International Journal of Biotechnology and Clinical Medicine ISSN 2583-4665
Vol.2, No.2, April - June 2023, pp. 41~49

A MINIREVIEW ON THE ROLE OF LIPOPROTEIN IN CHRONIC RENAL FAILURE

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Article Info

Article history:

Received May 8th, 2023
Revised May 25th, 2023
Accepted June 12th, 2023

Keyword:

Daibetes mellitus
Insulin
Lipoaldehyde
Therapy
Outpatients

ABSTRACT

Despite the fact that Lipoprotein (Lp(a)) levels are genetically predetermined and consistent throughout our lives, several factors might cause them to rise. These include, in that order, severe hypothyroidism, uncontrolled diabetes, renal failure, and estrogen deficiency. We explore how Lp(a) levels are genetically determined in this review, as well as if early diagnosis is feasible and avoiding these risk factors can assist in managing the Lp(a) levels.

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How to Cite:

Vasanthan M and Jayalakshmi G. A minireview on the role of lipoprotein in chronic renal failure. IJBTCM. 2023; Volume 2 (Issue 2): Page 41-49.

1. INTRODUCTION

An Egyptian text from around 1500 BC that mentioned "too considerable emptying of the urine" was used to define diabetes. Indian medical professionals have also called it madhumeha or honey urine. The term "diabetes" or "to pass through" was first used in 250 BC by the Greek Apollonius of Memphis. The Indian doctors Sushruta and Charaka initially distinguished between type 1 and type 2 diabetes about 400–500 BC, with type 1 being linked to youth and type 2 being linked to obesity [1,2]. Thomas Willis added the qualifier "mellitus" or "from honey" to the definition of diabetes in the late 1600s to distinguish it from diabetes insipidus, which is likewise characterized by frequent urination [3].

First century BC, Greek physician Aretaeus of Cappadocia provided the first comprehensive clinical description of diabetes. He also highlighted the enormous amount of urine that the kidneys produced. According to history, the first "dialysis" occurred at the Roman baths in 100 AD. To "sweat out" the toxins, people with an accumulation of urea in their systems bathed in baths. A renowned Chinese surgeon, Hua-To, supposedly replaced unhealthy organs with sick ones in about 200 AD. This is the first instance in which therapeutic organ transplantation has been mentioned [4].

It is evident from the statements above that research into illnesses, including diabetes and CRF, has been ongoing for many decades. In contrast, lipoprotein (a) is a relatively new name for this century. Kare Berg first identified lipoprotein (a) in 1963, and in 1998, scientists were able to clone the human gene that produces apolipoprotein(a). As a result, research involving diverse groups has been conducted worldwide to better understand this parameter [5].

2. PREVALENCE OF DIABETES MELLITUS (DM)

Over 240 million individuals worldwide today have diabetes. By 2025, this number is expected to climb to 380 million, mostly due to urbanization, aging, population expansion, bad eating patterns, rising body fat, and sedentary lifestyles. In South-East Asia, the Eastern Mediterranean, the Middle East, and Africa, the number of diabetics is predicted to quadruple by 2025. India, China, the United States, Russia, and Japan are the top five nations with the greatest prevalence of diabetes in that order [6]. Over 50% of diabetics worldwide are unaware of their illness and do not receive treatment. CRF will develop in around 40% of diabetics, increasing their risk of cardiovascular disease [7].

The growing prevalence of Chronic Kidney Disease worldwide due to both the prevalence of end-stage renal disease and the frequency of CRF are rising globally (ESRD). In addition to other factors, diabetes and hypertension are the two most common causes of CRF. Cardiovascular (CV) risk was increased in the presence of CRF 1s. In the most recent NHANES (National Health and nutrition assessment study), between 1999 and 2006, 26 million people (13%) were found to have CRF stages 1-4 [8,9]. According to the United States Renal Data System's most recent data, about 500,000 people received ESRD treatment in the US in 2004. By 2010, this number is predicted to rise by around 40%. Additionally, ESRD risk significantly increases in patients with CRF and pre-existing diabetes or hypertension. These findings have been corroborated across the industrialized globe and in underdeveloped nations like China, India, and Africa [10].

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3. PATHOPHYSIOLOGY

Peripheral insulin resistance and insufficient insulin production by pancreatic beta cells are two traits that define type 2 diabetes. According to a recent study, in-islet suppression of cells produces an insulin-to-glucagon ratio that preserves glycaemic stability even in extremes of glucose inflow or outflow. This demonstrates that type 2 diabetes is an islet paracrinopathy in which the reciprocal link between the beta cell that secretes insulin and the alpha cell that secretes glucagon is destroyed, resulting in hyperglucagonemia and the ensuing hyperglycemia [11].

