Review Article

Interventional Cardiology

The use of TyG and AIP: Evolution of indexes in atherosclerosis management

Abstract

The pathogenesis of atherosclerosis is complex and multifaceted. This directly affects our understanding of this pathology, its definition and treatment. One of the important indicators that help in determining the disease or predisposition to it are various indices. Among these indices, triglyceride-glucose index and plasma atherogenicity index stand out. The triglyceride-glucose index (TyG) is a reliable alternative marker for determining insulin resistance. To date, quite a lot of research has been conducted aimed at studying TyG. According to the results of these studies, it was found that the TyG index is directly related to the development of CVD. Also, other studies provide convincing evidence that in various clinical scenarios, the risk of CAD is associated with the plasma Atherogenicity Index (AIP). In this review, we have considered these two indices and tried to draw conclusions about their applicability.

Keywords: Atherosclerosis; AIP; TyG; Cardiovascular disease; Clinical indexes.

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Introduction

Atherosclerosis

Atherosclerosis is the most common anomaly that leads to the occurrence of cerebrovascular diseases, peripheral artery disease and CAD. The chronic accumulation of plaques clogging the vessels in the sub endothelial layer of the intima of large and medium-sized arteries causes significant stenosis. Stenosis restricts blood flow, which causes critical tissue hypoxia [1]. In most cases, spontaneous thrombotic vascular occlusion leads to complications. The most common complications are stroke and myocardial infarction, which are widespread cause of death. To date, clinical recommendations are aimed at the treatment of such complications. Effective in the prevention and treatment of atherosclerosis, treatment methods are mainly limited to drugs that reduce Low-Density Lipoprotein (LDL) cholesterol [2].

Atherosclerosis is a disease associated with the accumulation of cholesterol. Atherosclerosis occurs due to the retention of lipoproteins (including LDL) in the intimate space of the arteries. In this case, the stored LDL is modified and absorbed by phagocytosis. As a result of this process, fat infiltrates continuously grow [3]. They are rich in inflammatory leukocytes and macroscopically look like plaques. The levels of apolipoproteins (including apoB), LDL cholesterol and plasma cholesterol strongly correlate with clinical atherosclerosis. As a consequence, an increase in plasma cholesterol levels, which occurs due to the genetic knockout of LDLR or ApoE, C57BL/6 mice develop atherosclerosis. Despite the fact that under normal conditions, the disease does not develop spontaneously in these mice [4]. This model in mice, as well as other animal models, substantiate the causal relationship of the occurrence of atherosclerosis. In the course of studies aimed at studying genome-wide associations,

a correlation of many single-nucleotide polymorphisms was revealed in or near the genes that encode lipid-associated proteins. Similar examples include APOB, LDLR and PCSK9. They modulate LDL cholesterol levels as risk factors for myocardial infarction and atherosclerosis. It is also important to mention that atherosclerosis is accompanied by a chronic inflammatory reaction of low severity. Such a reaction attracts cells of the adaptive and innate immune systems to the atherosclerotic plaque. At the same time, some of them recognize apoB (the main protein of LDL particles) [5]. Thus, atherosclerosis is a chronic disease with an autoimmune component, which is clinically best documented by antibodies against LDL and other antigens. Similar results are confirmed on all human and animal models. Also, a number of studies demonstrate that high-affinity antibodies secreted by IgG-producing plasma cells positively correlate with atherosclerosis. And low-affinity natural antibodies against oxidative epitopes in LDL correlate negatively with atherosclerosis [6].

Literature Review

Atherosclerosis indexes

It has been established that for more than a hundred years, cardiovascular diseases have been the leading cause of death worldwide. There are also known risk factors that contribute to the emergence and development of CVD. These factors include; obesity, diabetes, dyslipidemia and hypertension. Recently, the main risk factor is considered to be the lipid profile of plasma, and it is also referred to as the main predictors of CVD. In recent studies, it has been revealed that dyslipidemia leads to atherosclerosis [7]. This is described as a decrease in HDL-C levels and an increase in LDL-C, TC, TG cholesterol levels. Previously, LDL-C was considered as the main target for therapy. But even after its reduction to the recommended levels, about 50% of the residual cardiovascular risk remained. It was this fact that caused the search for new CVD predictors. In the course of studying the results of research and literature, it becomes obvious the importance of numerous lipid ratios or 'atherogenicity indices' in optimizing the prognostic ability of the lipid profile. For example: LDL-C/HDL-C, TC/HDL-C, non-HDL-C (TC-HDL-C), non-HDL-C/HDL-C (atherogenicity index, AI) and TC*TG* LDL/HDL-C (combined lipoprotein index, LCI) are considered the best predictors of CVD [8].

