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Statin Associated New Onset Diabetes Mellitus – Myth or Reality?

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INTRODUCTION

As type 2 diabetes is accompanied by dyslipidaemia, statins provide a major role in preventing long term complications in diabetes and are also recommended in diabetics with normal LDL as well.

During the Jupiter trial (Justification for the Use of Statins in Primary Prevention Trial) a small but significant link between new-onset diabetes mellitus (NOD) and statin therapy was noted with rosuvastatin users . From thereafter multiple analyses have confirmed this association. Results of recent observational studies strongly correlate NOD with statin use. Due to this the United States Food and Drug Administration released changes to statin safety label in 2012 with a warning that statins can lead to impaired fasting serum glucose levels and increase in glycosylated haemoglobin.

A definitive patho-physiological link between statins and glucose impairment is not there although various mechanisms have been proposed:

1. Calcium channel blockade in beta cells: Insulin secretion from pancreatic cells is initiated by voltage gated calcium channels as intracellular calcium increases. Studies have shown that simvastatin leads to blockage of calcium channels, thereby causing diminished insulin secretion. Pravastatin has also been found to block calcium channels, but the doses required for this effect in higher for pravastatin.
2. Decreased GLUT 4 expression & Decreased levels of coenzyme Q10: One of the co effects of bloackage of the HMG-CoA reductase enzyme by statins is that it also blocks the production of other substances in the cholesterol pathway, like isoprenoids - coenzyme Q10 etc. These byproducts up regulate GLUT4, which mediates peripheral glucose uptake. Treatment with clinical doses of atorvastatin cause decreased GLUT 4 expression resulting in the pathology. Other statins (simvastatin, lovastatin) have shown similar effects on GLUT4 expression. Interestingly, Ganesan and Ito demonstrated that simvastatin-induced insulin resistance was reversed by adding coenzyme Q10. The same in vitro study, on the other hand, demonstrated that pravastatin and ezetimibe (cholesterol blocker) do not reduce GLUT4 expression, suggesting that NOD is not just due to lowering of cholesterol.
3. Diminished cholesterol uptake in pancreatic beta cells: Another proposed mechanism involves the observation that patients with familial hypercholesterolemia (ie, elevated LDL-C) have low rates of DM. As intracellular cholesterol is believed to inhibit cellular function and survival. Statins upregulate LDL receptors to increase cholesterol transport. This activity occurs not only in the liver but other tissues, including the pancreas. So, pancreatic LDL receptor upregulation causes increased intracellular cholesterol levels and potentially toxic effects in β cells.
4. Reduced adiponectin levels: A further proposed mechanism lies in the effect on the adiponectin metabolism. It is a hormone that modulates metabolic processes, including glucose regulation. It down regulates gluconeogenesis and increases glucose uptake; high levels of adiponectin have been associated with decrease in the risk of developing type 2 DM in a prospective study. Simvastatin has been reported to significantly reduce insulin sensitivity by virtue of decreasing adiponectin levels in hypercholesterolemic patients.

CLINICAL BENEFITS VERSUS DM RISK WITH STATINS

CV disease (CVD) is the leading cause of mortality and one of the most important causes of morbidity in the world. Statins have largely been shown in several landmark trials and meta-analyses to be beneficial in secondary prevention of CV events and primary prevention in patients belonging to high risk group.

1. Sattar and colleagues estimated that statin treatment lead to 5.4 fewer deaths from coronary heart disease and cases of nonfatal myocardial infarction per 255 patients after 4 years of therapy, for each 1-mmol/L (39 mg/dL) reduction in LDL cholesterol compared with controls. In contrast, the risk of developing DM was one additional case for every 255 patients treated with statins.
2. In the meta-analysis by Preiss et al. ,6.5 CV events were prevented in the intensive-dose statin group per 1,000 patient-years; this in turn translates into a number needed to treat (NNT) of 155 for CV events and a number needed to harm (NNH) of 498 for new-onset DM. Considering secondary prevention, benefits of statin therapy outweigh DM risk.
3. Another important scenario not fully exploited in low-risk patients is primary prevention in patients with no history of previous CVD, for whom statin therapy is increasingly used for vascular prevention

and in this scenario there has been controversy as to whether the absolute benefit of treatment outweighs the risk of developing DM.

4. Meta-analysis by Taylor et al. found that statins in the primary prevention of CVD cause insignificant reduction in all-cause mortality; this meta-analysis showed that a mortality relative risk reduction (RRR) of 17 % was observed with statin treatment. However, they concluded that there is not enough evidence to recommend the use of statins in the primary prevention of heart disease. The authors of this meta-analysis came to conclusion that the absolute benefits were rather small—1,000 people have to be treated for 1 year to prevent one death. When used among people at low absolute risk the advantage of statin therapy may become insignificant, and a higher NNT is required to gain some benefit. So, it is still uncertain where exactly the point lies beyond which the protective and beneficial CV actions of statins start to outweigh the diabetogenic risk in primary prevention.

