Lipid variability in patients with diabetes mellitus

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Diabetic dyslipidemia is characterized by hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), elevated low-density lipoprotein cholesterol (LDL-C), and the predominance of small dense LDL particles caused by insulin resistance in patients with type 2 diabetes mellitus (DM) or insulin deficiency in patients with type 1 DM. Dyslipidemia is a major risk factor for atherosclerotic cardiovascular disease in individuals with DM, and lowering lipid levels can reduce the associated morbidity and mortality. The current guidelines for dyslipidemia management recommend an LDL-C goal lower than 55 to 100 mg/dL, depending on the underlying risk factors. However, greater visit-to-visit variability in cholesterol levels might be an independent predictor of major adverse cardiovascular events, high incidence of atrial fibrillation, poor renal outcomes, and cognitive dysfunction in patients with DM. This review focuses on the clinical implications of lipid variability in patients with DM.

Keywords: LDL cholesterol; Diabetes complications; Dyslipidemias; Triglycerides

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD), which comprises ischemic heart disease, cerebrovascular disease, and atherosclerosis, is the second leading cause of death in Korea, surpassed only by malignant neoplasms. Dyslipidemia, a condition characterized by metabolic irregularities in plasma lipids and lipoproteins such as low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides, is a primary contributor to ASCVD [1]. Notably, ASCVD is a predominant cause of mortality among patients with diabetes mellitus (DM), and dyslipidemia, a significant risk factor for ASCVD, can be managed in these patients [2]. The typical dyslipidemia patterns seen in patients with DM include hypertriglyceridemia, elevated levels of small dense LDL-C (sdLDL-C), and reduced HDL-C, all of which are closely associated with hyperglycemia [3,4].

Since LDL-C has been identified as the most reliable predictor of ASCVD, statin therapy is primarily used to treat dyslipidemia and decrease the incidence and risk of ASCVD. This approach is based on prior research suggesting that "the lower, the better" [5,6]. Most earlier studies assessing lipid-lowering effects, such as those of statins, concentrated on lipid markers at the start and end of the studies. However, recent research has shed light on the connection...
between cholesterol variability and various diseases. Consequently, this review aims to summarize the impact of lipid variability in patients with DM.

**DYSLIPIDEMIA IN DM**

**Hypertriglyceridemia in DM**

Hypertriglyceridemia is the most prevalent form of dyslipidemia found in patients with DM. This elevation in serum triglycerides is primarily driven by insulin resistance, which is associated with hyperglycemia [7]. In patients with type 2 DM, insulin resistance results in an increase of free fatty acids due to lipolysis, which in turn leads to an increased secretion of very-low-density lipoproteins, including triglycerides. Conversely, patients with type 1 DM, which is characterized by insulin deficiency, do not see an increase in triglycerides due to the influx of free fatty acids into the liver. Instead, they develop hypertriglyceridemia as a result of impaired triglyceride clearance [3,8].

**Hypercholesterolemia in DM**

Severe dyslipidemia is not typically seen in the majority of patients with DM. As previously noted in the introduction, LDL-C is considered to be a predictive factor for ASCVD, and the importance of statin therapy is also underscored in patients with DM, in whom elevated levels of free fatty acids, due to insulin resistance and hypertriglyceridemia, cause an increase in LDL lipolysis. This results in the creation of smaller, denser LDL particles, referred to as sdLDL-C. Closely linked to ASCVD, sdLDL-C contributes to the higher incidence of CVD in patients with DM [9].

HDL is involved in the reverse transport of cholesterol from peripheral tissues back to the liver, and low HDL-C levels are another predictive indicator for ASCVD, in addition to high LDL-C levels. Elements such as advanced glycation end products, oxidative stress, and inflammatory responses triggered by hyperglycemia result in a reduction of HDL-C levels and interfere with cholesterol efflux [8,10].

**LIPID VARIABILITY IN DM**

As outlined in the introduction, the primary and secondary prevention of ASCVD relies heavily on lipid-lowering therapy, predominantly through the use of statins. Furthermore, it has been demonstrated that discontinuing statin therapy can lead to increased short- and long-term mortality rates, as well as a higher incidence of vascular events in patients with ASCVD [11–13]. Poorer outcomes have been reported in patients who discontinued statin therapy than in those who never started it [14,15]. The conversation around lipid variability originated from studies that explored the relationship between lipid variability and the prognosis of ASCVD in the context of large-scale statin trials. Research has been conducted on daily variability [16,17] and seasonal variability [18] in lipid levels in patients with type 2 DM, revealing the existence of biological variability in cholesterol levels. However, the clinical significance of short-term lipid variability remains unclear, and interest has grown in recent years in the impact of long-term (visit-to-visit) lipid variability in patients with DM.

