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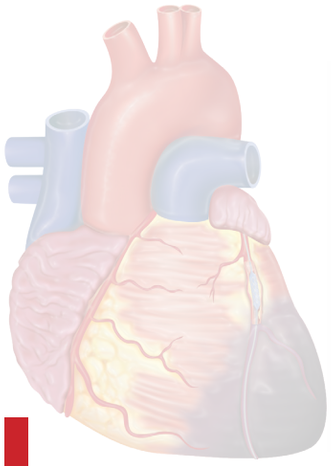

Statin-induced Diabetes: Evidence, Mechanisms, and Implications

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INTRODUCTION

Statin class of medicines has transformed the primary and secondary prevention of cardiovascular disease (CVD). Statins are specific, competitive, reversible, and potent inhibitors of the microsomal enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase that catalyzes the conversion of HMG-CoA to mevalonate, a rate-determining step during cholesterol synthesis. Low-density lipoprotein receptor (LDLR) is the primary route by which LDL-cholesterol (LDL-C) is removed from circulation, and its synthesis has been shown to be inversely correlated to the amount of cholesterol synthesized by cells.[1] Statin-mediated decrease in intracellular cholesterol content leads to up-regulation of the LDLR in the liver and peripheral tissues, resulting in decreased blood LDL-C. Thus, statins reduce the cellular cholesterol concentration, stimulating production of more LDLR, and promoting LDL-C removal from the bloodstream, ultimately reducing CVD risk. With moderate statin therapy, LDL-C levels are expected to decrease between 30% and 45%. If more aggressive reductions are necessary, high-intensity therapy can generally decrease LDL-C levels by over 50%.[2] Apart from the basic mechanism, there are several suggested positive pleiotropic effects of statins that serve to promote cardiovascular health. These include increasing the bioavailability of nitric oxide, decreasing C-reactive protein (CRP) concentrations, decreasing inflammatory cells in atherosclerotic plaques, and increasing the plaque stability through their combined reduction of lipids, macrophages, and matrix metalloproteinases (MMPs), and limiting the expression of monocyte chemo-attractant protein-1 thereby reducing the interaction between monocytes and the vascular walls, etc.[3]

Statins have been classified according to their solubility into hydrophilic statins (pravastatin and rosuvastatin) and lipophilic statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin).[4] Although the target of both types of statins is HMG-CoA reductase, the inhibitory mechanisms appear to be slightly different. Uptake of hydrophilic statins is carrier-mediated, and as a result, they target the liver more efficiently. On the other hand, lipophilic statins exhibit reduced hepatoselectivity, as they are able to passively diffuse through the hepatocellular membrane and similarly are also able to diffuse in extra-hepatic tissues. This influence on extra-hepatic tissues has been proposed to explain the higher incidence of adverse effects observed with lipophilic statins. A notable exception to this is rosuvastatin, which structurally is a hydrophilic statin but has been shown to possess similar activity profile to lipophilic statins.[5]

Despite the overall favorable safety and tolerability profile of statins, observational studies, clinical trials, and meta-analyses have found that statins can increase the risk of new-onset type 2 diabetes mellitus (T2DM). Although the lipid-lowering mechanism of statins is relatively well understood, the mechanisms underlying statin-induced new onset diabetes (NOD) seem to be multifactorial and remain unclear. Studies suggest that statins negatively impact insulin sensitivity and decrease insulin secretion by pancreatic β-cells.

STATIN USE AND NOD: CLINICAL EVIDENCE

Statins have been available for clinical use for around 4 decades now and have well-characterized benefits in terms of lowering LDL-C and cardiovascular risk. However, findings from several observational and interventional clinical studies have shown an increased risk of NOD following statin administration across different populations. This issue was first brought to attention by results of JUPITER (Justification

for the Use of statin in Prevention: an Intervention Trial Evaluating Rosuvastatin), a large primary prevention trial using rosuvastatin in middle aged to elderly individuals with elevated levels of CRP. Subsequent meta-analyses of both randomized controlled trials (RCTs) and observational studies have found a similar but varying increased risk of NOD with statins. Consequently, in February 2012, the US-FDA published a safety update indicating that statins can increase fasting blood glucose and HbA1c concentrations.[6]

