Decline in Low-Density Lipoprotein Cholesterol by Pharmacotherapy and the Risk of New-Onset Diabetes

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Abstract

There is evidence that lipid lowering therapy due to statins, niacin and PCSK9 inhibitors on long term use can predispose new onset incident diabetes. A recent meta-analysis demonstrated that statin therapy was associated with a risk of diabetes which needs further attention. The study revealed that relative reduction in low-density lipoprotein cholesterol (LDL-C) was a good indicator of the risk of new-onset diabetes. This meta-analysis included 14 clinical trials of which 8 trials with target LDL-C levels ≤ 100 mg/dL (2.6 mmol/L) or LDL-C reductions of at least 30% were extracted separately. The overall risk of incident diabetes increased by 11% and the group with intensive LDL-C reduction statin had an 18% increase in the likelihood of developing diabetes. The risks of incident diabetes were 13% and 29% in the subgroups with 30 - 40% and 40 - 50% reductions in LDL-C, respectively. These findings showed that LDL-C decrease may provide a dynamic risk assessment parameter for new-onset diabetes. It is possible that LDL-C lowering may be positively related to the risk of new-onset diabetes. It is important that blood glucose monitoring should be done, if there is 30% decline in LDL cholesterol during lipid lowering therapy, to detect incident diabetes in these populations. However, all statins do not have same effects; rosuvastatin and atorvastatin administration is more commonly and pitavastatin least commonly associated with diabetes. The new antibody PCSK9 inhibitor can also cause impaired glucose intolerance on long term administration without any weight gain which is common with statin therapy. Interestingly, dietary measures and physical activity used for lowering cholesterol also decreases diabetes which poses the possibility that these methods are not used properly when drugs are administered for reducing blood cholesterol as it may be due to decreased insulin sensitivity.

Keywords: LDL Cholesterol; Beta Cell Dysfunction; PCSK9 Inhibitors; Incident Diabetes

Introduction

There is robust evidence that reduction in serum cholesterol decreases risk of cardiovascular diseases (CVDs) in primary and secondary prevention trials [1-3]. All the statins available for general cholesterol lowering therapy are well known for their potency and efficacy but there are several adverse effects when statins are administered in high doses and in combinations. (Figure 1). Due to several pleiotropic effects for treatment of CVDs, statins continue to be most important in the prevention of CAD [1-3]. The US Preventive Services Task Force (USPSTF) for primary prevention of coronary artery disease (CAD) emphasized on use of low and moderate doses of statins in adults without giving much consideration to earlier views on statin therapy for primary prevention [4]. A new study compared the recommended eligibility for primary prevention statin therapy based on the US Preventive Services Task Force recommendations vs the ACC/AHA guidelines for prevention of CAD [4,5]. Approximately 9.3 million fewer Americans would be recommended statins for primary-prevention, if physicians followed 2016 recommendations based largely on LDL targets rather than competing 2013 guidelines based more on risk [9].

In the National Health and Nutrition Examination Survey (NHANES), involving 3416 subjects, the authors estimate that 15.8% of US adults aged 40 to 75 years without prior CVD would be started on statins if the 2016 US Preventive Services Task Force (USPSTF) guidelines were fully implemented vs 24.3% if the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines were followed [4,5]. This number is in addition to 21.5% of adults already taking lipid-lowering agents which translates into an estimated 17.1 million vs 26.4 million Americans, respectively, with a new recommendation for statins. Recently, proprotein convertase subtilisin nexin 9 (PCSK9) inhibitors have been used to decrease serum cholesterol by influencing lipoprotein metabolism which may also have adverse effects on muscle dysfunction and future cardiometabolic risk, similar to statins [6-8]. It is possible that cholesterol lowering by various agents; statins and PCSK9 inhibitors, would be increased in near future which may result in to further increase in the incidence of new onset diabetes [3-8]. This review aims to highlight available evidence on cholesterol lowering and risk of new onset diabetes.

**Figure 1:** Types of statins used for reducing blood and cell membrane cholesterol.

Statins administration and new onset diabetes

A recent meta-analysis demonstrated that statin therapy was associated with a risk of diabetes [9]. The study revealed that relative reduction in low-density lipoprotein cholesterol (LDL-C) was a good indicator of the risk of new-onset diabetes. This meta-analysis included 14 clinical trials of which 8 trials with target LDL-C levels ≤ 100 mg/dL (2.6 mmol/L) or LDL-C reductions of at least 30% were extracted separately. The overall risk of incident diabetes increased by 11% (OR = 1.11; 95% CI 1.03 - 1.20).