**Risk of DM incidence with lipid variability**

Studies based on data from Korea have reported a correlation between lipid variability and the risk of developing DM. One study [19], which utilized the Korean National Health Insurance Service (NHIS) database, divided total cholesterol variability into deciles. The results showed that the group in the highest decile had a 1.16-fold higher risk of developing DM than the group in the lowest decile, regardless of whether they were undergoing lipid-lowering therapy (95% confidence interval [CI], 1.57–1.63). Another study [20] examined the risk of DM based on HDL-C variability. In that research, both the average HDL-C and HDL-C variability were used as variables. The findings indicated that both men and women had a higher risk of developing DM if they had lower baseline HDL-C levels and greater variability. According to a multivariate analysis model, the group with a lower average HDL-C and higher variability had a 1.40 times higher risk (95% CI, 1.38–1.42) of developing DM compared to the group with a higher average HDL-C and lower variability. Previous studies have suggested that a chronic inflammatory state and nonenzymatic apolipoprotein glycation may play a role in the impairment of HDL-C function [20,21]. Additionally, HDL-C influences glucose metabolism through both direct and indirect pathways. Several mechanisms may account for the association between elevated levels of HDL-C and a decreased risk of diabetes,
encompassing anti-inflammatory response mechanisms, enhanced insulin secretion, and improved glucose uptake by peripheral muscles \[22\]. However, the exact impact of HDL-C variability on subsequent type 2 DM risk remains uncertain. A separate Korean study \[23\] that used data from a single institution consistently found that patients with persistent hypertriglyceridemia had a 1.58-fold higher risk for newly diagnosed DM. However, after adjusting for body mass index, the study found no statistically significant link between changes in triglyceride levels and the risk of DM (hazard ratio [HR], 1.25; 95% CI, 0.86–1.80). In analyses pre-adjusting the triglyceride group (from abnormal triglyceride levels to the normal range), there was no statistically significant correlation with DM risk. Moreover, the normal-abnormal group (those with normal levels in the first examination and abnormal levels in the second examination) showed no correlation with the development of DM. This implies that the development of diabetes due to hypertriglyceridemia may span several years, with insulin resistance emerging a decade or two before the onset of the disease. Nevertheless, it remains to be clarified whether variability in triglyceride levels serves as a predictive factor for heightened DM risk.

Long-term fluctuations in total cholesterol and HDL-C may increase the risk of developing DM. Cholesterol homeostasis is vital for pancreatic β-cells, influencing their survival, proliferation, and functional maturation \[24\]. Therefore, imbalances in cholesterol have been linked to DM. Cholesterol distribution is considered crucial for β-cell function, rather than its total level. However, more research is required to determine whether mitigating these fluctuations can effectively lower the incidence of DM.

### Lipid variability in DM and health outcomes

**Overall mortality and risk of CVD**

Research has consistently reported that lipid variability is associated with mortality and CVD risk since the Framingham Heart Study \[25\]. However, studies specifically targeting patients with DM are scarce. A recent study from Taiwan \[26\] identified LDL-C variability as a risk factor for CVD in patients with type 2 DM, but found no significant correlations with HDL-C or triglyceride variability. A relatively recent study conducted in Hong Kong \[27\] found that among type 2 patients with DM who did not have CVD, variability in LDL-C, the total cholesterol to HDL-C ratio, and triglycerides increased the risk and mortality rate of CVD by 1.27 times (95% CI, 1.20–1.34), 1.31 times (95% CI, 1.25–1.38), and 1.09 times (95% CI, 1.04–1.15), respectively. Another study by Wang et al. \[28\] discovered that variability in total cholesterol excluding triglycerides increased the risk of all-cause mortality and CVD mortality. With every 10% rise in variability in HDL-C, LDL-C, and total cholesterol, the risk of all-cause mortality increased by 1.30-fold (95% CI, 1.22–1.37), 1.05-fold (95% CI, 1.01–1.09), and 1.10-fold (95% CI, 1.03–1.16), respectively. Correspondingly, the risk of CVD mortality increased by 1.27-fold (95% CI, 1.16–1.39), 1.08-fold (95% CI, 1.02–1.15), and 1.16-fold (95% CI, 1.07–1.27), respectively. In the study based on the ACCORD (Action to Control Cardiovascular Risk in Diabetes)-Lipid trial in China \[29\], LDL-C variability was a strong predictor of both all-cause mortality and CVD mortality, showing a 1.22-fold increase (95% CI, 1.13–1.32). The study also analyzed the risk of non-CVD mortality, revealing that for every 10% increase in HDL-C variability, the risk of mortality from causes other than CVD increased by 31%. The most recent study based on the ACCORD-Lipid trial \[30\] revealed that variability in LDL-C within the highest quartile (Q4) was associated with a 1.61-fold increase in the risk of all-cause mortality and a 1.78-fold increase in the risk of CVD mortality compared to the lower quartiles (Q1–Q3). Notably, stratified analyses by quartiles of the variabilities and means in LDL-C, HDL-C, and triglyceride showed that higher variability in the lipid profile in the target range was a risk factor for CVD mortality. These study findings suggest that managing not only the absolute values of dyslipidemia-related parameters, but also their variability, is crucial in patients with DM.

