



The Relationship of Lipo (a) and Paraoxonase with Diabetes Mellitus

Lipo(a) ve Paraoksonazın Diabetes Mellitus ile İlişkisi

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Abstract

The aim of this review is to examine the relationship between diabetes mellitus and lipoprotein a (lipo a) and Paraoxonase-1 (PON1). For this, the original publications of the last decade have been scanned. Findings showed that; lipo (a) is associated with many chronic and high-mortality diseases. In the studies lipo (a) elevated diseases; myocardial infarction, chronic renal failure, lung cancer, stroke, diabetes mellitus (DM) and diabetic nephropathy. On the other hand, the level of lipoa (a) was found to be decreased in patients with liver cirrhosis. According to the data of these studies, extensive systemic involvement of DM was found to be effective on the level of lipo (a). A similar situation was found between DM and PON1. In addition, PON1 studies were performed with high density lipoprotein (HDL). In all of these studies, it was found that PON1 levels decreased with HDL. As a result many studies conducted in recent years show that; PON1 levels of patients with diabetes mellitus decrease, while lipo (a) levels are increased. (*Journal of Traditional and Complementary Anatolian Medicine* 2019, 1(2):5-8)

Keywords PON-1, lipo (a), diabetes mellitus

Öz

*Bu derlemenin amacı, diabetes mellitus ile Lipoprotein a (lipo a) ve Paraoksonaz-1 (PON1) arasındaki ilişkiyi incelemektir. Bunun için, son on yıldaki orijinal yayınlar taranmıştır. Elde edilen bulgular göstermiştir ki; lipo (a), birçok kronik ve yüksek mortaliteli hastalıkla ilişkilidir. Araştırmalarda lipo (a) seviyesi yüksek çıkan hastalıklar; miyokard enfarktüsü, kronik böbrek yetmezliği, akciğer kanseri, inme, diabetes mellitus (DM) ve diyabetik nefropati olarak tespit edilmiştir. Öte yandan, karaciğer sirozu olan hastalarda lipoa (a) seviyesinin azalmış olduğu görüldü. Yine bu araştırmaların verilerine göre, DM'in geniş sistemik tutulumunun lipo (a) seviyesindeki yüksekliğe etkili olduğu görülmüştür. Benzer durum DM ve PON1 düşüklüğü arasında da tespit edilmiştir. İlave olarak, PON1 araştırmalarının, yüksek yoğunluklu lipoprotein (HDL) ile birlikte yapıldığı görülmüştür. Tüm bu çalışmalarda, PON1 seviyelerinin HDL ile birlikte azaldığı tespit edilmiştir. Sonuç olarak, son yıllarda yapılan pek çok araştırma göstermektedir ki; diabetes mellituslu hastaların PON1 seviyeleri azalırken, lipo (a) seviyeleri yükselmektedir. (*Geleneksel ve Tamamlayıcı Anadolu Tıbbi Dergisi* 2019, 1(2):5-8)*

Anahtar Kelimeler

PON-1, lipo (a), diabetes mellitus

INTRODUCTION

Lipoprotein(a) (lipo(a)) was first described by Berg in 1963. Lipo(a) resembles to LDL moiety, containing an apolipoprotein B subunit (apo B-100) and another apolipoprotein(a) (apo(a)) attached to apoB-100 by a disulphide bridge (figure 1).¹

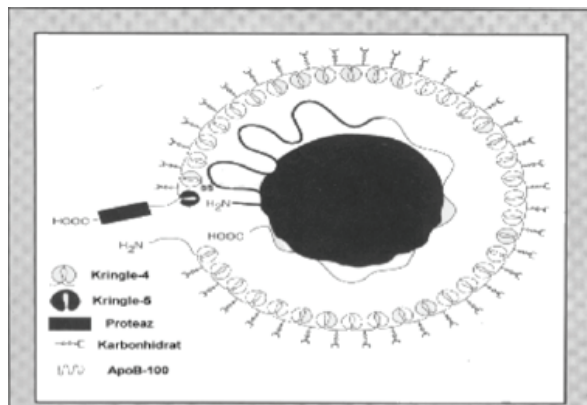


Figure 1. Hypothetical structural model of lipo(a) first described by Berg in 1963¹

The amino acid sequence of apo(a) is strikingly homologous to plasminogen, the zymogen of plasmin, a proteolytic enzyme of the fibrinolytic system. Apo(a) is genetically polymorphic, generating broad inter-individual differences. The size of apo(a) isoproteins is inversely correlated to the serum lipo(a) concentration. The serum lipo(a) concentration is an independent risk factor for coronary artery disease (CAD). This compound is thought to be synthesized in the liver and is associated with inflammation and recovery from tissue damage. Lipo(a) concentrations are not influenced by age, gender, diet or smoking habits and are genetically controlled. Lipoproteins are generally hydrophobic in their centers cholesterol esters and triglycerides (TG). The hydrophilic polar and free cholesterol, phospholipids and apoproteins in the region.²

