inflammatory and vasodilatory potential (28). Today, a variety of biomarkers are available to assess different aspects of HDL functional properties, although they still have a limited clinical use. Paraoxonase-1 (PON1) is HDL-associated enzyme which protects LDL and HDL particles against lipid peroxidation. At present, PON-1 activity is one of the most reliable biomarkers of HDL's antioxidative potential (31). So far, two studies have shown that patients with DF have lower PON-1 activity than healthy controls (23,32), indicating compromised antioxidative protection by HDL. Recently, it was postulated that HDL is able to promote wound healing by its anti-inflammatory and proangiogenic properties, as well as that reconstituted HDL nanoparticles could serve as an innovative therapeutic option for diabetic wounds (33). Studies on experimental models reported that the application of a reconstituted HDL stimulated wound healing and wound angiogenesis (33). Namely, topical application of reconstituted HDL increased blood flow and wound capillary density in treated animals (33). Moreover, Tsatralis et al. (34) observed an induction of pro-angiogenic molecules, such as vascular endothelial growth factor (VEGF), by reconstituted HDL in treated animals. Hence, attenuated anti-inflammatory and proangiogenic potential might present additional plausible mechanisms that link HDL's dysfunction with the development of DF.

It should finally be noted that circulating HDL particles are extremely heterogenic in terms of their density and size (33). Convincing evidence suggests that distinct HDL subclasses might have different functional properties and metabolic role. Similarly, the activity of PON1 within HDL particles recently emerged as a valuable biomarker of antioxidative potential inherent to each particular HDL subclass (35,36). To the best of our knowledge, no previous work has been reported on HDL subclasses profile in patients with DF and therefore this topic deserves further consideration in future studies.

Conclusion

Available data suggest that the parameters of a standard lipid profile, especially TG and HDL-C levels, might be useful in the assessment of the risk for the development of DF, whereas a predictive role of novel lipid biomarkers remains to be established. Although the mechanisms that might explain the role of atherogenic lipoproteins in the development of DF are not completely elucidated, it is possible that the interplay of dyslipidemia, hyperglycemia, oxidative stress and inflammation creates an environment that favors the progression of DN complications. One of the most important aspects of regular screening of lipid biomarkers could be the identification of patients with DN who would benefit the most from innovative diabetes therapies, able to significantly reduce the levels of atherogenic lipoproteins (8,28) in order to prevent or delay foot complications.

Acknowledgements

This work was supported by a grant from the Ministry of Education, Science and Technological Development, Republic of Serbia [Grant number 451-03-68/2022-14/200161].

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Biomarkeri dislipidemije kod pacijenata sa dijabetesnim stopalom

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Kratak sadržaj

Dijabetesno stopalo (DS) je hronična komplikacija dijabetesa koja značajno pogoršava kvalitet života pacijenata i doprinosi visokoj stopi smrtnosti. Noviji podaci ukazuju da i poremećaj metabolizma lipida može biti uključen u razvoj i progresiju DS. Dislipidemija u dijabetesu se odlikuje postojanjem tzv. aterogene trijade, koju čine povišena koncentracija triglicerida (TG), snižena koncentracija HDL-holesterola (HDL-h) i prisustvo malih, gustih LDL čestica. U nedavno sprovedenim studijama utvrđeno je da izražena hipertrigliceridemija i snižena koncentracija HDL-h, koje su najčešće prisutne kod pacijenata sa dijabetesnom neuropatijom, dodatno doprinose razvoju DS, amputaciji i mortalitetu. Poznato je da male, guste LDL čestice imaju važnu ulogu u razvoju kardiovaskularnih komplikacija u dijabetesu, ali je značaj ovih čestica kod pacijenata sa DS još uvek nedovoljno ispitan. U ovom radu ćemo razmotriti značaj određivanja standardnih i novih lipidnih biomarkera u cilju procene rizika za razvoj i progresiju DS.

Ključne reči: lipidni status, male guste LDL čestice, funkcionalnost HDL čestica, dijabetes