3.1. BETA-CELL DYSFUNCTION

From prediabetes to diabetes, beta-cell failure is a major contributor. Beta-cell dysfunction emerges early in the pathologic process and does not always follow the stage of insulin resistance, according to research by Bacha et al. on obese teenagers. Insulin resistance: Insulin resistance (IR) is a condition in which cells do not react to the effects of the hormone insulin as they should. Hyperglycemia results from the body's inability to adequately utilize the insulin produced because the cells grow resistant to it. Hyperinsulinemia is further exacerbated by beta cells in the pancreas increasing insulin production [12]. This often remains undetected and can contribute to a diagnosis of Type 2 Diabetes or latent autoimmune diabetes in

adults. In a healthy metabolism, the increased blood glucose level signals the beta cells in the pancreatic islets of Langerhans to release insulin into the blood. The insulin then causes the body's insulin-sensitive tissues to absorb glucose, especially in the liver, adipose tissue, and skeletal muscle cells. This lowers the blood glucose level [13]. As blood glucose levels drop, the beta cells produce less insulin, stabilizing blood sugar at a constant level of about five mmol/L (mM) (90 mg/dL). Normal insulin levels do not have the same effect on managing blood glucose levels in an insulin-resistant individual. Insulin levels are higher, and blood glucose levels are kept stable during the compensated phase of insulin resistance. If compensatory insulin production fails, either postprandial (impaired glucose tolerance) or fasting (impaired fasting glucose) glucose concentrations rise. Eventually, type 2 diabetes, also known as latent autoimmune diabetes, develops when compensatory insulin production fails and glucose levels rise throughout the day due to increasing resistance. Additional impacts of the high insulin levels throughout the body result in additional aberrant biological effects (see insulin) [14].

Metabolic syndrome, a disorder linked to obesity and overweight, is the most typical insulin resistance. Insulin resistance frequently develops into adult-onset latent autoimmune diabetes or full-blown Type 2 diabetes mellitus (T2DM). When pancreatic cells cannot generate enough insulin to maintain normal blood sugar levels (euglycemia) in the face of insulin resistance, hyperglycemia after a meal is frequently observed. The change from insulin resistance to DM 20 is characterized by the -cells' failure to generate enough insulin in a hyperglycemic situation [15,16]. Body tissues become more resistant to insulin's effects in several illness situations. Examples include acidosis and infection (driven by the cytokine TNFa). Adipokines, cytokines generated by fatty tissue, are the subject of recent studies on insulin resistance. Insulin resistance may also be linked to specific medications (e.g., glucocorticoids). Every time a cell is exposed to insulin, the synthesis of GLUT4 (type four glucose receptors) on the cell's membrane reduces somewhat, resulting in insulin resistance [17,18]. This down-regulation functions as positive feedback, increasing the requirement for insulin when there is a greater-than-normal level of insulin (often caused by insulin resistance). This process in muscular tissue is reversed by exercise [19].

People with visceral adiposity—a high level of fat tissue within the abdomen—as opposed to subcutaneous adiposity—fat between the skin and the muscle wall—hypertension, hyperglycemia, and dyslipidemia—characterized by elevated triglycerides, small dense low-density Lipoprotein (sdLDL) particles, and decreased HDL cholesterol levels—are more likely to have insulin resistance. Numerous pieces of data point to two distinct connections between visceral adiposity and insulin resistance [20]. First off, visceral adipose tissue produces far fewer proinflammatory cytokines than subcutaneous adipose tissue, such as tumor necrosis factor-alpha (INF-a), interleukin-1 and -6, etc. In various experimental paradigms, these proinflammatory cytokines interfere with normal insulin action in fat and muscle cells. They may play a significant role in whole-body insulin resistance in individuals with visceral adiposity. The IKK-beta/NF-kappa-B pathway, a protein network that promotes the transcription of inflammatory markers and mediators that can lead to insulin resistance, has received a lot of interest in studies on the generation of proinflammatory cytokines [21]. Second, non-alcoholic fatty liver disease, a disorder associated with visceral adiposity, is characterized by an accumulation of fat in the liver (NAFLD). NAFLD causes an excessive release of free fatty acids into the circulation, leading to increased lipolysis. It also causes an increase in hepatic glycogenolysis and hepatic

glucose synthesis, worsening peripheral insulin resistance and raising the risk of Type 2 diabetes mellitus. Additionally, hypercoagulability (impaired fibrinolysis) and elevated levels of inflammatory cytokines are frequently linked to insulin resistance [22]. Postprandial blood glucose levels rise initially as glucose tolerance transitions from normal to abnormal. Fasting hyperglycemia eventually arises due to the failure to control hepatic gluconeogenesis [23].