The physiological function Lipo(a), if any, has yet to be determined and understanding this may be useful in the current dilemma. Lipo(a) is an unusual lipoprotein that is a combination of an LDL-like particle to which is co-

valently attached an evolutionarily modified, remodelled and proteolytically inactive plasminogen-like molecule called apolipoprotein (apo(a)).^{3,4} The apo(a) component of Lipo(a) is not a lipoprotein per se, as it has no lipid binding domains, yet through its evolutionary lifetime has somehow found a way to covalently attach to LDL, so that lipo(a) circulates as a lipoprotein. Apo(a) is also not present in animals other than the hedgehog, African monkeys with tails, apes and humans⁵ but it appears to have undergone several modifications of remodelling from the plasminogen gene. First, KIII of plasminogen evolved in the hedgehog and is attached to apoB as a lipoprotein. Then, many millions of years later, in African monkeys KIV of plasminogen duplicated itself in multiple copies but lost its fibrin binding activity and it had an intact protease domain present but with loss of its protease activity without losing KV. Then both fibrin-binding deficient KIV and KV appeared in apes, and finally fibrin-binding competent KIV and KV appeared in humans. Additionally, thus far only plasminogen and human apo(a)/Lipo(a) have been documented to contain measurable levels of oxidized phospholipids.⁵ Whether these are all chance events or if there is a yet-to-be discovered evolutionary advantages of these changes, and how this might relate to incident DM, remain to be determined. As best as we can tell, lipo(a) has not any known physiological function in modern society, in spite of etiologically, it may have evolved to protect the host in many ways. Although they are speculative, there have been suggestions that lipo(a) can contribute to wound healing via its lysine binding component that can attach to lysine molecules at injured sites and deliver cholesterol for generation of new cell membranes.^{6,7} Like many other examples of evolutionary advantage of proteins that were modified in Africa, such as altered hemoglobin that protects against malaria but causes sickle cell anemia and apo(a) that protects against African sleeping sickness but is associated with renal failure,⁸ it is possible that since lipo(a) arose in Africa and the highest concentrations are in people of African descent, higher levels may protect against an unknown parasitic infection. However, the closest ex-

planation of lipo(a) biology, but not necessarily the correct one, likely has to do with the fact that the Lipo(a) gene has duplicated itself from the plasminogen gene, either to further enhance plasminogen activity or to act as a ying-yang balance to plasminogen pathophysiology. In fact, we have shown that the oxidized phospholipids that are primarily present on lipo(a) are associated with increased cardiovascular risk,^{9,10} but that the oxidized phospholipids present on plasminogen are associated with enhanced fibrinolysis in vitro and that higher levels are present post myocardial infarction (MI),^{11,12} a putative beneficial function to prevent thrombus propagation. In line with these relationships, several members of the plasminogen-related coagulation cascade, including tissue plasminogen activator that activates plasminogen to plasmin, are also associated with higher risk of incident DM^{13,14} another action that is seemingly opposed by elevated lipo(a) levels. An additional clinically-relevant issue that may have an impact if these associations are causal is whether drugs that lower lipo(a) can also induce the development of DM.¹⁵

PON-1 is an HDL-bound enzyme capable of hydrolyzing lipid peroxides and believed to be in part responsible for the protective effect of HDL against LDL oxidation. Low activity has been related to an elevated incidence of MI. Prolonged hyperglycaemia, dyslipidaemia and excessive oxidative stress are associated with oxidative and glycation damage to lipids and proteins, leading to the conversion of functional HDL into dysfunctional HDL. This status involves alterations in the reverse cholesterol transport, pro-oxidant, pro-inflammatory, pro-thrombotic and pro-apoptotic conditions, which are responsible for atherogenesis.¹⁶ There is a strong interaction between glucose and lipid metabolism, mainly elevated TG and low HDL-c levels; therefore, glycated haemoglobin (HbA1C) may play an important role in modulating this interaction. The altered metabolism of TG and HDL may not only be the consequence of disturbed glucose metabolism but also its cause.¹⁷ Some studies have examined an impact of glycation on the HDL composition (ApoA1 structure) and

HDL-associated PON-1 activity.¹⁸⁻²⁰ The authors observed that the susceptibility to lipid peroxidation was higher in the HDL isolated from subjects with low PON-1 activity than in subjects with higher PON-1 activity. Moreover, HDL glycation was associated with the conformational changes of ApoA1 at the tryptophan position. It appears that glycated HDL and altered PON-1 activity can potentiate the atherogenesis. Another study has shown that oxidative modification of tyrosine residues in the ApoA1 chain may worsen the antioxidant and anti-atherogenic functions of HDL (even at physiological HDL levels) and thus contribute to its dysfunction.²¹ Specifically, structural modification of crucial HDL components by glycation or oxidation can impair the binding ability of apolipoproteins or enzyme activity.²² Impaired binding ability of ApoA1 to the HDL particles and reduced PON-1 activity may significantly affect anti-oxidant, antiatherogenic and other HDL functions.^{23,24} In summary, HDL dysfunctionality may be linked to an increased incidence of atherosclerosis-related diseases in DM subjects due to the loss of essential functions of some components bound to this lipoprotein.

CONCLUSION

Levitssky et al,²⁵ it has been reported that there is a positive correlation between Lipo(a) levels and HbA1C levels in patients with DM. Brucket et al,²⁶ measured levels of Lipo(a) before and after regulating blood glucose. In unregulated DM patients, lipo(a) levels were significantly higher than non-DM patients. Haffner et al,²⁷ also found that Lipo(a) levels were higher in DM patients than in non-DM control group. Gürsu et al,²⁸ also found that lipo(a) levels were significantly higher and PON levels were lower in diabetic patients. Lower PON-1 activity and concentration were associated with an increased risk of developing DM when adjusted for many of the common risk markers for DM previously identified. Thus, PON-1 may have merit as a biomarker for the development of DM.²⁹ The literature review confirmed a strong relationship between low PON and high lipo(a) and DM.

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