Any assessment in role of statins in primary prevention should be made in light of patient CV risk and overall assessment

RATIONALE FOR TAILORED STATIN THERAPY

What is the rationale for individualized statin therapy? Different arguments are in favour of a more balanced tailored statin therapy based on clinical judgments, the patient's cardiovascular and metabolic risk profile, and the dose of statin and its type used.

A. In secondary prevention, the benefits of statin therapy clearly outweigh the risks of DM.

B. In primary prevention of low-risk patients, the benefits of such a strategy is less clear and has to be balanced against the risk of 'overmedicating' the general population.

Ideal study- (Incremental Decrease in Endpoints through Aggressive Lipid Lowering).

This study compared the incidence of new-onset DM to CV risk reduction among 15,056 patients with coronary heart disease or a history of myocardial infarction and non diabetics at baseline.

Significant finding of this analysis was that the increase in risk of DM was largest in patients who were benefitted the most in terms of CV risk reduction with statin therapy.

Pravastatin could be the right match for hyperlipidemic patients having low CV risk. But, despite its lower potential to lower LDL cholesterol, it seems to be the statin having least diabetogenic potential, currently available on the market. Although newer, more powerful, and more advertised statins are widely used, pravastatin could serve as a valuable alternative, especially for patients with a predisposition for DM.

It is crucial to remember that statins cannot account for all new cases of DM diagnosed during hypolipidemic therapy and the hazard of developing new-onset DM is directly connected with already existing DM risk factors.

EVIDENCE FROM CLINICAL TRIALS

Large and Short Randomised Control Trials

1. Jupiter Trial- Justification for Use of Statins in Prevention- An Intervention Trial Evaluating Rosuvastatin: Earlier to this trial there had been reports of impaired glucose tolerance and increased risk of diabetes associated with use of statins, the issue got attention after its publication in 2008, of results of (JUPITER), which was a large, randomized, placebo controlled, primary prevention trial.

   Increased incidence of diabetes in persons taking rosuvastatin was reported in this trial, which included 17,802 men and women (average age 66 years) who were randomized into two groups: rosuvastatin (20 mg/day) or an inactive placebo drug. There was a 26% higher incidence of diabetes in the rosuvastatin group. The results of JUPITER started a wave of discussion regarding potential risks and benefits of statin therapy (Figure 2).

2. Prosper Trial: Investigators reported a 32% higher incidence of DM for those taking pravastatin (40 mg/day) compared with controls in the Prospective Study of Pravastatin in the Elderly at Risk trial.

META ANALYTIC STUDIES - FURTHER EVIDENCE (TABLE 1)

In the background of varying and conflicting results of clinical trials, a few meta-analyses conducted in the past 5-6 years help to resolve the issue.

Have We Underestimated the Dimension of New Onset Diabetes Mellitus with Statin Use

Two of the arguments called to put light upon this evidence can be cited: (i) the single studies were not designed and powered to primarily address DM as an endpoint and maximum follow-up did not exceed 5 years; (ii) the definition of DM varied among the trials, mostly derived from non-standardized criteria and screening of new onset DM was not regularly done. So, we may conclude that we may even have underestimated the dimension of the problem.

POPULATIONS WITH METABOLIC SYNDROME RISK FACTORS MORE PRONE TO NOD WITH STATIN USE

Certain populations, particularly those with various features of metabolic syndrome, may be more prone to developing NOD with statin use risk factors such as:

Positive for hypertension, BMI >30, triglycerides >150 mg/dL, Asian ethnicity, fasting blood glucose >100 mg/dL, women, older adults, those with a family history of DM, extended duration of statin use.

Waters et al analyzed three large statin RCTs and concluded that in each fasting blood glucose, hypertension, BMI, and fasting triglycerides were independent risk factors for developing NOD with statin use. It was further determined that patients with two to four DM risk factors were more prone to developing NOD compared with those with zero to one risk factor.

IMPACT OF DIFFERENT TYPES AND DOSES OF STATIN – IS IT A CLASS EFFECT?

In recent years, the query remains as to whether or not the type of statin and the intensity of dose contribute to the conflicting results observed in RCTs and meta-analyses.

A. Carter and colleagues recently conducted a population-based study, showing in a real-world setting that, compared with pravastatin, there was an increased risk of incident DM with atorvastatin, rosuvastatin and simvastatin .

B. A published meta-analysis of five randomized trials (N = 32,752) found a higher incidence of new-onset DM in 1,449 (8.8 %) of the intensive-therapy group and 1,300 (8.0 %) of the moderate-therapy group. In contrast, incident CV disease occurred in 3,134 (19.1 %) of the intensive-therapy group and 3,550 (21.7 %) of the moderate-therapy group. Therefore, there was a 0.8 % absolute increase in DM cases on high-dose statins and a 2.6 % absolute reduction in adverse CV events.

