Acute effect of atorvastatin in comparison with rosuvastatin on glucose homeostasis in hypercholesteremic patients

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ABSTRACT

Short-term *in vitro* experiments provide evidence that lipophilic statin blocks K_{ATP} channel which may improve insulin secretion, whereas, short incubation with hydrophilic statins has no effect on K_{ATP} channel. The present study aimed at observing the early effect of atorvastatin and rosuvastatin on glucose levels of prediabetic patients with hypercholesterolemia given the well-established difference in lipophilicity of these two statins. In the present study, thirty-five prediabetic patients with hypercholesterolemia were randomly allocated to 2 groups atorvastatin (n = 20) and rosuvastatin (n = 15); each patient received 20 mg per day of either treatment for 6-weeks. Serum levels of fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) were analyzed before and after 6-weeks of administration. Besides significant improvement in lipid profile, atorvastatin consumption for 6-weeks significantly reduced serum levels of FBG (107.6 mg/dl ± 1.326 vs basal 124.5 mg/dl ± 1.381; P = 0.001) and HbA1c (5.616% ± 0.1039 vs basal 6.413% ± 0.1277 P < 0.0001). Similarly, rosuvastatin reduced FBG (109.6 mg/dl ± 3.124 6 vs basal 123.6 mg/dl ± 1.536), and HbA1c (5.075% ± 0.1181 vs basal 5.925% ± 0.1548). However, there was no statistically significant difference between atorvastatin and rosuvastatin on FBG and HbA1c after 6-weeks treatment. In conclusion, both atorvastatin and rosuvastatin exert early improvement in plasma glucose in prediabetic patients with hypercholesterolemia. Further and more powered studies are needed to confirm this observation in diabetic patients; moreover, the studies should include groups on long-term therapy with statin to improve the quality of the result and to reduce the limitation of short-durations.

KEYWORDS: atorvastatin, rosuvastatin, prediabetes, cholesterol, lipophilic, hydrophilic.

INTRODUCTION

Statins competitively inhibit 3-hydroxy- 3-methylglutaryl CoA reductase, the rate-limiting step in cholesterol biosynthesis (Figure 1) [1]. In fact, they are considered the mainstay in reducing LDL cholesterol and decreasing cardiovascular mortality with an impressive safety record; they reduce the incidence of cardiovascular problems in patients with recent stroke [2-5]. Moreover, statins have beneficial therapeutic effects in hyperlipidemic patients with metabolic syndrome. Several factors may predispose the progression of atherosclerosis like hyperlipidemia, endothelial dysfunction, obesity, oxidative stress and metabolic disorders [6-8]. In fact, patients with hyperglycemia and diabetes are much more prone for cardiovascular problems than normal persons, and thus the full medical history of should be taken into consideration to assess all factors predisposing to glycemic intolerance, such as, hyperlipidemia. The beneficial effects of statins are associated not only with lipid lowering capacity but also with other pleiotropic actions, such as improved endothelial function and nitric oxide