Several large observational studies carried out in UK, Canada, Italy, and USA have examined the association between statin administration and NOD. These analyses have revealed considerable variability among studies and with various statins, with hazard ratios (HR) ranging from 1.19 to 1.57 (statistically significant), after follow-up durations of 3–6 years **(Table 1)**. Further, the effects of statin treatment on the risk of T2D and hyperglycemia deterioration have been assessed in the metabolic syndrome in men (METSIM) study cohort, which found that statin therapy was associated with a 46% increased risk of T2DM along with worsening of hyperglycemia. In addition, the study found statin use to be associated with a 24% reduction in insulin sensitivity and a 12% decrease in β-cell count compared to individuals not taking statin therapy. Remarkably, treatment with both simvastatin and atorvastatin was associated with reductions in insulin sensitivity and secretion in a dose-dependent manner.[8]

The first study to report the effect of statin use on glucose homeostasis was WOSCOPS (West of Scotland Coronary Prevention Study), a primary prevention trial conducted among men aged 45–64 years old.[13] After 5 years of treatment, a 30% reduction in the incidence of NOD was recorded in the pravastatin-treated group (40 mg) versus the placebo group. However, concerns have been raised on the clinical implications of this finding as the upper boundary of the 95% CI for this observation was 0.99 and the WOSCOPS investigators used nonstandardized criteria for diagnosis of NOD (as defined by at least 2 mmol/L (36 mg/dL) rise in blood glucose above baseline values).[14] On the contrary, in 2008, the JUPITER study reported increase in the incidence of diabetes among patients taking rosuvastatin, triggering wide discussion on the direction and strength of the association between statin therapy and diabetes. JUPITER was a large, randomized, placebo controlled, primary prevention trial including 17,802 men and women (average age 66 years) who were randomized into two groups: rosuvastatin (20 mg/day) or placebo.[15] This trial was stopped early at 1.9 years when an interim analysis found a 44% lower incidence of adverse vascular events in the rosuvastatin group. Significantly increased incidence of diabetes in persons receiving rosuvastatin was reported in this trial (26% higher incidence of diabetes in the rosuvastatin group) compared to placebo over a median of 1.9 years ($p = 0.01$). In addition, a posthoc analysis of the JUPITER trial showed that participants with one or more major diabetes risk factor were at higher risk of developing T2D than were those without a major risk factor (incidence rate 1.88 vs. 0.18 per 100 person years, HR = 10.5, 95%CI 6.98–15.8, $p = 0.001$).[16]

Diabetes Prevention Program (DPP) was a landmark randomized clinical trial testing interventions to prevent or delay the development of diabetes mellitus among a cohort of 3,234 overweight and obese individuals at high risk for diabetes, followed specifically for incident diabetes.[17] Eligible participants received standard advice on healthy diet and physical activity, and were randomly assigned to an intensive lifestyle intervention, metformin or placebo. Statins use was also recorded along with other concomitant medications based on self-report. After an average follow-up of 2.8 years, lifestyle intervention reduced the incidence by 58% (95% CI, 48–66%) and metformin by 31% (95% CI, 17–43%), as compared with placebo; the lifestyle intervention was significantly more effective than metformin. A post-hoc analysis of data from

TABLE 1: Population-based studies evaluating effect of statins on NOD.

Study	*n*	*Age (years)*	*Follow-up duration (years)*	*Adjusted HR (95% CI)*	*Comments*
Culver et al. Women's Health Initiative (WHI)[7]	153,840	50–79	3.0	1.48 (1.38–1.59)	Only 7.4% were on atorvastatin, none on rosuvastatin
Cederberg et al. METSIM (Finnish men)[8]	8,749	43–73	5.9	1.46 (1.11–1.74)	Risk dose dependent for atorvastatin and simvastatin
Castro et al., USA[9]	18,071	45–73	6.0	Normoglycemic: 1.19 (1.05–1.35) Impaired fasting glucose: 1.24 (1.11–1.38)	Mortality reduced in both groups on statin
Corrao et al. Lombardy, Italy[10]	115,709	62	6.4	1.12–1.32 per statin adherence	
Ko et al. Ontario, Canada[11]	17,080	65–78	5.0	Incidence rates for intensive vs. moderate statin: 13.6 vs. 13.0% (NS)	Mortality and acute coronary syndrome rates lower with intensive statin: 44.8 vs. 46.5% ($p = 0.044$)
Macedo et al. UK practice database[12]	2,016,094	30–85	5.4	1.57 (1.55–1.60)	HR increased to 3.63 (95% CI 2.44–5.38) by 15–20 years

