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More Than Diabetic Dyslipidaemia: The Dynamic Relationship between Glucose and Lipid Metabolism

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Abstract
Glucose and lipid metabolism are interconnected in various ways. A key clinical manifestation of this interaction is diabetic dyslipidaemia, which is characterized by high triglycerides, low HDL cholesterol levels, and a predominance of small, dense LDL particles. Over the past decade, our understanding of this interaction has expanded, revealing its complexity. Not only can hypertriglyceridemia and low HDL-C result from disrupted glucose metabolism, but they can also contribute to it. Additionally, it has been established that statins are linked to a modest but significant increase in the risk of developing new-onset diabetes. The exact mechanisms are not entirely understood, but genetic data suggest that lower activity of HMG CoA-reductase, the enzyme targeted by statins, is associated with obesity, higher glucose levels, and diabetes. Interestingly, this increased risk of type 2 diabetes from statin use is not observed in individuals with familial hypercholesterolemia. Moreover, these patients appear to have a lower risk of type 2 diabetes, with higher LDL cholesterol levels correlating with a reduced risk. The potential relationship between lipoprotein and diabetes remains uncertain.
Keyword: Glucose, Lipid metabolism, Diabetic dyslipidaemia, Statins, Hypercholesterolemia

INTRODUCTION

Type 2 diabetes is often accompanied by dyslipidaemia, which involves increased triglycerides, lower HDL-C (High density lipoprotein-C), and a higher prevalence of small, dense LDL (Low density lipoprotein) particles[1]. While not all diabetic patients exhibit every symptom, 60% to 70% experience some form of lipid abnormality. This dyslipidaemia is a significant (and possibly the most crucial) connection

between diabetes and cardiovascular disease. These characteristic lipid alterations are observed not only in individuals with diagnosed diabetes but also in those with metabolic syndrome, suggesting a link to insulin resistance rather than just high blood sugar levels[2]. Additionally, it's recognized that while good glucose management can improve dyslipidaemia, it doesn't completely resolve it. Dyslipidaemia is driven by inflammatory processes and an excess of energy-rich substances in the body, which leads to an overproduction of lipoproteins in the liver and intestines, resulting in hypertriglyceridemia[3,4]. High levels of triglyceride-rich lipoproteins cause the body to break down HDL faster, resulting in lower HDL-C levels, and cause LDL to shift to a more athero-genic small dense form[5,6]. While hypertriglyceridemia and low HDL-C are often the main concerns, reducing low-density lipoprotein cholesterol (LDL-C) provides the greatest benefit to patients. Numerous studies have demonstrated that lowering LDL-C with statins reduces the risk for diabetic patients as effectively as for non-diabetic patients[7]. Hence, The main approach is to reach the target LDL-C level[8]. For diabetic patients who have additional cardiovascular risk factors or atherosclerotic disease, the target is less than 70 mg/dL (1.8 mmol/L). For all other diabetic patients, the target is less than 100 mg/dL (2.3 mmol/L). If statins alone do not achieve these targets, combination therapy with ezetimibe is recommended[9]. Recent findings from the IMPROVE-IT trial suggest that diabetic patients could gain significant advantages from combining statins with ezetimibe. However, the effectiveness of additional treatments like fibrates or omega-3 fatty acids for managing the commonly observed hypertriglyceridemia in these patients remains controversial[10]. Despite the negative results from large outcome trials, these studies were compromised by methodological issues[11-13].

Modifications in lipid profiles contributing to Type 2 diabetes

Recent observations have identified that alterations in lipid levels could both result from and contribute to disruptions in glucose metabolism. Notably, high triglyceride levels and low HDL-C are significant factors. Increased triglycerides can raise free fatty acid levels, potentially causing insulin resistance and β-cell dysfunction[14,15]. It appears that high levels of free fatty acids interfere with or alter the pathway connecting insulin receptors to glucose transporters, which negatively affects the normal function of β-cells[16]. Additionally, free fatty acids play a crucial role in modulating inflammation. Consequently, elevated triglyceride levels may trigger subclinical inflammation, which can then contribute to insulin resistance and β-cell dysfunction.

This relationship is clinically significant as it explains why managing hyperglycemia is more challenging in patients with hypertriglyceridemia compared to those with normal triglyceride levels. It also accounts for why patients typically need less intensive anti-diabetic therapy once their hypertriglyceridemia is under control. It was recently demonstrated that HDL can also have a direct impact on glucose metabolism[17].