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bioavailability [9, 10] improved flow mediated relaxation [10-13], reduced oxidative stress and vascular inflammation. Ultimately statins play a role in reducing CVD accident in T2DM patients [14-16]. Results have shown that treatment with statins significantly reduce the risk of vascular accidents in elderly patients with diabetes and hypercholesterolemia [17, 18]. Similarly meta-analysis results from 18000 patients with diabetes showed that statins have a beneficial effect in reducing cardiovascular accidents [19, 20]. Thus, according to guidelines of the American Diabetes Association in 2019, statins are highly advised in T2DM patients [21]. Based on this evidence, patients with type 2 diabetes may be candidates for statin therapy regardless of LDL cholesterol level [22, 23]. However, with regard to metabolic effects, especially those related to glucose and insulin homeostasis, the use of statins remained a concern particularly in elderly, obese patients with predisposing factors for DM and those receiving intensive statin therapy [24-29]. In fact, multiple studies have found a clear relation of statins and diabetes mellitus [30-32]. A significant association between the use of statin and the incidence of diabetes has been reported in a meta-analysis trial and a nationwide cohort study [33-36]. Recent large-scale clinical studies have demonstrated that some statins, particularly at high dose, increased the rate of onset of new diabetes [27, 37]. Although the effect of statin group on glucose is a class effect, different statin members have different impact in the induction of diabetes mellitus. Regarding physiochemical characteristics, stains can be subdivided into lipophilic statins like atorvastatin, simvastatin and lovastatin, and hydrophilic statins like pravastatin and rosuvastatin, Previous results have shown that the diabetogenic effects of stains are related to the efficacy of the statin to inhibit mevalonate pathway, the dosage used and the physiochemical properties of the drug used [27, 29, 38-40]. In general, the lipophilic statins are more likely to be diabetogenic than those with the hydrophilic nature, and this effect may be related to the ability of the lipophilic statins to penetrate extrahepatic tissue like pancreas, muscle and adipocyte [41].

Conversely the hydrophilic statins are selectively taken up by the liver with minimal penetration to extrahepatic tissue i.e. hepato-selectivity; accordingly they have minimal interference with cholesterol metabolism in extrahepatic tissue and thus less diabetogenic effect with chronic use [41, 42]. They also do not readily penetrate to intracellular compartment with acute term use. In fact, clinical studies have suggested that lipophilic statins are more likely associated with new diabetes than with hydrophilic statins [28, 38, 43-48]. Similarly, population-based results suggested that the incidence of diabetes was increased in elderly patients on atorvastatin, simvastatin and rosuvastatin treatment while pravastatin had neutral or even a protective effect [49]. Studies also revealed that atorvastatin worsens glucose tolerance in streptozotocin-induced diabetic rats [50]. Simvastatin, another lipophilic statin, worsened insulin sensitivity in diabetic patients and suppresses *in-vitro* insulin release from the rat islet β-cells [39]. Statin therapy also can lead in some conditions to metabolic side effects, for example interference with insulin secretion and/or sensitivity especially those induced by the lipophilic statins i.e. atorvastatin, simvastatin and lovastatin [44]. The proposed reason was that the lipophilic statins had increased penetration to the cellular membrane directly affecting the membrane channels e.g. K_{ATP} channels and voltage-gated Ca^{2+} channels; in addition lipophilic statins have the ability to penetrate to the intracellular compartment like mitochondria affecting insulin synthesis or release [39]. On the other hand, rosuvastatin, despite its hydrophilic nature, has a high, carrier-mediated mechanism to transport to the intracellular compartment, which in turn can predispose to rosuvastatin effects on insulin secretion [41]. By contrast, clinical results suggested that the hydrophilic statin, pravastatin, had no effect on insulin secretion or insulin resistance [38, 51-53]. Results even suggested that pravastatin might reduce the onset of new diabetes [54]. However, this opposes the observed diabetogenic effects of rosuvastatin [51], which is known to be a hydrophilic molecule. In fact, studies reported a dose-dependent increase in the incidence of type 2 diabetes in rosuvastatin-treated patients [55]. The effect of rosuvastatin has been examined *in vitro* on human islets and the results referred to reduced insulin secretion [56], while others have found that rosuvastatin increases insulin secretion but with decreased insulin sensitivity [51]. Therefore, the effect of rosuvastatin on glucose homeostasis is very intriguing and not clearly defined. Despite the hydrophilic nature of rosuvastatin, which

predisposes to its effects on insulin secretion [41], the mechanism of how statins induce glucose intolerance or enhance insulin secretion is not clearly identified and probably there are off-target effects in addition to the on-target mechanism.