TABLE 2: Meta-analyses of randomized controlled trials evaluating effect of statins on NOD.

Study	*n*	*Age (years)*	*Follow-up duration (years)*	*Adjusted HR (95% CI)*	*Comments*
Sattar et al. 13 trials, statin vs. placebo[19]	91,140	55–76	4.0	1.09 (1.02–1.17)	Highest risk in older patients; unrelated to % LDL-C reduction
Preiss et al. 5 trials, more- vs. less-intensive statin[20]	32,752	58–64	4.9	1.12 (1.04–1.22)	Odds ratio for incident CVD 0.84 (95% CI, 0.75–0.94)
Navarese et al. 17 trials, various statins and doses[21]	113,394	55–65	2.0–6.0	Pravastatin 40 mg vs. placebo: 1.07 (0.89–1.30) Atorvastatin 80 mg vs. placebo: 1.15 (0.90–1.50) Rosuvastatin 20 mg vs. placebo: 1.25 (0.82–1.90)	Odds ratio unrelated to % LDL-C reduction

DPP was subsequently carried out to evaluate the statin–diabetes association within this randomized clinical trial.[18] The most commonly used statins in DPP were simvastatin and atorvastatin (40% and 37%, respectively). Statin use was associated with greater diabetes risk irrespective of treatment group, with fully-adjusted pooled HR (95%CI) for incident diabetes of 1.27 (1.08–1.50). Point estimates of the HRs suggest that this risk is increased by close to 30% (HR 1.33; 1.01–1.76) in metformin arm; and more than 40% (HR 1.43; 1.06–1.94) in lifestyle intervention arm. Further, longer duration of statin use was significantly associated with greater diabetes risk in the lifestyle group (HR per visit with statin use: 1.06 (1.02–1.11), $p = 0.007$). These observations, along with the significantly higher estimates of statin-associated HRs observed in JUPITER study suggest that the statin effect is more important among those with prediabetes and those having risk factors for developing diabetes. Apart from observational studies and RCTs, several meta-analyses have confirmed a smaller but significant increase with various statins **(Table 2)**.

Different statins have been shown to exert different effects on the glycemic parameters. Thus, although some statins have been associated with increased HbA1c levels in patients receiving intensive therapy, other statins have demonstrated neutral or favorable effects on glucose control in patients with and without T2D. A subanalysis of data from the PROVE-IT TIMI 22 trial showed that, among the 3,382 patients without preexisting T2D, HbA1c levels increased by 0.12% in patients treated with pravastatin 40 mg and by 0.30% in those receiving atorvastatin 80 mg ($p < 0.0001$).[22] However, these results must be interpreted with caution as they were derived from a posthoc analysis. Similarly, in a study involving 279 patients with T2D receiving atorvastatin 10 mg, pravastatin 10 mg. or pitavastatin 2 mg/day, glycemic parameters (arbitrary blood glucose levels and HbA1c) only increased among atorvastatin-treated patients.[23] Again, as this was a retrospective, single-site study, these data need to be interpreted with caution. Another recently published post-hoc analysis of a prospective, single-blinded, randomized study compared the risk of NOD between the highest dose of pitavastatin (4 mg) and the lowest dose of pitavastatin (1 mg) over a 3-year follow-up in patients with acute coronary syndrome. Among 1,044 patients of the original study, 667 patients at high risk of developing T2D were in the subgroup analysis. It was seen that incidence of NOD was similar between the pitavastatin 1 mg and 4 mg groups [12 of 289 patients (4.2%) and 8 of 289 patients (2.8%), respectively; $p = 0.36$]. Moreover, various risk factors for NOD such as metabolic syndrome components, glucose intolerance, dyslipidemia, obesity, or hypertension did not affect the development of NOD during pitavastatin administration.[24] These findings suggest possible molecule-specific effects on diabetogenesis, although the data thus far are inconclusive. If confirmed in a large RCT, differences in pharmacodynamics and pharmacogenomics on diabetogenecity need to be considered while choosing a statin.