3.2. GENOMIC FACTORS

Single-nucleotide polymorphism (SNP) genome-wide association studies have shown a variety of genetic variations linked to beta-cell activity and insulin resistance. Some of these SNPs seem to make type 2 diabetes more likely. More than 40 distinct loci correlate with a higher risk of type 2 diabetes [24].

3.3. AMINO ACID METABOLISM

Early in the onset of type 2 diabetes, amino acid metabolism may be important. In normoglycemic people with high fasting plasma concentrations of 3 amino acids, It was found that the risk of developing diabetes was at least 4-fold greater (isoleucine, phenylalanine, and tyrosine) [25]. Before the onset of diabetes, these amino acid concentrations were increased for 12 years [26].

3.4. DIABETES COMPLICATIONS

Pathophysiology of Microvascular Complications of Diabetes in Diabetic Nephropathy: Renal failure has diabetes as its primary cause of diabetic nephropathy. When diabetes is present, proteinuria > 500 mg in 24 hours defines it, but smaller levels of proteinuria, or "microalbuminuria," come before this. Microalbuminuria is an excretion of 30 to 300 mg of albumin per 24 hours. At the time of their diabetes diagnosis, as many as 7% of type 2 diabetes patients may already have microalbuminuria. A spot urine measurement of microalbumin or a 24-hour urine collection can be used to screen for diabetic nephropathy or microalbuminuria [27].

4. LIPOPROTEIN(a)

The unique apolipoprotein(a) [apo(a)], which is covalently linked to the apoB of the LDL-like particle, and an LDL-like particle make up [Lp(a)]. Plasma levels of Lp(a) are mostly regulated by the apolipoprotein (a) gene [LPA] on chromosome 6 and are highly heritable. The size polymorphism [KIV-2 VNTR] of apo(a) proteins results from various kringle IV repeats in the LPA gene. Apop, (a) proteins with 10 to > 50 kringle IV repeats are produced as a result of this size variation at the gene and protein levels (each of the variable kringle IV consists of 114 amino acids). The term "apo(a) isoforms" refers to these different apo(a) sizes. The Lp(a) plasma concentration and the size of the apo(a) isoform are often inversely correlated [28,29]. One explanation for the relationship between size and plasma level is that variable protein synthesis rates exist. The processing time of the precursor apo (a) protein and the quantity of Kringle repeats appear correlated. In other words, the more apo(a) precursor protein accumulates intracellularly in the endoplasmic reticulum, the bigger the isoform. Since the bigger isoforms of lipoprotein (a) are produced slower than the smaller isoforms because lipoprotein (a) is not fully synthesized until the precursor protein is expelled from the cell, the plasma concentration is restricted. The mechanism and sites of Lp(a) catabolism are largely unknown. Uptake via the LDL receptor is not a major Lp(a) metabolism

pathway. The kidney has been identified as playing a role m Lp(a) clearance from plasma [30].

4.1. FUNCTIONS

Lp(a)/apo(physiological)'s role remains a mystery. Given the feature of the high homology between apo(a) and plasminogen, a role within the coagulation system appears conceivable. The plasminogen gene was duplicated to create the LPA gene [31]. Other roles have been connected to angiogenesis, wound healing, and the recruitment of inflammatory cells via contact with Mac-I integrin. People without Lp(a) or with very low Lp(a) levels, however, appear to be in good health [32]. Plasma Lp(a) is optional, at least not in a typical context. Since apo(a)/Lp(a) evolved relatively recently in mammalian evolution—only old-world monkeys and humans have been found to contain Lp(a)—its function may not be necessary but rather simply advantageous for evolution under specific environmental circumstances such as when exposed to specific infectious diseases. Another hypothesis by Linus Pauling is that Lp(a) is a primate response to the L-gluconolactone oxidase (GULO) defect, unique to specific mammalian lineages. After losing GULO, primates who chose diets lower in vitamin C may have employed Lp(a) as an ascorbic-acid substitute to mend artery walls. GULO is necessary for converting glucose to ascorbic acid (vitamin C), essential to healing arteries.

