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Review

Statin treatment and new-onset diabetes: A review of proposed mechanisms

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ABSTRACT

New-onset diabetes has been observed in clinical trials and meta-analyses involving statin therapy. To explain this association, three major mechanisms have been proposed and discussed in the literature. First, certain statins affect insulin secretion through direct, indirect or combined effects on calcium channels in pancreatic β-cells. Second, reduced translocation of glucose transporter 4 in response to treatment results in hyperglycemia and hyperinsulinemia. Third, statin therapy decreases other important downstream products, such as coenzyme Q10, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and dolichol; their depletion leads to reduced intracellular signaling. Other possible mechanisms implicated in the effect of statins on new-onset diabetes are: statin interference with intracellular insulin signal transduction pathways via inhibition of necessary phosphorylation events and reduction of small GTPase action; inhibition of adipocyte differentiation leading to decreased peroxisome proliferator activated receptor gamma and CCAAT/enhancer-binding protein which are important pathways for glucose homeostasis; decreased leptin causing inhibition of β-cells proliferation and insulin secretion; and diminished adiponectin levels. Given that the magnitude of the risk of new-onset diabetes following statin use remains to be fully clarified and the well-established beneficial effect of statins in reducing cardiovascular risk, statins remain the

Abbreviations: CVD, cardiovascular disease; HMG-CoA, 3-hydroxy-3-methyl-glutaryl coenzyme-A; LDL-C, low density lipoprotein-cholesterol; Ca^{2+}, calcium; HOMA-β, Homeostatic Model Assessment; GLUT4, glucose transporter; IRS-1, Insulin receptor substrate; IGF, insulin like growth factor; PI3K, phosphatidylinositol 3-kinase; IR, insulin receptor; PPARγ, proliferator activated receptor gamma; C/EBP, CCAAT/enhancer-binding protein; TNF-α, tumor necrosis factor alpha; FPP, farnesyl pyrophosphate; GGPP, geranylgeranyl pyrophosphate; CoQ10, coenzyme Q10; knockout, (KO); QUICKI, Quantitative Insulin-Sensitivity Check Index; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; UCP3, Uncoupling protein 3; miRNA, microRNA; ABCA1, ATP-binding cassette transporter A1.

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first-choice treatment for prevention of CVD. 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.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, causing approximately 17.3 million deaths in 2008 [1]. Hypercholesterolemia is one of the major CVD risk factors, and therefore is a very important therapeutic target [2]. Several clinical trials have justified the role of statins, also known as 3-hydroxy-3-methyl-glutaryl coenzyme-A (HMG-CoA) reductase inhibitors, in primary and secondary CVD prevention [3]. Statins mainly act to decrease low density lipoprotein-cholesterol (LDL-C), yet pleiotropic effects have been identified, such as improvements of endothelial function, stabilization of atherosclerotic plaques, and anti-inflammatory actions [4]. However, as the prescription rates for statins have increased, more adverse effects have been identified, with the most common being increased liver enzymes and myopathy [5]. Recently, there has been much investigation into the potential unforeseen adverse effects of statins, specifically the development of type 2 diabetes mellitus (T2DM).

Trials and meta-analyses have reported conflicting results regarding new-onset diabetes with statins. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, a double-blind randomized study of 17,802 subjects assigned to rosuvastatin 20 mg or placebo, was the first to report an increased incidence of diabetes with statins [6]. However, the West of Scotland Coronary Prevention Study (WOSCOPS) suggested that pravastatin decreased the frequency of diabetes [7]. Moreover, a recent population-based study showed that when compared with pravastatin, patients treated with atorvastatin, simvastatin or rosuvastatin had a 22%, 10% and 18% increased risk of new-onset diabetes, respectively [8]. A meta-analysis combining data from 13 large population trials found a 9% increased risk of diabetes development with statins, resulting in one case of new-onset diabetes for every 255 patients using statins for four years [9]. A more recent meta-analysis reported that the dose and type of statin may affect differently the risk of new-onset diabetes, with pravastatin 40 mg/day associated with the lowest risk at 7%, and rosuvastatin 20 mg/day with the highest risk at 25% [10]. On the other hand, another meta-analysis reported no significant class effect on insulin sensitivity [11]. However, when pravastatin was individually studied a significant improvement in insulin sensitivity was found, whereas the combination of all other included statins (atorvastatin, rosuvastatin, simvastatin) exhibited a detrimental effect [11].

In March 2012, the US Food and Drug Administration (FDA) decided there was sufficient evidence to support the addition of a warning label about diabetes risk to statin packaging [12].

The evidence of new-onset diabetes has brought into question whether this adverse effect is restricted to certain populations with specific risk factors predisposing them to development of diabetes with statins. To investigate possible risk factors, Waters and colleagues pooled data from three large trials with atorvastatin and found that across all three trials fasting glucose higher than 5.6 mmol/L, fasting triglycerides >1.7 mmol/L, body mass index >30 kg/m^2, and history of hypertension were all associated with a higher risk of developing T2DM [13].

Subsequently, a re-analysis of the JUPITER trial aimed to illustrate the balance between benefits and diabetes risk by grouping participants based on presence of risk factors for diabetes including metabolic syndrome, impaired fasting glucose, body mass index ≥30 kg/m^2, and glycated hemoglobin A_1c greater than 6% at entry. When no diabetes risk factors were present, rosuvastatin compared with placebo resulted in a 52% reduction in primary endpoints (first-event myocardial infarction, stroke, admission to hospital with unstable angina, arterial revascularization, or cardiovascular death), while no increase in diabetes occurrence was noted. For individuals with one or more risk factors for diabetes, rosuvastatin resulted in a 28% increase in diabetes occurrence, with a 39% reduction in primary endpoints, showing that even in high-risk participants the benefits outweigh the risk of diabetes development.

Although meta-analyses and reviews of statins have shown that there is an increased risk of new-onset diabetes, statins' ability to decrease major cardiovascular events and mortality outweighs this risk, and no change in clinical practice is currently recommended [14,15]. Molecular mechanisms are often briefly discussed, and currently they remain unclear. However, new-onset diabetes has not been found to be influenced by the ability of statins to decrease cholesterol, pointing toward other mechanisms responsible for diabetes development [10]. The aim of this review is to summarize the proposed mechanisms of new-onset diabetes with statin therapy.

2. Methodology

Medline and Embase were systematically searched to identify the relevant literature, without a start date limit and until December 2013 with the help of a McGill University librarian, Martin Morris. Pubmed and Google scholar were also searched. The search was performed independently by two authors (MB and JR) and confirmed by all authors. Manual searches were also performed to identify further relevant literature. Articles in both English and French were retained and reviewed.

3. Primary Mechanisms of Statins [Fig. 1]

Statins were first approved for clinical use by the FDA in 1987 and remain the drug of choice for their potent LDL-C lowering