The group with intensive LDL-C reduction statin had an 18% increase in the likelihood of developing diabetes (OR = 1.18; 95% CI, 1.10-1.28). The risks of incident diabetes were 13% and 29% in the subgroups with 30 - 40% and 40 - 50% reductions in LDL-C, respectively [9]. These findings showed that LDL-C decrease may provide a dynamic risk assessment parameter for new-onset diabetes. It is possible that LDL-C lowering may be positively related to the risk of new-onset diabetes. Blood glucose monitoring is indicated if there is 30% decline in LDL cholesterol during lipid lowering therapy, to detect incident diabetes in these populations. The effect of statin therapy on lipid peroxidation and activities of antioxidants enzymes in patients with dyslipidemia revealed a significant decline in the markers of oxidative stress and an increase in antioxidant enzymes which are protective against CVDs and diabetes [10].

Decline in Low-Density Lipoprotein Cholesterol by Pharmacotherapy and the Risk of New-Onset Diabetes

After approval of statins by the Food and Drug Administration (FDA), several large randomized trials were conducted to find out the beneficial and adverse effects of statins on CVDs. Several trials with statins have reported that these agents have powerful cardio protective effects in the general population [11-15]. In many of these trials, there was a significant reduction in CVDs, with intensive low-density lipoprotein cholesterol (LDL-C)-lowering therapy [11-13]. Therefore, in patients with a high risk of cardiovascular disease, The European Guidelines on prevention of CVDs in clinical practice recommend an LDL-C goal of < 100 mg/dL (2.6 mmol/L) or a ≥ 30% reduction in LDL-C in patients with high risk of CVDs [16]. In a further study using rosuvastatin, it has been reported that some participants using this agent developed diabetes [17]. Hence a meta-analysis was conducted comprising of 13 trials, involving 91,140 individuals which revealed that statin therapy was associated with a 9% increased risk of new-onset type 2 diabetes mellitus (T2DM) over a 4-year period compared with that of patients randomized to the placebo or standard care groups [18]. However, no consistent relationship was reported between standard LDL-C lowering with statin therapy [trials with a target LDL-c level > 100 mg/dL (2.6 mmol/L) or relative LDL-C reduction < 30%] and incident diabetes compared with that of the placebo [19]. Those subjects who receive intensive-dose statin therapy are generally at a high risk of both CVDs and incident diabetes which was confirmed in a meta-analysis of five trials, among those treated with intensive-dose statin therapy compared with the risk of those receiving moderate-dose statin therapy [20].

All the statins do not appear to increase the risk of diabetes. In a randomized controlled trial from Japan, 1,269 individuals with impaired glucose tolerance (IGT) were randomized to either the pitavastatin group (lifestyle modification and pitavastatin [1 - 2 mg/day]) or the control group (lifestyle modification only) [21]. The incidence rates for the onset of diabetes were significantly higher for pitavastatin compared to control groups (n = 163 vs 163 cases per 1,000 person-years, respectively). The hazard ratio for progression from IGT to diabetes in the pitavastatin group was 0.82 (95% CI: 0.68 - 0.99; P = 0.041) but with heterogeneity in hypertension. In any subgroups, pitavastatin did not accelerate the incidence, unlike the effects of statins in previous reports. It is possible that pitavastatin in combination with lifestyle modification was associated with a lower incidence of diabetes than was lifestyle modification alone in Japanese patients with IGT. It is possible that in other controlled trials lifestyle modification was not given due consideration hence it was necessary to consider that all statins increase the risk of developing diabetes.

Out of 14 major randomized controlled trials, 6 showed a positive but non-significant association between statin therapy and incident of diabetes. However, remaining 3 trials (PROSPER \( p = 0.022 \), JUPITER \( p = 0.013 \), and SPARCL \( p = 0.002 \)) reported significant association \( p < 0.05 \) of incident diabetes with statin therapy [9,18]. Interestingly, a positive effect of statins on diabetes mellitus appeared after the sixth study, and significance observed after the eleventh study. Although all the statins reported substantial reduction in LDL-C, rosuvastatin was recorded as the highest percentage reduction over 12 months of treatment. However, a proved association of rosuvastatin with incidental diabetes and poor effects on case fatality after myocardial infarction, demands a reconsideration of this statin for use with cardioprotective purpose [9,17].