MECHANISMS OF STATIN-INDUCED NOD

Statins lower cholesterol and risk of CVD, but at the same time, may increase blood glucose and risk of NOD. The exact mechanisms between the opposing effects of statins on lipids versus glucose are still unclear. It is known that statins have cholesterol-independent pleiotropic effects that influence both insulin and glucose control.

A number of potential deleterious effects of statins on β cell function have been proposed, including the effects of increased influx of cholesterol due to inhibition of HMG-CoA-mediated intracellular cholesterol synthesis, inhibition of ubiquinone (CoQ 10) synthesis leading to mitochondrial oxidative stress, and β cell apoptosis.[14] It has been proposed that chronic statin treatment increases gluconeogenesis by upregulating gene expression of key enzymes that increase glucose production in the liver. Additionally, it has been shown that statins can impair the insulin signaling pathway as well as downregulate the GLUT-4 transporter, which is responsible for the uptake of glucose in peripheral cells. Statins can also induce changes in circulating free fatty acids (FFA), changes in hormones such as adiponectin and leptin,

impairment of β-cell function, β-cell damage, and adipocyte maturation/differentiation. Additional mechanisms involving epigenetic regulation mediated by specific microRNAs have also being involved in the reduction of insulin secretion. These complex pathophysiologic molecular mechanisms of statin-induced NOD are summarized in **Figure 1**.

Recently, it has been suggested that statin-induced activation of the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome contributes to insulin resistance **(Fig. 2)**. Although, the pleiotropic effects of statins are thought to be largely anti-inflammatory, activation of the NLRP3 inflammasome promotes adipose tissue inflammation, which can precipitate insulin resistance.[25] In the first step known as priming, transcriptional events induced by nuclear factor kappa B (NF-κB) following pattern recognition receptor (PRR) stimulation increase levels of inflammasomes like NLRP3 and inflammasome effectors like pro-IL-1beta. This leads to immune activation where inhibition of HMGCR with statins decreases protein prenylation, triggering signals that promote NLRP3 inflammasome activity.