4.2. PATHOLOGY

Lipoprotein (a) 1 shares structural similarities with plasminogen and tPA (tissue plasminogen activator), and since it outbids plasminogen for its binding site, fibrinolysis is decreased. Additionally, Lp(a) promotes thrombogenesis by stimulating the release of PAI-1, a plasminogen activator inhibitor. Lp(a) also produces cholesterol, which aids atherosclerosis development [33]. Additionally, Lp(a) transfers the more pro-inflammatory and atherogenic oxidized phospholipids, which draw inflammatory cells to vessel walls and promote the growth of smooth muscle cells. Disease and lipoprotein (a) High blood levels of Lp(a) are associated with an increased risk of stroke, atherosclerosis, cerebrovascular disease (CVD), coronary heart disease (CHD), and thrombosis. Compared to cardiovascular disease, there is less correlation between Lp(a) levels and stroke [34]. [Il Lp-a concentrations may be impacted by disease conditions, such as renal failure, although nutrition, exercise, and other environmental variables have a minimal impact. The Lp(a) concentration is little or unaffected by the most frequently administered lipid-reducing medications. Although a meta-analysis published in 2012 indicated that atorvastatin may be helpful, the results of most studies using statins have needed to be more consistent [35,36]. Niacin (nicotinic acid) and aspirin are two generally safe, widely accessible, and reasonably priced medications that have been shown to considerably lower Lp(a) levels in some people with high Lp(a); they should be taken under the guidance of a trained medical professional.

Independent of other cardiac risk variables like LDL, high Lp(a) predicts the likelihood of developing early atherosclerosis. Advanced cardiovascular disease patients with Lp(a) show a coagulant risk of plaque thrombosis. Domains in apo(a) are remarkably similar to those in plasminogen (PLG). Lp(a) builds up in the vessel wall and prevents PLG from attaching to the cell surface, which lowers plasmin production and increases clotting. Lp(suppression)'s of PLG also encourages the growth of smooth muscle cells. These distinctive characteristics of Lp(a) imply that it contributes to developing blood clots and atherosclerosis. One homogenous tribal group in Tanzania found that vegetarians had

greater levels of Lp-a than fish eaters, which suggests that taking fish oil supplements in therapeutic doses could help decrease Lp-a levels [37].

4.3. DIAGNOSTIC TESTING

The agreement is that Lp(a) is a significant, independent predictor of cardiovascular disease, with several research showing a high link between increased Lp(a) and heart disease. Animal investigations have demonstrated that Lp(a) may directly contribute to atherosclerotic damage by enhancing plaque size, inflammation, instability, and smooth muscle cell development. Genetic evidence also supports the hypothesis that Lp(a) causes cardiovascular disease [38]. The European Atherosclerosis Society advises people with a moderate to high risk of cardiovascular disease to have their lipoprotein (a) levels tested. Any patient with one of the risk factors listed below, including familial hypercholesterolemia, recurrent cardiovascular illness despite statin therapy, early cardiovascular disease in the family, and increased lipoprotein (a), should be examined. If the level is high, therapy should begin with the objective of lowering the level to 50 mg/dL or below. The patient's other cardiovascular risk factors, particularly LDL levels, should also be addressed as best as possible. In addition to the overall Lp(a) plasma levels, the apo(a) isoform may also be a significant risk factor. Results from earlier research on the connection between LP(a) and ethnicity have been erratic. Varied groups appear to have different amounts of lipoprotein (a) [39].

For instance, using a risk threshold of 30 mg/dl would classify up to >50% of the individuals as higher risk in some African populations, where Lp(a) levels are, on average, higher than other groups. This complexity may be related to the various genetic factors determining Lp(a) levels. One recent study revealed that among various ethnic groups, various genetic alterations were associated with Lp(a) levels. More recent findings imply the prior investigations needed more power. 3467 African Americans and 9851 white people were monitored for 20 years by the Atherosclerosis Risk in Communities (ARIC) study [40]. The researchers discovered that each group was exposed to the same risk when their Lp(a) was increased. However, Lp(a) levels were nearly three times higher among African Americans, and Lp(a) also indicated a higher risk of stroke. The data below indicate risk levels, while other ways exist to quantify Lp(a). The Worldwide Federation of Clinical Chemistry and Laboratory Medicine and the WHO Expert Committee on Biological Standardization have both approved a standardized international reference guide that has been established. Although there is room for improvement in standards, creating reference material is a crucial first step.

5. CONCLUSIONS

There is widespread consensus that Lp(a) is a strong, independent predictor of cardiovascular disease, with several studies demonstrating a strong association between elevated Lp(a) and cardiovascular issues. Increasing plaque size, inflammation, instability, and smooth muscle cell growth have all been linked to Lp(a) in animal studies, suggesting that Lp(a) may directly contribute to atherosclerotic damage. The link between Lp(a) and cardiovascular disease has also been genetically confirmed. The European Atherosclerosis Society now recommends testing for Lipoprotein (a) levels for those with a moderate to high risk of cardiovascular disease. Familial hypercholesterolemia, recurring cardiovascular

sickness despite statin medication, early onset of cardiovascular disease in the family, and elevated lipoprotein (a) are all reasons to investigate a patient.

FUNDING

Nil

ETHICAL APPROVAL

Nil

COMPETING INTEREST

The authors declare no conflict of interest.

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