**Pcsk9 inhibitors and new onset diabetes**

It is noteworthy that increase in blood cholesterol is the indirect result of decline in LDL receptor activity which should be ideally treated by agents such as PCSK9 inhibitors, that increase the LDL receptor function. However, recent studies indicate that cholesterol lowering by PCSK9 inhibitors also causes increased risk of incident diabetes, which may be because cause of LDLR dysfunction remains untreated [7]. A more recent study used genetic scores consisting of independently inherited variants in the genes encoding PCSK9 and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR; the target of statins) as markers among 112,772 participants from 14 studies, with 14,120 cardiovascular events and 10,635 cases of diabetes [8]. The findings revealed that variants in both the markers; were associated with nearly similar protective effects on the risk of CVDs according to decline of 10 mg per deciliter (0.26 mmol per liter) in the LDL cholesterol level: odds ratio for cardiovascular events, 0.81 (95% confidence interval [CI], 0.74 to 0.89) for PCSK9 and 0.81 (95% CI, 0.72 to 0.90) for HMGCR [8]. The risk of diabetes was identical for variants in these two genes. The odds ratio for each 10 mg per deciliter

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Decline in Low-Density Lipoprotein Cholesterol by Pharmacotherapy and the Risk of New-Onset Diabetes

decrease in LDL cholesterol, 1.11 (95% CI, 1.04 to 1.19) for PCSK9 and 1.13 (95% CI, 1.06 to 1.20) for HMGCR were significant. The increased risk of diabetes was confined to persons with impaired fasting glucose levels and if present together, PCSK9 and HMGCR variants had additive effects on the risk of both CVDs and diabetes. Thus, variants in PCSK9 may have the same effect as variants in HMGCR on the risk of CVDs and diabetes per unit decrease in the LDL cholesterol level and effects of these variants were independent and additive [8].

Mechanisms

The exact mechanisms, how statins and PCSK-9 inhibitors increase the risk of diabetes are not clear [23-26]. Most statins are now used with the understanding that a slightly increased risk of diabetes is outweighed by cardiovascular benefits of the drugs. In a genetic study comprising of 223 463 subjects from 43 genetic studies, risk of diabetes in relation to HMGCR was examined [22]. Each additional rs17238484-G allele was associated with a mean 0.06 mmol/L (95% CI 0.05 - 0.07) lower LDL cholesterol and higher body weight (0.30 kg, 0.18 - 0.43), waist circumference (0.32 cm, 0.16 - 0.47), plasma insulin concentration (1.62%, 0.53 - 2.72), and plasma glucose concentration (0.23%, 0.02 - 0.44). The rs17238484-G allele seemed to be associated with higher risk of type 2 diabetes. In controlled trials among 129 170 subjects, statins lowered LDL-C by 0.92 mmol/L at 1-year of follow-up, increased bodyweight by 0.24 kg in all trials; 0.33 kg, in placebo or standard care controlled trials and -0.15 kg, in intensive-dose vs moderate-dose trials, at a mean of 4.2 years of follow-up, and increased the odds of new-onset type 2 diabetes (OR 1.12, 95% CI 1.06 - 1.18 in all trials; 1.11, 95% CI 1.03 - 1.20 in placebo or standard care controlled trials and 1.12, 95% CI 1.04 - 1.22 in intensive-dose vs moderate dose trials). The rs12916 SNP had similar effects on LDL cholesterol, bodyweight, and waist circumference. The increased risk of type 2 diabetes noted with statins is at least partially explained by HMGCR inhibition [22]. Singh has proposed that the decline in cholesterol may cause decline in cell membrane cholesterol from neurons, causing damage to POMC neurons and arcuate nucleus, resulting in to reduction in IGF 1 and IGF 2, leading to insulin resistance and diabetes. Therefore, some experts believe that diabetes mellitus is a disease of the brain.

Figure 3: Mechanism of action of statin and increase in diabetes.
In vitro experiments have demonstrated that atorvastatin, but not pravastatin have impaired glucose handling, which indicates a variation in clinical effects observed with different statins [25,26]. These studies indicate that alteration in glucose uptake by decreased glucose transporter type 4 expression or translocation might be the mechanism for decreased glucose handling. Statin can interfere with intracellular insulin signal transduction pathways via inhibition of necessary phosphorylation events and reduction of small GTPase action. In a clinical trial, plasma glucose and insulin concentrations were measured during an oral glucose tolerance test among 10 intervention and 9 control subjects [24]. Simvastatin-treated patients showed an impaired glucose tolerance and displayed a decreased insulin sensitivity index. There was a decline in Co Q10 content (p = 0.05), whereas mitochondrial content was similar between the groups. Mitochondrial OXPHOS capacity was comparable between groups when complex I- and complex II-linked substrates were used alone, but when complex I + II-linked substrates were used, there was a decreased (p < 0.01) capacity in the patients compared with the control subjects. It is possible that simvastatin-treated patients were glucose intolerant. A decreased CoQ10 content was accompanied by a decreased maximal OXPHOS capacity in the simvastatin-treated patients. It is plausible that this finding partly explains the muscle pain and exercise intolerance that many patients experience with their statin treatment [24].