C. Navarese and colleagues published the largest and most comprehensive meta-analysis so far, by comparing rates of new onset DM among different types and doses of statins. The main findings, derived from a population of 113,394 patients, were as follows:

i. There was a gradient in the risk for new-onset DM with different types and doses of statins

ii. Pravastatin therapy was numerically associated with the lowest OR of new-onset DM compared with placebo; whereas treatment with rosuvastatin was numerically associated with a 25 % increased risk of DM compared with placebo

iii. The cumulative probabilities indicated that high-dose pravastatin had the highest probability of it being the safest treatment in terms of probability of causing new-onset DM, with simvastatin & rosuvastatin performing least well in this ranking

iv. High-dose pravastatin when compared with placebo provided the most robust safety profile compared with the other high-dose statins;

As an additional datum, by meta-regression analysis, the risk for developing DM did not get influenced by the different abilities of statins to reduce cholesterol.

The benefits of statins outweigh the increased risk of DM in people with CVD or at moderate to high risk of CVD. In such patients, a powerful statin like rosuvastatin or atorvastatin should be recommended.

1. Individuals with high CV risk (10-year risk >20 %, according to the Framingham risk score) or existing CVD should receive statin therapy as indicated.
2. Individuals with moderate CV risk (≥2 risk factors, 10-year risk ≤20 %) should also be prescribed a statin.
3. In high-risk subgroups such as following an acute coronary syndrome (ACS) episode, high doses of rosuvastatin or atorvastatin or any other powerful statin are highly recommended.
4. The potentially raised DM risk exceeding benefits should be particularly considered in individuals with low CV risk (0–1 risk factors).
5. Prior to initiation of statin therapy, screening for DM and metabolic syndrome risk factors may help identify patients at high risk of DM requiring closer monitoring. According to the recent evidence, pravastatin can be the statin of choice in such populations.

There is thus far a lack of conclusive evidence in favour of statin administration in low-risk patients for primary prevention.

CLINICALLY USEFUL CONCLUSIONS TO MINIMISE RISK OF NOD

FOLLOWING clinical considerations can be implemented to minimize the risk of statin-associated NOD:

1. Screen patients to determine baseline glycemic values. This is especially important among those with risk factors for DM (eg, BMI >30 kg/m^2, hypertension, elevated triglycerides, fasting glucose 100–125 mg/dL, family history of DM, ethnic group [eg, Asians]). If baseline values are not established and glucose impairment is noted after statin initiation it may be naturally assumed that the elevation is statin related.
2. Avoid changes for patients with existing coronary heart disease and for high-risk primary prevention patients. The proven benefits of statin therapy surely outweigh the risk of glucose impairment in high-risk populations. Close monitoring of glycemic parameters for those on intensive statin therapy is important.
3. Understand that certain less-intensive statins appear to have minimal impact on glycemic indices. Practitioners may consider these for lower-risk patients, those with risk factors for DM, or in individuals with risk factors for NOD. Studies have generally demonstrated that pravastatin, pitavastatin, lovastatin and fluvastatin have neutral to modest effects on glycemic markers; however, practitioners should be mindful of lovastatin due to its known drug interactions. The optimum moderate to maximum daily doses of these "moderate-intensity" statins (fluvastatin 80 mg, pravastatin 40–80 mg, pitavastatin 2–4 mg, lovastatin 40 mg) achieve the 30% to 50% LDL-C reduction suggested by cholesterol guidelines.
4. Consider a nonstatin to achieve additional LDL-C reduction. Although they provide greater efficacy, higher statin doses generally demonstrate higher rates of NOD. As a result, practitioners may want to choose a less-intensive statin in certain patients, but are then faced with the dilemma of a diminished ability to reduce LDL-C. By adding a nonstatin option to the less-intensive statin may

help resolve this issue. Ezetimibe is glucose neutral and it causes modest but significant reductions in CV events when added to a statin. Bile acid resins effectively reduce HbA1c by approximately 0.5%.

5. Proprotein convertase subtilisin kexin type 9 inhibitors are an approved medication class and their role has shown promising results in select high-risk populations, such as those with heterozygous familial hypercholesterolemia, to achieve further LDL-C reduction. Although it is undetermined at this time their future use in the general dyslipidemia population, available data up to this point have not shown an increased risk for NOD.

6. Choose concomitant antihypertensive agents wisely. As a co morbidity hypertension is a commonly associated with dyslipidemia. Older agents, such as β-blockers and also thiazide diuretics, increase NOD by 22% to 43%. On the other hand, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have demonstrated insulin-sensitizing properties and a reduced incidence of NOD, whereas calcium channel blockers are considered glucose neutral.

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