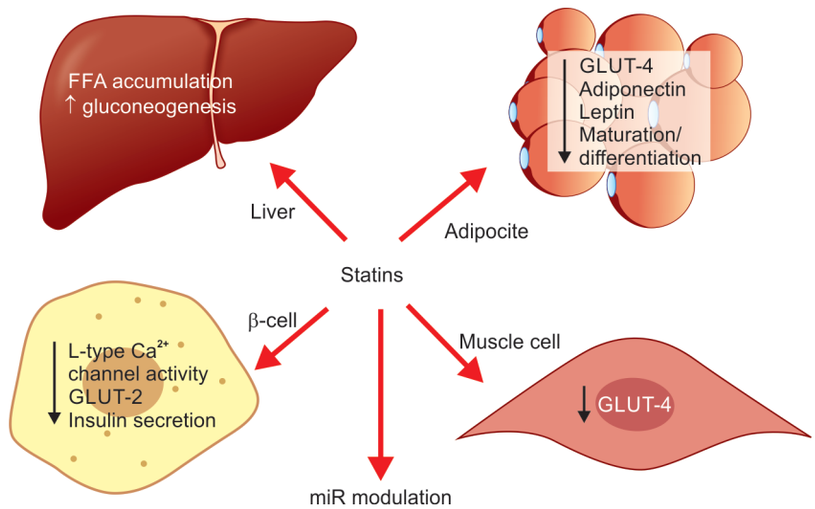

Fig. 1: Principal proposed mechanisms for statin-induced NOD. (FFA: free fatty acid; GLUT: glucose transporter; NOD: new onset diabetes)
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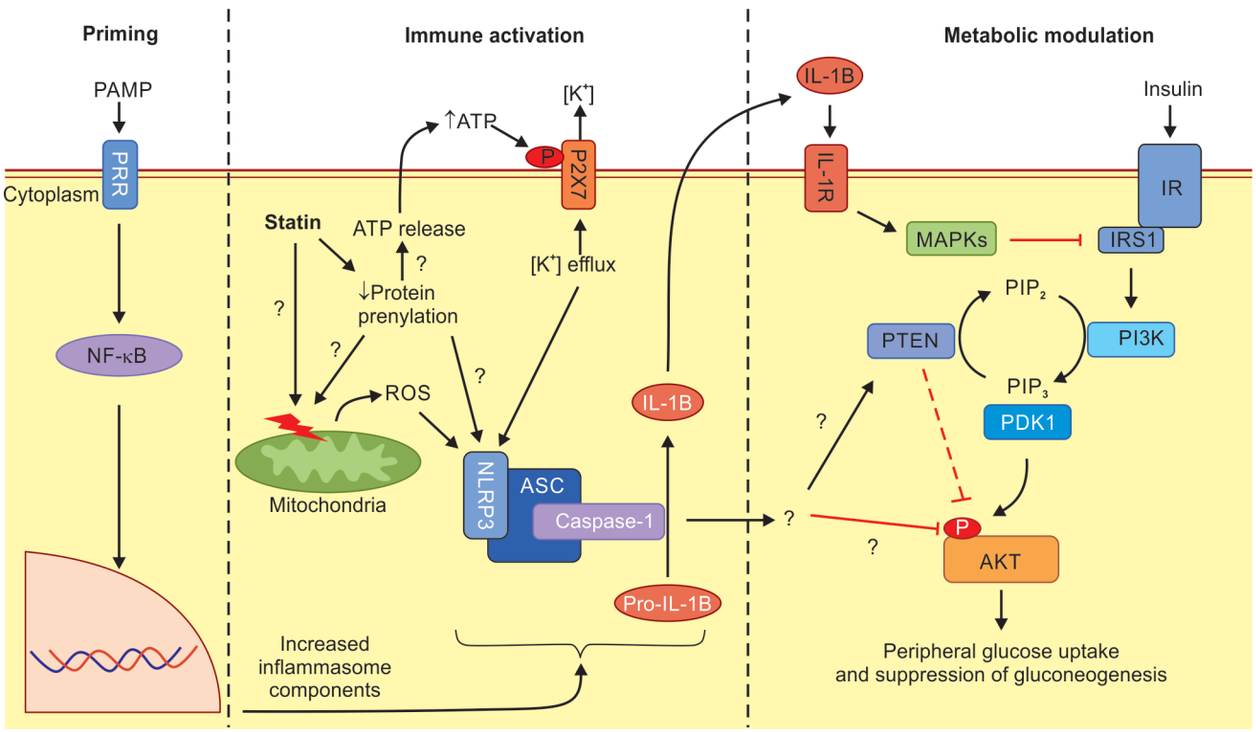

Fig. 2: Statin-induced activation of the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome contributes to insulin resistance.

Also, statins cause variety of other effects including promotion of intracellular adenosine triphosphate (ATP) release, which promotes potassium efflux, a key trigger for increased NLRP3 inflammasome activity. This activity causes cleavage of pro-IL-1beta into active IL-1beta by caspase-1, promoting metabolic modulation. IL-1beta-mediated inflammation and activation of mitogen-activated protein kinase (MAPK) inhibit insulin signaling either at receptor substrate-1 level (IRS1), or through an unknown target of caspase-1 that inhibits downstream signaling through a suspected number of pathways.[26]

Recently, parallels have been drawn between the dysregulation of insulin producing β-cells and insulin resistance in adipocytes caused by statin lowering of isoprenoids.[25] Statins may engage a similar isoprenoid-mTOR mechanism to promote cholesterol independent side effects in insulin-producing cells and insulin-responsive cells. Thus, it appears worthwhile to further investigate the role of m-TOR-NLRP3 pathway and restoring specific isoprenoids to mitigate glycemic side effects of statins.