There is some evidence that statin therapy may cause leptin deficiency which is a hormone, released from the adipocytes [26-28]. Inhibition of adipocyte differentiation leads to decreased peroxisome proliferator activated receptor gamma and CCAAT/enhancer-binding protein which are important pathways for glucose homeostasis. It is proposed that deficiency of leptin may cause increase in ghrelin (more appetite and weight gain) and cortisol, which may damage beta cells of pancreas as well as circadian system, resulting in to circadian dysfunction in metabolism and insulin resistance, leading to diabetes. decreased leptin causing inhibition of β-cells proliferation and insulin secretion; and diminished adiponectin levels. Alternative mechanisms could be; inhibition of glucose-induced cytosolic calcium signaling and insulin secretion through blockage of L-type calcium channels [29] as well as impaired insulin release via an indirect mechanism related to chronic cholesterol depletion and statin associated overweight [30] which need substantial future research to explain the role of statin in the pathogenesis of diabetes. It is also possible that a better feeling of safety and improved survival may alter outlook of the patients, leading to change in diet and lifestyle with statin therapy which may promote diabetes [31,32]. Lastly, different methods have been employed for the diagnosis of diabetes by the researchers in the included trials, with variations in diet and lifestyle and cholesterol lowering therapy, which may be confounders [31-34]. Some of the statins can influence insulin release via direct, indirect or combined effects on calcium channels in pancreatic β-cells [23], apart from decrease in translocation of glucose transporter 4 in response to statin therapy which may result in hyperglycemia and hyperinsulinemia [25,26]. Other possible mechanisms implicated in the effect of statins on new-onset diabetes are that statins decrease other important downstream products, such as coenzyme Q10, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and dolichol; their depletion leads to reduced intracellular signaling [34-38]. Elucidation of the mechanisms underlying the development of diabetes in association with statin use may help identify novel preventative or therapeutic approaches to this problem and/or help design a new generation statin without such side-effects [37-42]. However, combining physical activity and prudent diet with drug therapy for reducing blood cholesterol, which is also advised by most agencies, have been reported to cause decline in diabetes in all the dietary trials [43-45].

Mitochondrial dysfunctions causing damage to beta cells have also been suggested to be important in the pathogenesis of diabetes [23,46].
Figure 4: Statin-induced mitochondrial myopathy [46].

Complexes of respiratory chain I, II, III, IV, V; Q-cycle – cycle of CoQ10; Cyt c – cytochrome C; e - electron; NADH – reduced nicotinamide adenine dinucleotide; NAD+ – nicotinamide adenine dinucleotide; FADH2 – flavine adenine dinucleotide reduced; FAD+ – flavine adenine dinucleotide; O2 - superoxide radical; H2O2 – hydrogen peroxide; DNA – deoxyribonucleic acid; O2 – oxygen; H2O – water; ADP – adenosine diphosphate; ATP – adenosine triphosphate; Pi – inorganic phosphate

Figure 5: Intracellular actions of statins [23].
Decline in Low-Density Lipoprotein Cholesterol by Pharmacotherapy and the Risk of New-Onset Diabetes

In brief, cholesterol lowering by statins; in particular atorvastatin and rosuvastatin can cause significant increase in the risk of new onset, incident diabetes. Treatment with PCSK9 inhibitors can also cause impaired glucose tolerance which may result in to diabetes on long term administration. The most appropriate mechanism could be beta cell dysfunction due to reduction in LDL cholesterol causing weakening of the epithelial cell membranes resulting in to adverse effects on insulin sensitivity. If adequate physical activity and prudent diet are also combined with drug therapy for reducing blood cholesterol, diabetes can be easily prevented. However, further studies would be necessary to establish that these agents can predispose diabetes in randomized trials.

Conflict of Interest
Conflict of interest has not been declared by the authors.

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Decline in Low-Density Lipoprotein Cholesterol by Pharmacotherapy and the Risk of New-Onset Diabetes


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