Regarding cholesterol, results have shown that elevated level of cholesterol can impair insulin secretion [57]; nevertheless sufficient cholesterol levels in cell membranes are essential for cellular function [58, 59]. In fact, depletion of cholesterol with chronic statin therapy could impair insulin secretion by inhibition of Ca^{2+} channel currents [58]. In addition, the chronic inhibition of mevalonate pathway with statins results in downstream inhibition of many cellular intermediates with resultant induction of glucose intolerance [31]. In addition, with chronic treatment the rate of gluconeogenesis was upregulated in the liver [60], an action which could be inhibited with prolonged statin use [61].

On the other hand, acute statin treatment could inhibit voltage-gated Ca^{2+} channel [26, 62-64],

and there was evidence from *in vitro* studies of direct inhibition of the Ca^{2+} channels by the lipophilic statins while the hydrophilic pravastatin had no effect. Recently, statins have been suggested to inhibit mitochondria and depolarize the membrane potential. Mitochondrial inhibition decreased ATP production, thus decreasing the signal for K_{ATP} closure, and subsequently decreasing Ca^{2+} channel activation with decreased Ca^{2+} influx. In addition, data demonstrated that the lipophilic statin could also directly block K_{ATP} channel opening in the pancreatic β-cells and coronary smooth muscle [65, 66]; the latter would subsequently increase insulin secretion. Thus, statins are expected to have acute effects on glucose level.

Both atorvastatin and rosuvastatin have the character of long plasma half-life [67, 68]. Rosuvastatin is a widely used water-soluble statin with a good safety profile [69], and has a high binding affinity to the active site of the target enzyme HMG-CoA with a powerful efficacy in reducing LDL level compared with other statins (Figure 1) [68, 69].
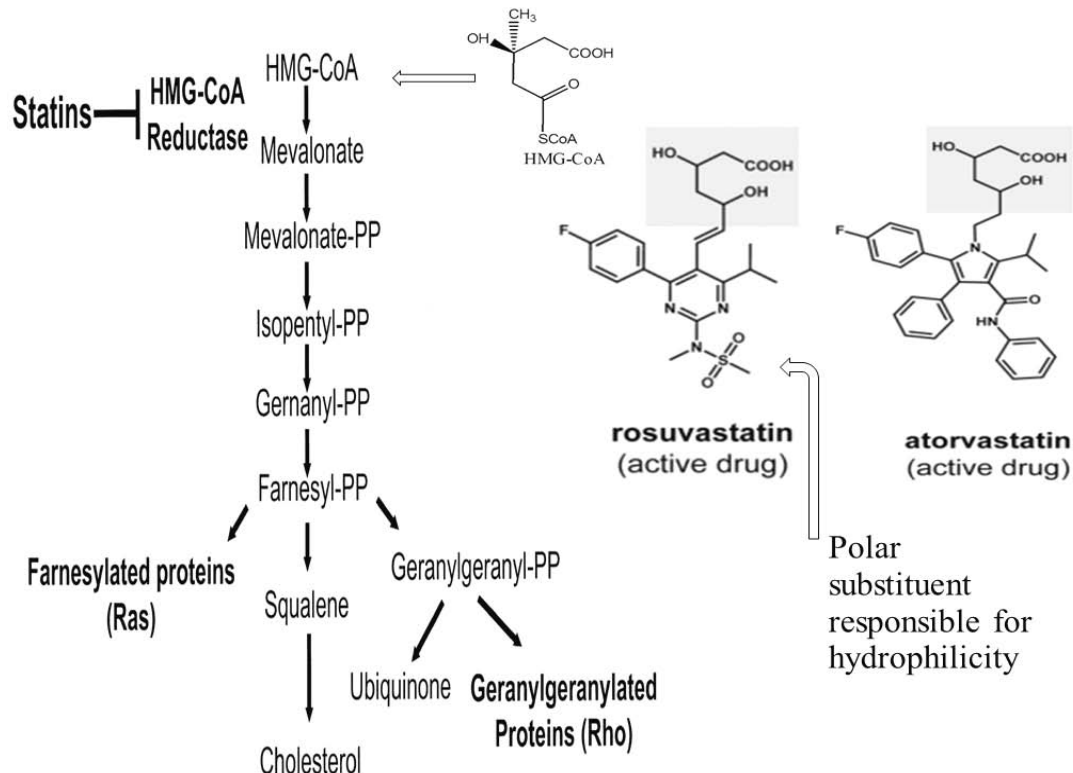

Figure 1. Mechanism of action of statins with special reference to the lipophilic atorvastatin and the hydrophilic rosuvastatin.

