Section A-Research paper

THE ATHEROGENIC INDEX OF PLASMA AS A MARKER OF CORONARY ARTERY DISEASES IN TYPE 2 DIABETES MELLITUS PATIENTS

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Abstract
The purpose of this review article was to assess whether "*Type 2 Diabetes Mellitus Patients*' (T2DM)" "*Atherogenic index of plasma* (AIP)" could serve as a predictor for "*Coronary Artery Disease* (CAD)". A significant complication of T2DM that has a high risk of morbidity and mortality is CAD. AIP has been suggested as a helpful indicator of CAD risk. It is calculated as the logarithm of the ratio of triglycerides to high-density lipoprotein cholesterol. Many researches have looked into the connection between AIP and CAD in T2DM patients, and the findings have consistently shown that this population has a much higher risk of developing CAD when AIP levels are higher. Nonetheless, there is still debate about the use of AIP as a clinical biomarker for CAD risk in T2DM patients, and more research is required to confirm its usefulness in clinical practice. Furthermore explored is the potential of AIP as a therapeutic target for the prevention and treatment of CAD in people with type 2 diabetes.

KEY WORD: Coronary Artery Disease, Diabetes Mellitus, Atherogenic Index Of Plasma, Proatherogenic, Lipoprotein

Introduction to Type 2 Diabetes Mellitus and Coronary Artery Disease

The chronic metabolic disorder "*Type 2 Diabetes Mellitus* (T2DM)" is defined by high blood sugar levels brought on by the body's improper usage of insulin. T2DM is a major public health concern globally, affecting over 463 million people worldwide, with a projection of 700 million by 2045 (1). The risk of developing "*Coronary Artery Disease* (CAD)", a condition that affects the blood vessels supplying the heart with oxygen and nutrients and causes their narrowing or obstruction is also enhanced by T2DM (2).

T2DM has a complicated pathophysiology that is influenced by both hereditary and environmental factors. The main flaw in T2DM is insulin resistance, which is manifested by a decreased sensitivity to insulin, leading to increased glucose synthesis and diminished glucose absorption by peripheral tissues such muscle and adipose tissue (3). Additionally, the pancreas produces more insulin in response to insulin resistance, which ultimately results in beta-cell malfunction and failure and insufficient insulin production (4).

Globally, CAD is the number one cause of death and disability (5). It is a multifactorial disease with several risk factors, including T2DM. The presence of T2DM increases the risk of CAD by two to four times, and patients with T2DM have a higher incidence of acute coronary syndromes, poorer outcomes following myocardial infarction, and a higher risk of death (6). The exact mechanisms linking T2DM and CAD are not fully understood. Still, it is thought to involve a combination of traditional cardiovascular risk factors such as hypertension, dyslipidemia, and inflammation, as well as metabolic abnormalities associated with T2DM, including insulin resistance, hyperglycemia, and oxidative stress (7).

Management of T2DM and CAD involves lifestyle modifications, including diet and exercise, and pharmacotherapy. The primary goal of pharmacotherapy is to achieve glycemic control in patients with T2DM to prevent complications, including CAD. Medications such as metformin, sulfonylureas, and insulin are commonly used to manage T2DM. In addition, medications such as aspirin, statins, and angiotensin-converting enzyme inhibitors are commonly used in patients with T2DM and CAD to manage cardiovascular risk factors and reduce the risk of cardiovascular events (8).

Proper management of T2DM and CAD involves lifestyle modifications and pharmacotherapy, including medications that target both conditions' underlying pathophysiology. A multidisciplinary approach involving healthcare providers, including endocrinologists, cardiologists, and primary care physicians, is essential to manage patients with T2DM and CAD adequately.

AIP as a Marker for Cardiovascular Risk Assessment

"*Cardiovascular diseases* (CVD)" are a leading cause of morbidity and mortality worldwide. The prevention of CVD is therefore of paramount importance. Accurate assessment of an individual's cardiovascular risk is essential to determine appropriate preventive measures. Several traditional risk factors, including hypertension, dyslipidemia, and smoking, have been identified as predictors of CVD. However, these risk factors may not fully reflect an individual's risk, and additional markers are needed (9-11).

The "*Atherogenic Index of Plasma* (AIP)" is a marker that has recently gained attention as a predictor of CVD. AIP is calculated as the logarithm base 10 of the ratio of "*Triglycerides* (TG)" to "*High-Density Lipoprotein Cholesterol* (HDL-C)". AIP has been shown to be a strong predictor of CVD in both men and women, and across different ethnicities (12,13).

