Review

What Is Currently Understood and Remains Undiscovered regarding Lp(a) in the Context of Metabolic Syndrome?

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What is Currently Understood and Remains Undiscovered Regarding Lp(a) in the Context of Metabolic Syndrome?

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Abstract: Lipoprotein (a) is a highly atherogenic, lipid particle whose concentration is genetically determined, and represents an independent risk factor for cardiovascular disease. On the other hand, metabolic syndrome represents a cluster of interconnected cardiovascular risk factors (obesity, insulin resistance, arterial hypertension, dyslipidaemia) that are direct consequence of an unhealthy lifestyle. There are some evidences suggesting a connection between each component of metabolic syndrome and high levels of lipoprotein (a), but the exact mechanisms are not fully understood and may involve complex interactions between various metabolic pathways. High levels of lp(a) are associated with the insulin resistance, a key feature of type 2 diabetes mellitus and obesity. Although, there is no significant association between lp(a) and other lipid levels (LDL-C, HDL-C, triglycerides), studies have shown a strong synergistic effect of genetically elevated LDL-C and Lp (a) on the development of cardiovascular events. Also, there are supporting evidences that hypertensive patients with high levels of lp(a) have higher cardiovascular risk, there is no direct association between hypertension and lp (a). Treatment of metabolic syndrome is often long-term and challenging but very important in order to reduce the overall cardiovascular risk, especially in individuals with higher levels of Lp (a), in whom the risk of developing cardiovascular disease much higher.

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What Do We Know about Lipoprotein (a)?

Lipoprotein (a), often abbreviated as Lp(a), is a lipid particle similar in structure to low-density lipoprotein (LDL), but with an additional protein called apolipoprotein (a) attached. It was discovered by a scientist named Kare Berg in 1963. and led the foundation for further research into the role of this particle in cardiovascular health and disease. Lp(a) is very atherogenic particle and promotes oxidation of LDL. Oxidazed LDL is more likely to be taken up by immune cells in the arterial wall, leading to the formation of foam cells and the initiation of atherosclerotic plaque formation [1]. On the other hand, Lp(a) promotes inflammation in the arterial wall that contributes to the recruitment of immune cells and endothelial remodelling, leading to plaque formation and instability. Taking into account the described properties, it is not surprising that high levels of Lp(a) are considered a risk factor for cardiovascular disease, independent of other traditional risk factors such as LDL-cholesterol [2]. Unlike LDL cholesterol, whose level is largely influenced by external factors (diet, smoking, drugs, etc.), the values of Lp(a) are genetically determined. LPA gene is located on chromosome 6q26-27 and contains the genetic information necessary for the synthesis of apolipoprotein (a), which is the unique protein component. LPA gene contains the protease domain and the kringle domains (KIV, KV). The KIV type II encodes the size of apo (a) and the number of repeating sequences (2-43) determines the size of the particle affecting their clearance from the

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bloodstream and their atherogenic properties. It also affects the serum concentration of Lp (a) and explains most of the variability (30-70%) [3]. Individuals that have more repeats generally have higher levels of Lp(a) and smaller, proatherogenic isoforms of particle. However, the exact mechanisms by which KIV-2 repeats influence Lp(a) biology and atherogenicity are still being investigated. On the other hand, there are several frequent and rare functional SNPs that profoundly modify size and concentration of Lp(a). Rs10455872 and rs3798220 are associated with elevated levels of Lp(a) and coronary disease [4, 5]. Several studies have demonstrated that elevated levels of Lp(a) are associated with and increased risk of cardiovascular disease. The Copenhagen City Heart, ARIC (the Atherosclerosis Risk in Communities) and MESA (Multi-Ethnic Study of Atherosclerosis) study have shown consistent finding linking high Lp(a) levels with a greater risk of cardiovascular events such as heart attack, ishemic stroke, peripheral artery disease and stenosis of aortic valve [6, 7]. Studies have also estimated that 20% of population (1.4 billion people) may have elevated levels of Lp(a). Levels above 50 mg/dL (or 75 nmol/L) are often considered elevated depending on the laboratory and the reference range used. Taking into account the proatherogenic properties of the particle, European Atherosclerosis (EAS) and Cardiology Society (ESC) recommend measuring Lp(a) once in a lifetime to identify those with very high levels (>180 mg/dl or > 430 nmol/L) who may have a lifetime risk of ASCVD [8].

What Do We Know about Metabolic Syndrome?

Metabolic syndrome (also known as syndrome X, insulin resistance) is a pathological condition defined as a cluster of interconnected risk factors that occur together, increasing the risk of cardiovascular diseases, type 2 diabetes, and other health problems. These risk factors include abdominal obesity, insulin resistance, high blood pressure, and dyslipidaemia. The precise criteria for defining metabolic syndrome vary depending on the institution providing the definition. For example, IDF 2006 criteria diagnose metabolic syndrome with increased waist circumference for gender-specific thresholds and the presence of two or more of the following: elevated blood glucose or diagnosed diabetes, low HDL cholesterol or HDL-C treatment, high triglycerides or triglyceride treatment, and elevated blood pressure or hypertension treatment [9]. Parallel to the increase in the prevalence of obesity and diabetes type 2, the prevalence of metabolic syndrome has been rapidly increasing throughout the years. According to the US National Health and Nutrition Examination Survey (NHANES), the prevalence of metabolic syndrome in the US has increased up to 41.8% [10]. In addition, results from the China Health and Nutrition Survey (CHNS) show that the incidence of metabolic syndrome has risen from 9.8% in 2001 to 33.26% in 2017 [11, 12]. Its prevention is of great importance given the fact that the metabolic syndrome significantly increases risk for various health complications, including cardiovascular disease, type 2 diabetes and stroke.