TyG index

TyG index is calculated as formula: ln (fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2) [9]. In a recent study by Liu, et al., in comparison with a lower TyG index, a higher TyG index was associated with an increase in CAD, MI and CVD frequency [10]. Also, a potential linear dose-response relationship was revealed between the CAD/CVD frequency and the TyG index. For 1 unit increase in the TyG index, the risks of CVD and CAD increased by 23% and 35%, respectively. At the same time, a higher TyG index was not statistically associated with mortality from CVD. Based on the totality of the available data, it can be assumed that a higher TyG index may be associated with a higher risk of CVD [11]. It can also be said that, independent of the traditional clinical information on the incidence of CVD, the index can be used as a risk factor.

The Hyperinsulinemic Euglycemic (HIEG) clamp test previously acted as a reference indicator for measuring insulin resistance. However, the high cost and labor cost of this procedure greatly limited the use of this indicator. Recently, new standards for measuring insulin sensitivity have been emerging [12]. These include: QUICKI, HOMA-IR, as well as the ratio of TG to HDL-C [13]. A reliable indicator of insulin resistance is TyG. The results of a recent study conducted in Mexico indicate that when detecting insulin resistance, the TyG index is more accurate than the HIEG clamp test. TyG sensitivity was 96.5%, and specificity was 85%. TyG also shows similar good results in assessing insulin resistance in comparison with HOMA-IR. Sensitivity-89% and specificity-67% [14]. Glucose and triglyceride measurements are not expensive and are readily available during hospitalization. Based on this, we can say that the TyG index does not affect the increase in both healthcare costs in general and patient expenses in particular. Summing up, we can talk about using the TyG index as a reliable indicator for measuring insulin resistance and predicting the occurrence of CVD in the general population [15].

The relationship between hypertension and the TyG index has been confirmed in several large prospective cohort studies. The meta-analysis data indicate that the TyG index is suitable as a predictor of the risk of hypertension in the adult population as a whole [16]. Ding, et al., in their study concluded that in people without Atherosclerotic Cardiovascular Disease (ASCVD) at the initial level, a higher TyG index may be associated with a higher frequency of ASCVDs [17]. Also, Barzegar, et al., in their study of lipids and glucose conducted in Tehran, revealed a greater risk of CAD and CVD with a higher TyG index [18]. Two other major studies conducted by Liu, et al., [10], and Hong, et al., [15], also confirmed the relationship between MI and TyG index.

Different studies provide contradictory data on the relationship between the TyG index and mortality from CVD, as well as from other causes in the general population. Thus, the results of Vega's study suggest that the previously confirmed link between mortality risk and the TyG index disappeared after adjustment [19]. The adjustment was based on age, resting systolic blood pressure, body mass index and smoking. Despite this, the analysis carried out in the work of Liu, et al. [10], indicated a positive correlation. When such a dual interpretation is manifested, obtained in parallel, unrelated studies, it is necessary to approach the interpretation of

the results with special care. Similar positive correlation was also indicated by the results of other studies. For example, in patients with established coronary angiography with a high TyG index and acute MI, the risk of mortality due to cardiovascular diseases was higher RR=2.71; 95% CI 1.92-3.83. Mortality from all causes was also overestimated RR=2.35; 95% CI 1.72-3.20 [20]. In his study, Guo cites data that in people with T2DM (RR=4.42; 95% CI 1.49-13.15), as well as with established chronic heart failure, the TyG index was associated with mortality from cardiovascular diseases [21]. A similar association of mortality from all causes and the TyG index was also found in people with ischemic stroke and chronic coronary syndrome. In particular, a prospective study was conducted among middle-aged men in Finland, without established diabetes [22]. According to its results, HOMA-IR was associated with death from coronary heart disease (HR=1.69; 95% CI 1.15-2.48). This suggests a confirmed relationship between death and insulin resistance. Also, based on this, we can talk about the relationship between death and the TyG index. Statistical significance may be reduced due to the limited follow-up time, as well as due to the limited number of studies included. Additional prospective studies are required to verify and confirm the assumption of a relationship between mortality and the TyG index in the general population [23].