Variability in lipid levels has the potential to harm the endothelium, and fluctuations in lipid efflux can compromise plaque stability, consequently elevating the risk of plaque rupture \[31\]. In turn, this leads to the release of atherogenic substances and therefore an increased mortality risk \[32\].

**Atrial fibrillation**

Although dyslipidemia is widely acknowledged as a significant risk factor for CVD, as mentioned previously, such recognition has not been equally established for atrial fibrillation (AF). Dyslipidemia appears to be associated with a lower prevalence of AF, commonly referred to as the “cholesterol paradox” in AF \[33\].
In contrast to the consistent research on lipid variability and CVD risk, conflicting results have been reported regarding the association between lipid variability and AF. A comprehensive Korean study involving 3,660,385 adults [34] observed that a lower incidence of AF was correlated with elevated levels of total cholesterol, LDL-C, HDL-C, and triglycerides, with approximately 22%, 19%, 6%, and 12% reductions in risk, respectively. High lipid variability was associated with a higher risk for AF. The highest variability (Q4) in total cholesterol was correlated with a 1.09-fold increase in AF risk (95% CI, 1.06–1.13), a 1.12-fold increase (95% CI, 1.08–1.16) in LDL-C variability, a 1.08-fold increase (95% CI, 1.04–1.12) in HDL-C, and a 1.05-fold increase (95% CI, 1.01–1.08) in triglycerides. In another study conducted in Hong Kong [35], which involved 23,329 patients with DM (mean glycated A1c, 8.6%), it was observed that high levels of LDL-C were associated with an approximately 21% reduction in the risk of AF (95% CI, 0.73–0.85). Similarly, high levels of HDL-C demonstrated about a 33% risk reduction (95% CI, 0.57–0.78), and high total cholesterol levels decreased the risk of AF by 13% (95% CI, 0.82–0.93). Conversely, a high total cholesterol level was correlated with an approximately 1.04-fold higher risk of developing AF (95% CI, 1.01–1.07). However, high lipid variability based on the coefficient of variation in LDL-C, HDL-C, and total cholesterol was a significant risk factor for AF. In the coefficient variation, approximately 1.02 times increased risk per increment were shown in LDL-C (95% CI, 1.01–1.02), HDL-C (95% CI, 1.02–1.03), and total cholesterol (95% CI, 1.01–1.02). In contrast, variability in triglyceride levels was not found to be associated with AF, with a corresponding risk reduction of approximately 12% (95% CI, 0.85–0.92).

Cholesterol levels and their fluctuations could be associated with the development of AF through various mechanisms. Cholesterol serves as a component of cell membranes that modulates alterations in membrane properties, impacting membrane permeability and proteins such as ion channels, pumps, and receptors. These alterations may disrupt the electrical balance and resting state of cell membranes, increasing the likelihood of arrhythmia development [36]. Inflammation is also linked to the onset and persistence of AF. Lipid variability contributes to oxidative stress and chronic inflammation. Higher levels of LDL-C and low levels of HDL-C are correlated with an increased state of inflammation [37,38].