A study on the cholesterylester transfer protein inhibitor torcetrapib found that increased HDL-C levels were linked to a reduction in hyperglycemia[18]. It was also shown that administering recombinant HDL can enhance glucose metabolism in patients with type 2 diabetes[19].

Relationship between statins and newly diagnosed diabetes

In the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study, it was initially noticed that patients on high-dose rosuvastatin had a greater likelihood of developing type 2 diabetes compared to those on a placebo[20]. This differed from earlier research, such as the West of Scotland Coronary Prevention Study, which found no effect or even a protective effect[21]. After the WOSCOP study, several smaller trials attempted to clarify the impact of statins on insulin resistance and insulin secretion, but they did not yield definitive results[22].

Following the JUPITER trial, multiple data sets were reviewed, revealing an elevated risk of developing diabetes with statin use. This increased risk was also observed in the Women's Health Initiative, with an odds ratio of 1.7[23]. A Finnish observational study involving nearly 8,500 non-diabetic men also found an odds ratio of 1.24[24]. One meta-analysis examined whether achieving specific LDL-C levels correlates with a higher risk of developing type 2 diabetes. The study found that the odds ratio (OR) for diabetes is 1.33 for individuals with LDL-C levels below 70 mg/dL (<1.8 mmol/L), whereas the OR is 1.16 for those with LDL-C levels between 70 and 100 mg/dL (1.8 to 2.3 mmol/L). There is no increased risk for those with LDL-C levels exceeding 100 mg/dL (2.3 mmol/L) [25].

While all statins can raise the risk of type 2 diabetes, atorvastatin and rosuvastatin might present a higher risk compared to pravastatin and lovastatin. This variation in risk is likely due to differences in their effectiveness, their fat- or water-loving properties, and their target organs. Typically, the risk increases with higher statin doses[26]. Additionally, research has demonstrated

that during statin therapy, people with metabolic syndrome are most at risk of acquiring diabetes. However, there is no proof that statins have a direct effect on how glucose is metabolized. Very intriguing genetic data show that mutations impair HMG-CoA-reductase activity are linked to increased body weight, higher plasma glucose concentrations, and a higher chance of developing diabetes in addition to decreased LDL-C and cardiovascular risk. It's interesting to note that statin medication also contributes to a small but noteworthy rise in body weight (0.24 kg) [27]. It is conceivable that altering HMG-CoA reductase activity influences glucose metabolism because statins block this enzyme. The observation, however, may possibly be related to a more widespread phenomena, which is the modulation of glucose metabolism by lipid content in specific intracellular compartments. This can lead to a decreased insulin impact in the muscle and liver, but it can also cause dysregulation of insulin secretion in the pancreatic β-cells. It's interesting to note that proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies and ezetimibe (at least when used with statins) do not appear to affect glucose metabolism[28].

This suggests that regulating HMG-CoA-reductase activity is the main cause of the elevated risk. Since the majority of cases had a significant benefit from statin-induced LDL-C lowering over new-onset diabetes risk, the clinical significance of the reported elevated risk for new-onset diabetes with statin medication is unclear. In primary and secondary preventive settings, statin medication also lowers overall mortality. That being said, it could be wise to routinely check glucose levels in individuals with metabolic syndrome who are taking larger dosages of statins[29].

Familial-Hypercholesterolemia and Type-2-diabetes

Patients with familial hypercholesterolemia have been back in the spotlight for lipid-ology in recent years[30]. Mutations affecting the LDL-receptor gene, the gene producing apolipoprotein B, the protein that binds to the LDL-receptor, or the gene encoding PCSK9, a regulator of LDL-receptor recycling, can all result in familial hypercholesterolemia[31]. Through the LDL receptor, all mutations cause a reduction in the catabolism of LDL particles. Elevated LDL-C levels are closely correlated with impaired LDL catabolism. Cardiovascular disease is causally associated with increased cholesterol levels. Furthermore, the presence of high plasma lipoprotein concentrations may cause lipids to accumulate in several other organs, leading to the development of xanthomas and arcus lipoides[9]. Therefore, elevated LDL-C plasma concentration, early cardiovascular disease, skin manifestation, and typically a significant