Intercourse can be a significant modifier of the effect. The gender difference in the correlation between subclinical atherosclerosis and a high TyG index in people without established diabetes was revealed due to the longitudinal study of aging I-Lan (ILAS) [24]. Separately, it is worth noting that, unlike men without diabetes, women without diabetes in the group with a high TyG index revealed an overestimated prevalence of subclinical atherosclerosis. Similar results indicate the need to take gender into account when developing a strategy for the treatment and prevention of atherosclerosis [25].

Diabetes is a vital factor that can introduce ambiguity. Previous studies have found that in patients without established diabetes, an increased risk of cardiovascular events is directly related to increased insulin resistance. At the same time, in patients suffering from diabetes, such a relationship has not been reliably identified and remains controversial [26]. So, based on the presence or absence of diabetes, it is important to determine the relationship between the presence and severity of cardiovascular diseases in the general population. During one of the conducted studies, it was revealed that in patients with established diabetes, the prevalence of CAD and obstructive CAD was higher. In patients with diabetes, the prevalence of CAD was 59%, and obstructive CAD was 15%. In patients without diabetes, the prevalence of CAD was 39%, and obstructive CAD 6.6% [27]. Thanks to the adjusted results, it was possible to establish that the TyG index was associated with CAD and obstructive CAD only in the second case, without association with the first. Based on these results, it can be assumed that in patients without diabetes, insulin resistance has a significant effect on coronary atherosclerosis. At the same time, in patients with established diabetes, the primary mechanisms of atherosclerosis progression may be associated with other means. It is also worth mentioning that the Si article provides data on the relationship between CAD/T2DM and the TyG index. Based on the results obtained, the author concludes that for patients with T2DM and coronary heart disease, the TyG index is a risk factor. It is also assumed that the TyG index can be used as a predictor of T2DM in combination with coronary heart disease [28].

In all included studies, patients with CVD were excluded. The relationship between the frequency of CVD and the TyG index was also established. While diabetes is an important risk factor for CVD, it has been excluded in several studies, as has CVD. In one of the other retrospective cohort studies, it was found that after a median follow-up of 5.6 years, an increase in the frequency of CVD in the non-diabetic population was associated with the TyG index. This relationship was also confirmed in another prospective cohort study, after 6 years of follow-up, among patients without CVD and diabetes mellitus. In their work, Park, et al., pointed out the significance of CAD frequency for the TyG index among people without established diabetes [29]. (HR=2.28; 95% CI 1.69-2.40). At the same time, according to the results of the meta-analysis of data obtained among people without diabetes, a significant relationship between the TyG index and the MI frequency was not established. (HR=1.55, 95% CI 0.88-2.74, I2=98%). Additional research will be required to effectively apply the TyG index in assessing morbidity and mortality from CVD. In order to reduce the inverse causal relationship, these studies should be conducted among people who do not suffer from diabetes mellitus [30].

According to the results of a study conducted by Wang, et al., it was found that in the general adult population, the TyG index is associated with the risk of hypertension [31]. At the same time, Li, et al., found that among patients with established acute coronary syndrome, the TyG index can predict adverse events [32]. During the meta-analyses that were conducted earlier, the main attention was paid to the possible relationship between the prognosis of patients with acute coronary syndromes and TyG. The research conducted later was aimed at studying the general population. It is also worth mentioning that this study was aimed at studying large types of CVD and mortality. And to determine more detailed results, the relationship between TyG and CVD was analyzed separately.