CLINICAL IMPLICATIONS

The benefits of clinical use of statins in reducing CVD have been proven beyond any doubt. In the JUPITER study, although diabetes was diagnosed more frequently in patients receiving rosuvastatin compared with placebo, patients receiving the statin had a significant 54% lower risk of heart attack, 48% lower risk of stroke, and 20% lower risk of death from any cause. The meta-analysis by Sattar et al., from 13 individual studies showed that treating 255 patients with statins for 4 years led to one extra case of diabetes mellitus, whereas 5.4 CV events were prevented.[19] Therefore, although the risk of NOD is higher in patients receiving statins, statins ultimately reduce CVD in people with established heart disease or risk factors for heart disease.

On the other hand, T2D is a well-established risk factor for CVD. The Emerging Risk Factors Collaboration published their meta-analysis of 102 prospective studies (n = 698,782) and demonstrated that T2D confers approximately a twofold excess risk for a wide range of vascular diseases, including coronary heart disease (HR = 2.00, 95% CI = 1.83–2.19), ischemic stroke (HR = 2.27, 95% CI = 1.95–2.65), hemorrhagic stroke (HR = 1.56, 95% CI = 1.19–2.05), and other vascular deaths (HR = 1.73, 95% CI = 1.51–1.98).[27] Also, it is important to remember that although statins prevent heart disease in patients at high risk or with established CVD, the use of statins in patients at lower risk (for primary prevention before any cardiac events have occurred) is less certain.[28] Although large studies suggest that using statins to achieve lower LDL-C may benefit lower-risk populations, it is important to consider the risk of statin-induced diabetes mellitus and its impact on CV outcomes in this population. Particularly, the use of statins in the prediabetes population and its effects on conversion to NOD must be carefully weighed against the anticipated benefits. It must be stressed that statin-induced NOD is not an uncommon entity in clinical practice with incidence ranging from 9 to 57% in various studies in different populations as discussed earlier. It is of particular concern in Indian population due to the unique Indian phenotype with higher visceral adiposity, high triglycerides, low high-density lipopolysaccharides-cholesterol (HDL-C), increased insulin resistance, and high-inflammatory load. This is all the more important because Asian Indians have been shown to progress faster through the prediabetes stage than do people of other ethnic groups.[29] The ICMR–INDIAB study, largest study of diabetes in India (representing 51% of India's adult population), estimated the overall prevalence of diabetes in India to be 7·3% and the prevalence of prediabetes to be 10.3%.[30] It was also noted that in several states (especially in urban areas), the prevalence of prediabetes was lower than or similar to the prevalence of diabetes, which might be suggestive of fast conversion to diabetes. This is in contrast with the US population, where the prevalence of prediabetes (88 million) is nearly 2.5 times higher than the T2D prevalence of 34.2 million currently.[31] While the use of statins is absolutely imperative to reduce CV risk, it is equally important to further investigate the role of statins in increasing the prevalence of T2D due to acceleration of converting prediabetes to diabetes. This finding assumes more clinical importance considering the findings from the substudy of the landmark DPP discussed above; wherein it was reported that in patients of prediabetes taking statins, both metformin and lifestyle were not effective in preventing diabetes. Clinicians need to be aware of these glycemic effects of statins and ideally, a baseline HbA1C and/or fasting blood sugar levels must be checked in patients before starting statins. We also suggest that, benefits of regular exercise and dietary modifications should be stressed at every contact with the patient, and statins must be started at low doses particularly in primary prevention setting and based on clear therapeutic rationale. While starting statins, clinicians must inform patients about the possible risk of NOD with statin use; and fasting sugar level and HbA1c should be regularly monitored in patients on intensive-dose statin therapy.