positive family history for hypercholesterolemia and atherosclerotic disease are the characteristics of patients with familial hypercholesterolemia. Those with the condition have a 10–20 fold increased risk of cardiovascular events compared to those without it[3,6]. Numerous studies have demonstrated that statins combined with LDL-C lowering treatment can significantly improve these patients prognosis[32,33]. Because of this, it is advised that statin therapy be started as early as possible in life (during infancy or young adulthood), with some variance based on the LDL-C level, family history, and the existence of additional risk factors[30,31]. It is especially important to assess the relationship between glucose metabolism and familial hypercholesterolemia and its treatment, given the elevated risk of new-onset diabetes connected to statin therapy. Research indicates that people with familial hypercholesterolemia experience a nearly 40% decrease in relative risk (with type 2 diabetes frequency of 2.93% in unaffected relatives and 1.75% in those with familial hypercholesterolemia). Once potential confounders including age, body mass index, statin use, etc. were taken into account, the relative risk dropped even further (OR, 0.49). Additionally, it appeared that this relationship was dosage dependent because individuals with apoB mutations, which often result in lower LDL-C concentrations, were at intermediate risk of developing diabetes, while patients with LDL receptor mutations had the lowest diabetes prevalence. LDL receptor deficient carriers had a higher risk than LDL receptor negative carriers, who had the greatest concentration of LDL-C. These findings support earlier, more limited research[34].

This begs the question once more of what mechanisms underlie this discovery. Certain intracellular compartments may have lower cholesterol concentrations due to familial hypercholesterolemia's impaired uptake of LDL via the LDL-receptor. HMG-CoA-reductase activity may also rise concurrently[35]. These two occurrences are not what is seen when taking statins. This suggests once more that glucose metabolism is directly correlated with either the intracellular lipid concentration or the regulation of HMG-CoA-reductase. It is clearly important to assess if people who use statins for the majority of their lives also exhibit alterations in glucose metabolism, given the elevated risk for diabetes with new onset that is linked to this medication. Recent research show that long-term statin medication is not linked to an increased risk of developing diabetes in people with familial hypercholesterolemia[36].

In a study, over a ten-year period, researchers tracked children with familial hypercholesterolemia and their unaffected siblings and found no difference in the incidence of new onset diabetes[37]. Similarly a study presented 10-year data in adult patients with familial hypercholesterolemia and once more found that statin therapy did not raise the risk of diabetes. However, it is unclear from the data available whether statin medication increases the risk of diabetes in patients with familial hypercholesterolemia from subnormal levels to normal levels or if the risk stays decreased[38]. In conclusion, these findings show that patients with family hypercholesterolemia are less likely to develop diabetes mellitus and that statin medication does not raise the risk of developing diabetes in patients with familial hypercholesterolemia. This is in contrast to non-familial hypercholesterolemia populations, where statin medication is dose-dependently linked to new onset diabetes. These results have significant therapeutic implications because there was previously some debate regarding the long-term use of statins in the treatment of individuals with familial hypercholesterolemia, particularly children. These findings, however, suggest that this kind of treatment does not raise the risk of type 2 diabetes.

Lipo-protein and Glucose-Metabolism

It's still up for debate whether lipoprotein concentrations or metabolism are linked to problems with glucose metabolism or the onset of type 2 diabetes. According to certain research, the incidence of type 2 diabetes and lipoprotein concentrations are negatively correlated[39]. Some exhibit a substantial positive correlation[40], whereas others show no correlation[41]. The fact that increased lipoprotein concentration is only weakly linked with other lipid abnormalities further complicates the association between raised lipoprotein and glucose metabolism. As a result, the concentration of lipoprotein has an inverse relationship with triglyceride levels and a positive correlation with apoB100 levels and non-HDL-C concentration[42]. Therefore, it's possible that the relationships shown in certain studies are a reflection of indirect factors rather than a direct relationship between lipoprotein concentrations and glucose metabolism.

CONCLUSION

Lipids and glucose play significant roles in the metabolism of energy. Therefore, it is not unexpected that there is a close relationship between lipid metabolism and glucose metabolism. There are significant clinical ramifications to this. As a result, typical dyslipidemia, which is

strongly associated with cardiovascular disease in these patients, is a characteristic of diabetic patients. Nevertheless, low HDL-C and hypertriglyceridemia can also cause problems with glucose metabolism, which means that they could both cause and be the cause of hyperglycemia. Remarkably, statin medication raises the incidence of diabetes mellitus by a tiny but significant amount; yet, in nearly all clinical scenarios, the benefits of statin therapy exceed the risks. Lastly, depending on the degree of the LDL elevation, persons with familial hypercholesterolemia have a lower risk of developing type 2 diabetes (the higher the LDL-C the lower the risk). Comprehending the fundamental pathophysiology is crucial for improving therapeutic management and devising innovative approaches to combat diabetes and dyslipidemia.

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Conflicts of interests

There are no conflicts of interest.

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