Potential mechanism

TyG can be selected as an effective indicator of insulin resistance. In the course of one of the previous studies, its efficacy as a marker of insulin resistance was determined (specificity 85.0%; sensitivity

96.5%). Based on this, it can be assumed that by determining the frequency of CVD and the level of the TyG index, insulin resistance can be determined [33]. At the same time, insulin resistance is mainly characterized by a low degree of systemic inflammation. This inflammation leads to endothelial dysfunction. At the same time, insulin resistance also contributes to the development of atherosclerosis and plaques. This happens with the help of different mechanisms. Such mechanisms include suppression of insulin signaling pathways, as well as changes in classical CVD risk factors [34].

Some of the risk factors that characterize the development of CVD are also associated with the results of measurements of the TyG index. Calcification of the coronary arteries also belongs to such factors. In his study, Park conducted an observation for 4.2 years among 1,175 participants [29]. Based on the results, Park suggested that the TyG index is an independent predictor of the development of calcification of the coronary arteries (OR=1.82, 95% CI 1.20-2.77). Also, in the course of a study conducted in Korea, it was found that the TyG index is more effective than HOMA-IR in determining calcification of coronary arteries. Separately, it should be said that the development of calcification of coronary arteries provides evidence for the development of CAD [35].

Based on the estimates obtained using the Archimedes model, it can be argued that an important cause of coronary heart disease is insulin resistance. At the same time, it can be estimated thanks to the TyG index. To investigate this issue, a genetic study was conducted among 130,681 healthy people and 63,746 people with CAD [10]. According to its results, it was found that inflammation and lipid metabolism are the most important biological processes that take part in the development of coronary atherosclerosis. This is due to the maintenance of the role of insulin resistance in the pathophysiology of CAD. It is also worth mentioning that insulin resistance has an effect on macrophages, endothelial cells and blood pressure. It can also cause atherosclerotic dyslipidemia, increase the release of inflammatory markers, and cause a low-grade inflammatory condition [36].

Atherogenic index

In the course of a recent study, it was found that the plasma atherogenicity index, which was calculated using the log (TG/HDL-C) formula, reflects the true relationship between atherogenic and protective lipoproteins. In addition, it was also found that this index can act as an alternative predictor of CAD and atherosclerosis. At the same time, a controversial situation arises, since in the course of research conducted in the past, contradictory results were obtained [37]. For example, in their work, Hartopo, et al., conducted a prospective cohort study among patients who had suffered an acute myocardial infarction during intensive hospitalization in the past [38]. The results revealed a relationship between the AIP value and major adverse cardiovascular events (MACE). AIP<0.24–in the group with low AIP; AIP ≥ 0.24 in the group with high AIP. It is on the basis of such results that we can talk about the role of a low AIP value as a predictor of mortality from all causes. And in a study conducted by Nansseu, et al., among postmenopausal Cameroonian women, it was revealed that AIP cannot act as an independent risk factor for CAD [39].

Among the elderly, AIP is independently associated with CAD. At the same time, AIP is superior to other lipid indicators. But it should be said that during the analysis of subgroups, among older women, this assumption was not confirmed [40].

Coronary atherosclerosis is the pathological basis of CAD. At the same time, the leading cause of coronary atherosclerosis is the deposition of lipids. The main causal factor is LDL-C. Its cumulative effect is a more significant risk factor for CAD, especially among the elderly. Accordingly, it can be said that a decrease in LDL-C levels can cause a decrease in cardiovascular events [41].

sdLDL is a small dense low-density lipoprotein. It is also a component of LDL particles with a small volume and high density. At the same time, sdLDL is more easily oxidized, and also more easily damages vascular endothelial cells, in comparison with other LDLs. After that, the sdLDL passes through the cells. As a result of such exposure, cholesterol accumulates, which in turn causes the appearance and development of atherosclerosis [42]. Due to the combination of sdLDL indicators and normal blood lipid indicators, it is possible to comprehensively assess atherosclerosis, which was caused by lipids. But, the sdLDLs evaluation procedure itself is quite expensive and complicated. Therefore, the widespread use of this assessment cannot be carried out in clinical practice. Accordingly, a new, simpler and cheaper method will be required to determine the indirect measurement of LDL particle size [43].