Kidney disease
End-stage kidney disease is one of the major complications of DM and is closely linked to increased mortality rates. Variability in blood pressure and blood glucose levels are recognized risk factors for albuminuria and a reduced glomerular filtration rate [39–41]. However, there is limited research on the relationship between lipid variability and diabetic kidney disease. In a small-scale study conducted in Taiwan involving patients with type 2 DM [42], variability in HDL-C was the only lipid-related factor that was identified as a risk factor for diabetic kidney disease. An Italian study [43] found that variability in LDL-C and HDL-C in patients with type 2 DM was associated with a decrease in the glomerular filtration rate. A recent small-scale study in Japan [44] examined the risk of microalbuminuria and diabetic kidney disease in relation to postprandial triglyceride variability. The study found that the group with high postprandial triglyceride variability had a 49% increased risk of developing microalbuminuria. In a large-scale study conducted in Hong Kong [45], researchers analyzed the prognostic significance of variability in LDL-C, the total cholesterol to HDL-C ratio, and triglyceride levels for kidney disease over a median follow-up period of 66.5 months. The study found that for every 1 mmol/L increase in LDL-C variability, the incidence rate of kidney disease showed a 1.20-fold rise increase (95% CI, 1.05–1.25), and the occurrence of end-stage kidney disease increased by 2.08-fold (95% CI, 1.74–2.5). The association between variability in the total cholesterol to HDL-C ratio and kidney disease was similar to that of LDL-C variability. However, no significant correlation was found between triglyceride variability and kidney disease.

The relationship between lipid variability and kidney disease in patients with DM is predominantly attributed to fluctuations in LDL-C levels. This is due to the same pathophysiological factors that contribute to ASCVD, including disorders in lipid metabolism (specifically cholesterol and chylomicron metabolism), oxidative stress, and inflammation, all of which adversely affect the glomeruli [46]. Therefore, it may be necessary to minimize lipid variability to prevent the onset of kidney disease in patients with DM.

Cognitive dysfunction and dementia
The brain contains abundant lipids, particularly glycerophospholipids, sphingolipids, and cholesterol. Research has shown that levels of lipid oxidation products are elevated in tissues from aged mice [47]. Several studies have demonstrated that variability in the lipid profile was a risk factor for cognitive dysfunction. A cross-sectional study from PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) [48] revealed that greater variability in LDL-C levels was associated with reduced cognitive function in older individuals at a high risk of vascular disease. Lee et al. [49] found that increased variability in total cholesterol levels was associated with a higher risk of developing all-cause dementia, Alzheimer disease, and vascular dementia in the general population. Another representative Korean study [50] showed that higher variability in total cholesterol was a risk factor of all-cause dementia. Abnormal lipid metabolism is a common characteristic shared by both DM and dementia. Dyslipidemia promotes amyloid-β (the main component of senile plaques and one of the histopathological markers) pathology and induces oxidative stress with mitochondrial dysfunction [51]. However, there are limited studies reporting an independent association between lipid variability and the development of cognitive dysfunction or dementia in individuals with DM. In a recent study from Hong Kong [52] including 273,876 patients with type 2 DM, lipid levels were not a significant risk factor for dementia.

Management of lipid variability

Many studies have attributed lipid variability to the use of statins. Patient nonadherence to medication is often identified as a cause of this variability, with LDL-C variability even suggested as a specific test for evaluating adherence [53]. Other elements, such as lipid variability resulting from weight changes [54], chronic kidney disease, or genetic factors, may also be linked to lipid variability and contribute to the differing responses to treatment [55].

The impact of statin therapy and dosage on lipid variability remains unclear. In the TNT (Treating to New Targets) trial [38], administering a high dose of atorvastatin (80 mg/day) significantly decreased LDL-C variability compared to a low dose of atorvastatin (10 mg/day). Intermittent statin dosing has been proposed as a way to save costs or manage statin intolerance. However, for statins with a short half-life, this approach could increase lipid variability and potentially introduce risks [56]. Research is currently being conducted on the use of long-acting proprotein convertase subtilisin kexin-9 inhibitors as a means to reduce lipid variability, but further evidence is needed to assess potential risks [57]. Therefore, maintaining stable lifestyle habits through consistent treatment, dietary modifications, and regular exercise is important.

It is imperative to underscore the significance of regular lipid profile monitoring in clinical practice, ensuring that patients prescribed statins undergo routine assessments to track lipid levels, and tailoring treatment strategies for optimal cardiovascular risk management.

CONCLUSIONS

Lipid variability in patients with DM has been shown to increase the risk of ASCVD and mortality, similar to its impact in individuals without DM. Lipid variability also has an impact on diabetic kidney disease, although the magnitude of this effect may vary depending on certain lipid parameters. The management of dyslipidemia in patients with DM should focus on both keeping LDL-C levels below the target and minimizing variability.

ARTICLE INFORMATION

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