It is important to explore options to delay the progression of prediabetes to T2D. Hydroxychloroquine (HCQ), an anti-inflammatory agent approved for use in T2D in India, appears to be one such interesting candidate. It has shown some signals of mitigating the increased risk of diabetes when used in combination with statins (along with improved reduction in the lipid parameters). In a double-blind, randomized, out-patient study conducted across India, 328 patients with primary dyslipidemia were randomized to receive either atorvastatin 10 mg or atorvastatin 10 mg + HCQ 200 mg for 24 weeks.[32] At Week 24, percentage reduction in LDL-C, TC, and non-HDL-C was significantly greater in combination treated patients. In exploratory analysis of data from this study, it was found that 15% patients with prediabetic dyslipidemia from the statin monotherapy group developed diabetes at Week 24, while just 2% from the statin-HCQ combination group developed diabetes at Week 24. Thus, combining HCQ with statin could be a useful strategy to not only enhance the reduction in lipid levels, but also to mitigate the risk of NOD with statins; and must be evaluated in larger prospective RCTs. This hypothesis is further corroborated in a US-wide longitudinal observational cohort wherein during a median

4.6 years of follow-up in 13,669 patients with rheumatoid arthritis, 1,139 incident DM cases were observed. Adjusted HR (95% CI) for DM were 0.67 (0.57–0.80) for HCQ, and 1.56 (1.36–1.78) for statins.[33] The therapeutic advantage of using concomitant HCQ use with statins to attenuate the NOD risk associated with statins was also suggested in this study as the adjusted HR for concomitant HCQ use with statins was reduced to 0.92 (0.68–1.25).[34]

We suggest several mechanisms by which HCQ could attenuate the diabetogenic effects of statins. Mechanistic studies showed that HCQ could inhibit the priming of the NLRP3 inflammasome by down-regulating its triggers including cathepsins and NF-κB signaling.[35] It has also been suggested that HCQ affects the NLRP3 activation process, resulting in the impaired IL-1β production.[36] Another interesting aspect is the role of the ATP-binding cassette transporters -A1 and G1 (ABCA1, ABCG1) in T2D and their modulation by statins and HCQ. It has been demonstrated that the gene expression, protein concentrations, and transporter functions of ABCA1 and ABCG1 are reduced in patients with T2D.[37,38] Statins have been shown to downregulate ABCA1 and ABCG1 gene expression.[39,40] On the other hand, it has been suggested that hepatic ABCA1 improves glucose tolerance by improving β-cell function through both HDL production and interaction with β-cell ABCA1;[41] and adiponectin has been shown to upregulate ABCA1 expression through liver X-receptor alpha-signaling pathway.[42] In a randomized, double-blind, parallel-arm trial at the University of Pittsburgh involving 32 nondiabetic volunteers with one or more markers of insulin resistance, treatment with HCQ 400 mg/day for around 13 weeks was shown to increase adiponectin levels, improve insulin sensitivity, and β-cell function with reduction in fasting plasma glucose and HbA1c.[43] These metabolic effects may explain why HCQ treatment is associated with a lower risk of T2D. Larger clinical studies must be carried out to further evaluate these effects of HCQ in attenuating statin-induced NOD; and more such strategies must be devised to continue the effective use of statins in the target populations.

CONCLUSION

Various studies, ranging from observational cohort studies to meta-analyses, confirm and reinforce the diabetogenic effect of statins. Although a number of questions remain unanswered, the available evidence supports that statins do increase the chances of T2D with some statins being more strongly related (e.g., simvastatin, rosuvastatin, and atorvastatin) than others (e.g., pravastatin). The exact mechanisms behind the diabetogenic effect of statins are not yet clearly elucidated, but several mechanisms have been proposed through which statins lead to reduction in insulin secretion as well as development of insulin resistance. Considering all the evidence, although there is a clear advantage of statin therapy, due to the large reductions in cardiovascular risk, the adverse effect of NOD is also quite significant. Clinicians must continue using statins in patients with dyslipidemia at high CVD risk, but the risk of incident diabetes with statin therapy must be borne in mind and glycemic parameters must be regularly monitored in at-risk patients. The risk of statin-induced NOD is of particular concern in the Indian context, which has a huge population suffering from pre-diabetes. HCQ, approved as anti-diabetic in India, has been shown to exert effects which may be useful in mitigating the risk of diabetes with statins. Further research is required to better elucidate these effects and to identify more such strategies to enable clinicians to continue using statins effectively for CV risk reduction.

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