Lipoprotein (a) and Diabetes Mellitus Type 2

Population-based studies (Copenhagen City Heart Study, The Women's Health Study) have indirectly suggested a potential inverse relationship between low levels of Lp(a) and risk of diabetes mellitus which is contradictory considering that both high levels of Lp(a) and diabetes increase cardiovascular risk [12]. On the other hand, several studies have found that individuals with diabetes mellitus type 2 tend to have higher levels of Lp(a) compared to those without diabetes. Additionally, elevated levels of Lp(a) have been associated with insulin resistance, a key feature of type 2 diabetes [13]. However, the exact mechanisms underlying this association are not fully understood and may involve complex interactions between Lp(a) metabolism, inflammation and insulin signalling pathways.

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Lipoprotein (a) and Obesity

Since the values of Lp(a) are primarily genetically determined, diet does not have significant effect on Lp(a) levels. On the other hand, obese individuals may have higher Lp(a) levels due to other related factors such as insulin resistance, inflammation or dyslipidemia. There are studies suggesting changes in Lp(a) in obese individuals during weight reduction but with opposite results Most studies showed increase of Lp(a) levels during dietary weight reduction which is explained with altered metabolism of Lp (a) [14, 15], but bariatric surgery-induced weight loss was accompanied by a decrease in Lp (a) serum levels [16]. There is not a direct link between obesity and Lp (a) since the exact mechanisms are still being studied and multiple factors contribute to this relationship. However, obesity represents a major risk factor for cardiovascular disease, so obese individuals with higher levels of Lp (a) should be treated as high risk group of patients.

Lipoprotein (a) and Dyslipidemia

Dyslipidemia is one of the key risk factors in the development of cardiovascular diseases. It can manifest in various forms, including high levels of LDL-C, low levels of HDL-C, and high levels of triglycerides. Dyslipidemia is a component of metabolic syndrome, primarily in the form of low HDL-C levels and high triglyceride levels [17]. Although LDL-C is not a defining component, high levels of LDL-C can often be found in patients with metabolic syndrome. Published studies, such as the Framingham Offspring study [18], have shown that there is no significant association between lp(a) and most traditional cardiovascular risk factors (LDL-C, HDL-C, triglycerides) in general population. Supporting this is that standard medications for dyslipidemia, such as statins and ezetimibe, and diet do not significantly lower lp(a) [19, 20]. A study in patients with premature acute coronary syndrome also showed no statistically significant association between lp(a) and HDL-C or triglycerides. However, it did show a significant association between lp(a) and LDL-C [21]. A study by Langsted et al. has shown a significantly higher risk of myocardial infarction development in patients with familial hypercholesterolemia who simultaneously have elevated lp(a) compared to other groups [22]. This shows that attention should also be paid to the synergistic effect of genetically elevated LDL-C and lp(a) [23] While the European Atherosclerosis (EAS) and Cardiology Society (ESC) recommend measuring Lp(a) once in a lifetime [8], special caution should be exercised when dealing with patients with familial hypercholesterolemia, family history of premature acute coronary syndrome, and LDL-C higher than 3.5 mmol/L.

Lipoprotein (a) and Hypertension:

Hypertension, also known as „silent killer", due to its often asymptomatic nature, is one of the most important modifiable global risk factors for morbidity and mortality according to the Global Burden of Disease Study 2017 [24, 25]. While the etiology of elevated blood pressure in most patients with essential hypertension is not known, questions have been asked about the connection of lp (a) and hypertension, due to them both playing a significant role in the development of cardiovascular disease as independent risk factors [26]. A study done in patients with stable coronary artery disease showed that hypertensive patients with high levels of Lp (a) have had a higher risk of cardiovascular events (CVEs) [27]. On the other hand, there are conflicting reports on the association between the prevalence of hypertension and Lp (a). While some studies show significant associations [28], most studies do not [22, 29, 30]. To this date, there has not been published data that directly and distinctly proves a causal association between circulating lp(a) levels and hypertension. However, due to the significant effect of high lp (a) levels on the development of cardiovascular diseases, circulating levels of lp (a) should be assessed in high-risk hypertensive patients.

Conclusion

There are evidences suggesting a connection between metabolic syndrome and high levels of lipoprotein (a). Studies have shown that individuals with metabolic syndrome tend to have higher levels of Lp(a), which further contributes to their increased risk of cardiovascular disease. However,

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the exact mechanisms linking metabolic syndrome and Lp(a) are not fully understood and may involve complex interactions between various metabolic pathways. Regardless, each component of the metabolic syndrome should be taken seriously and treated in order to reduce the overall cardiovascular risk, especially in individuals with higher levels of Lp (a), in whom the risk of developing cardiovascular disease is much more higher.

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