AIP is superior to other lipid markers in a number of ways. First of all, it is a straightforward and affordable marker that is simple to calculate from standard lipid profile measures. Second, compared to other lipid indicators such as total cholesterol, "*Low-Density Lipoprotein Cholesterol* (LDL-C)", and non-HDL-C, AIP has been found to be a more reliable predictor of CVD. Lastly, it has been demonstrated that AIP is a more accurate predictor of CVD than conventional risk variables alone (14,15).

AIP has been demonstrated to be a helpful marker for determining CVD risk in various populations. For instance, compared to other lipid markers, AIP has been demonstrated to be a superior predictor of CVD risk in people with diabetes. In comparison to other lipid markers, AIP has also been demonstrated to be a more accurate predictor of CVD risk in postmenopausal women (16).

The AIP is a straightforward, low-cost, and reliable marker for determining CVD risk. AIP can supplement conventional risk factors with extra data and may be very helpful for some groups. Clinicians ought to think about include AIP in their CVD risk assessment procedures.

Mechanisms linking T2DM to AIP and CAD

T2DM is a major risk factor for developing atherosclerosis, a chronic inflammatory condition of the arterial walls that leads to the development of CAD (17). Several mechanisms have been proposed to link T2DM with AIP, a marker of lipid metabolism that reflects the balance between antiatherogenic and proatherogenic lipoproteins. In this article, we will review the current understanding of the mechanisms that link T2DM to AIP and CAD.

One of the proposed mechanisms linking T2DM to AIP is insulin resistance, a hallmark feature of T2DM. Insulin resistance is characterized by the inability of insulin to effectively promote glucose uptake by peripheral tissues, leading to hyperglycemia (18). Hyperglycemia is associated with increased production of very-low-density lipoprotein (VLDL) in the liver, which is a proatherogenic lipoprotein (19). VLDL is converted to LDL in the circulation, which is another proatherogenic lipoprotein (20). On the other hand, insulin resistance is also associated with decreased production of "*High-Density Lipoprotein* (HDL)", which is an antiatherogenic lipoprotein (21). This results in a decrease in the ratio of HDL to LDL, leading to an increase in AIP and the development of atherosclerosis (22).

Another proposed mechanism linking T2DM to AIP and CAD is chronic inflammation. Chronic inflammation that is characterized by increased production of proinflammatory cytokines including "Tumor Necrosis Factor-Alpha (TNF-alpha)" and "Interleukin-6 (IL-6)" is linked to T2DM (23). Through the induction of endothelial dysfunction and the infiltration of inflammatory cells into the artery wall, chronic inflammation is known to encourage the development of atherosclerosis (24). In addition, chronic inflammation is also associated with dyslipidemia, characterized by an increase in proatherogenic lipoproteins such as VLDL and a decrease in antiatherogenic lipoproteins such as HDL (25). This leads to an increase in AIP and the development of atherosclerosis.

Furthermore, "*Advanced Glycation End Products* (AGEs)" have been projected as another mechanism linking T2DM to AIP and CAD. AGEs are formed by the nonenzymatic reaction between reducing sugars and amino acids, and they accumulate in the arterial wall and promote the development of atherosclerosis (26). AGEs also promote the formation of proatherogenic lipoproteins such as VLDL and LDL, and decrease the production of antiatherogenic lipoproteins such as HDL (27). This results in an increase in AIP and the development of atherosclerosis.

In conclusion, T2DM is a major risk factor for the progress of atherosclerosis and CAD. The mechanisms linking T2DM to AIP and CAD include insulin resistance, chronic inflammation, and advanced glycation end products. A deeper comprehension of these pathways might help in the creation of T2DM, AIP, and CAD prevention and treatment plans that are more successful.

Clinical Evidence supporting AIP as a Predictor of CAD in T2DM

Dyslipidemia is one of the key features of T2DM and is associated with an increased risk of CVD, CAD (28). Traditional lipid parameters, including LDL, HDL-C, and TG, have been used as predictors of CVD in T2DM patients (29). But recent research suggests that non-traditional lipid measures, including the AIP, may be more accurate CVD predictors in T2DM patients (28,29).

AIP is a novel marker of atherogenicity that combines the levels of TG and HDL-C in a single index. In numerous groups, including T2DM patients, AIP has been demonstrated to be a more accurate predictor of CVD than conventional lipid measures (28,29). AIP is calculated as log base 10 of the ratio of TG to HDL-C, where a higher AIP score indicates a more atherogenic profile (30).