The AIP concept was first introduced in 2001 in a study conducted by Dobiásova, et al., [44]. In their work, the researchers pointed out that AIP has a better value for clinical use, in comparison with a single traditional lipid index. Later, other evidence was given that indicated that AIP correlates negatively with the particle size of LDL. It was also mentioned that AIP can indicate the size of sdLDL. Other studies have also found that AIP is associated with the following factors: Non-alcoholic fatty degeneration, abdominal obesity, T2DM, etc. Another study was also conducted among 3,600 patients who underwent CAG [45]. In the course of this work, it was found that AIP is quite effective in the diagnosis of CAD (specificity 61.8% and accuracy 76.4%). In another study conducted in Mexico among young people aged 18-22 years, aimed at studying AIP, it was confirmed that AIP can be considered as a risk factor for cardiovascular diseases [46].

Women of the older age group are least affected by estrogen. From

this fact, the question follows, why does the difference in the ratio of CAD and AIP persist in both women and men? To answer this question, several circumstances should be taken into account. To begin with, it should be said that the average AIP level was significantly higher in older women. In addition, affecting AIP, PLT levels differed in the control group and the CAD group of older men, but not in older women. At the same time, it is worth mentioning that physical data (diet, sports) were not obtained in this study. However, due to the fact that these circumstances may affect the levels of HDL-C and TG, the results may not be reliable [47].

Also in this study, it was found that AIP was closely associated with the proportion of patients with T2DM and PH, as well as with the levels of BMI, LDL-C, SUA, PLT, WBC, eGFR and other lipid indices. And all these factors in the previous study were taken into account as CAD risk factors. Given the existence of this relationship, in order to reduce the level of AIP, the maintenance of a healthy lifestyle among all older people should be encouraged. Even though the association between CAD risk and AIP has not been established among older women [48].

Also, Onat, et al., conducted another prospective study of 2,676 middle-aged people for 7.8 years [49]. In the course of this work, it was found out that AIP can be used as a reliable biomarker for the prognosis of CVD. To test the assumption that AIP can predict the risk of developing type 2 diabetes better than conventional lipid markers, an extensive meta-analysis was conducted. This meta-analysis included 15 studies. To identify the relationship between the presence of CAD and the concentration of sdLDL in the elderly, Toft-Petersen, et al., conducted a cross-sectional study [50]. In the course of this study, the link between mortality and AIP in the elderly was confirmed. In patients from Turkey with subclinical atherosclerosis who were on supportive hemodialysis, a significant increase in AIP and intima-media thickness of the carotid artery was found. The results confirming the usefulness of using AIP in the diagnosis of CVD were also obtained from another study conducted in Morocco [51]. It is also worth mentioning that during a study conducted in Nigeria; this index was used to predict the risk of atherosclerosis in older women with hypertension [52]. A recent study also found that, regardless of hypertension, smoking and diabetes, an increased apoB: ApoA1 ratio is a significant risk factor for CAD. It also remains predictable after adding other confounding factors. sdLDL was identified as a major CAD risk factor and recommended for detection by the National Cholesterol Education Program in 2002 [53]. At the same time, those methods of determining sdLDL that are currently used are quite expensive and have limitations. At the same time, the AIP accurately reflects the sdLDL level, and it is easy to calculate it. Accordingly, we can say that AIP should be used to control CVD among the population.

Discussion and Conclusion

Today, it is clear that simple measurements such as total cholesterol are not sufficiently indicative of atherosclerosis or predisposition to it. Simultaneously with attempts to determine the central mechanism for the development of this pathology, researchers are trying to develop the most optimal index that would allow predicting the development of diseases at an early stage. In our opinion, the indices described in the article, TyG and AIP have the greatest potential. This is confirmed by a number of studies, as well as by the fact that when calculating these indices, events that are most significant for the pathogenesis of atherosclerosis, as well as some modifiable risk factors, are taken into account. Of course, indexes are not a universal tool, but they are a significant help for clinicians in making a diagnosis.

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