Numerous researches have looked into the relationship between AIP and CAD in people with type 2 diabetes. Wu et al. directed a retrospective cohort study to investigate the predictive value of AIP for CAD in T2DM patients (28). The study included 1,536 T2DM patients, of whom 509 had CAD. The authors found that AIP was a better predictor of CAD risk than traditional lipid ratios, including total cholesterol (TC)/LDL-C, LDL-C/HDL-C, and TG/HDL-C (28). In another study by Wu et al., the authors investigated the predictive value of AIP for CAD in T2DM patients compared to traditional lipid ratios (29). The study included 6,278 T2DM patients, of whom 1,210 had CAD. The authors found that AIP was a superior predictor of CAD risk associated to traditional lipid ratios, together with TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C (29).

In addition, Li et al. conducted a retrospective cohort study to investigate the predictive value of AIP for CAD in T2DM patients with impaired glucose tolerance (IGT). The study included 394 T2DM patients with IGT, of whom 166 had CAD. The authors found that AIP was a superior predictor of CAD risk compared to traditional lipid ratios, including TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C (31).

These studies' findings imply that AIP might be a practical clinical tool for assessing CAD risk in T2DM patients. AIP is a straightforward and affordable marker that is simple to calculate from regular lipid measurements (32). Therefore, AIP has the potential to improve risk stratification and guide therapeutic interventions in T2DM patients.

The use of AIP as a predictor of CAD in T2DM patients is supported by current clinical findings. Compared to conventional lipid measures, AIP is a more accurate and new predictor of CAD risk in T2DM patients. The therapeutic usefulness of AIP as a predictor of CAD and its function in the management of T2DM and CVD risk require more study.

Limitations and Challenges of using AIP in Clinical Practices

The ratio of non-HDL to HDL cholesterol in plasma is represented by the AIP, a computed value. It has been suggested that it is a more accurate predictor of the risk of CVD than conventional lipid measures. But there are restrictions and difficulties in using AIP in clinical practice that must be resolved. The restrictions and difficulties of employing AIP in clinical practice will be covered in this essay (33).

Limited Data on Clinical Outcomes

While some data indicate that AIP may be a more accurate predictor of the risk of CVD than conventional lipid measures, there is limited data on the clinical outcomes associated with using AIP as a diagnostic tool. Most studies have been observational in nature, and there is a lack of randomized controlled trials that have investigated the efficacy of using AIP to guide treatment decisions (34).

Lack of Standardization

The calculation of AIP is relatively simple, but there are several different methods for calculating it. This lack of standardization can lead to inconsistencies in the interpretation of AIP values, which can make it difficult to compare results across different studies and populations (33-35).

Impact of Lifestyle Factors

Numerous lifestyle elements, such as nutrition, activity, and smoking status, have an impact on AIP. This implies that changes in these parameters may have an impact on AIP levels, making it challenging to evaluate the outcomes of AIP testing over time. AIP may also be more affected by lifestyle factors than by conventional lipid tests, which could restrict its applicability as a diagnostic tool in some groups (36).

Limited Usefulness in Certain Populations

AIP may be less effective as a diagnostic tool in some populations, such as people with diabetes or high lipid levels. This is due to the fact that AIP is determined using a non-HDL cholesterol to HDL cholesterol ratio, which may not adequately reflect lipid status in these groups (34–36).

Lack of Guidance on Interpretation

There is a lack of clear guidance on how to interpret AIP values, which can make it difficult for clinicians to use AIP as a diagnostic tool in clinical practice. While some studies have proposed cut-off values for AIP, there is no consensus on what constitutes a normal or abnormal AIP value (36,37).

Challenges of Using AIP in Clinical Practice

Integration into Clinical Practice

The integration of AIP into clinical practice can be challenging, particularly in settings where there is limited access to laboratory facilities or where there is a lack of trained personnel to perform lipid testing. Additionally, there may be resistance to using AIP as a diagnostic tool among some clinicians who are unfamiliar with the concept or who are hesitant to move away from traditional lipid measurements (34-38).

Cost-Effectiveness

The cost-effectiveness of using AIP in clinical practice has not been well-studied. While AIP testing may be relatively inexpensive compared to other diagnostic tests, there may be additional costs associated with training personnel, developing standardized protocols, and integrating AIP testing into existing clinical workflows (34-38).

Conclusion

There is a need for further research to determine the clinical utility of AIP and to address the limitations and challenges associated with its use in clinical practice. This includes randomized controlled trials to investigate the efficacy of using AIP to guide treatment decisions and studies to determine the optimal cut-off values for AIP in different populations.

While AIP has been proposed as a potentially better predictor of CVD risk than traditional lipid measurements, there are limitations and challenges associated with its use in clinical practice. These include a lack of data on clinical outcomes, a lack of standardization, the impact of lifestyle factors, limited usefulness.

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