Similarly, the lipophilic atorvastatin is very effective in reducing LDL cholesterol in comparison with other statins [70, 71]. Rosuvastatin and atorvastatin may have differential acute metabolic effects in hypercholesterolemia patients due to differences in their solubility [72, 73]. Accordingly, the aim of the current study was to investigate the effects of short-term, low-dose treatment of the lipophilic atorvastatin in comparison with the hydrophilic rosuvastatin on glucose homeostasis in prediabetic hypercholesterolemia patients.

MATERIALS AND METHODS

A total of 35 patients were enrolled in the study, their demographic parameters mentioned below (Table 1). Patients were eligible for the study if they were apparently healthy apart from hypercholesterolemia and glucose intolerance as their primary diagnosis. The diagnosis was made by a cardiologist at the outpatient clinic in Mosul city, and the level of cholesterol and glucose was estimated by the central lab. Patients with overt liver disease, chronic renal failure, uncontrolled diabetes, and severe hypertension were excluded. No patient had taken any lipid-lowering agent or hormone replacement therapy during the 2-months preceding our study. Patients were given rosuvastatin 20 mg or rosuvastatin 20 mg once daily during a 6-week treatment period. Data of fasting glucose, HbA1c and lipid profile were collected both at pre- and post-treatment.

Patients from the outpatient clinic in Mosul city were randomly assigned to rosuvastatin 20 mg/daily (15 patients) or atorvastatin 20 mg/daily

Table 1. Demographic characteristics of patients and control groups.

Parameters	Treated groups	
	ATG (n = 20)	RTG (n = 15)
Gender (male: female)	11:9	13:17
Age (year)	43-55	48-57
BMI (kg/m^2)	27.5	26
Smoking: not smoking	0:20	0:15

ATG: Atorvastatin-treated group, RTG: rosuvastatin-treated group, BMI: body mass index, kg: kilogram, m^2: square meter.

(20 patients) according to the cardiologist's choice for about 6 weeks. All patients presented with hypercholesterolemia and glucose intolerance.

Fasting blood sugar (FBS) was measured for each patient, before and after treatment, by using enzymatic colorimetric kit supplied by Randox, UK. The measurement of HbA1c in human blood was done by using the principles of ion exchange (Adams A1c, Japan), whereas serum total cholesterol (TC), triglycerides (TG), and serum high density lipoprotein cholesterol (HDL) were determined by the enzymatic method (Biomerieux, France). Serum low density lipoprotein cholesterol (LDL) was estimated by the Friedewald equation [LDL=TC-HDL-(TG/5)].

Statistical analysis

Data were expressed as the mean ± standard error. Comparisons between the two groups were conducted using the Paired sample t-test. $P<0.01$ was considered to indicate a statistically significant difference. Statistical calculations were analyzed using GraphPad Prism 5.0 (GraphPad Software Inc., La Jolla, CA, USA).

RESULTS

Both atorvastatin and rosuvastatin significantly changed the glucose levels after 6-week administration when compared with pretreatment levels (Table 2 and 3, Figure 2, 3). Although the effects of atorvastatin on glucose level may have been relatively more prominent (***$P<0.001$) compared to those of rosuvastatin (**$P<0.01$,), there was no statistically significant difference between the two treatments (data not shown). Similarly, both treatments also significantly decreased HbA1c as illustrated in Table 2 and 3, and Figure 3 without significant difference between the two treatments on HbA1c level. The effect of short-term use on LDL level was also examined; both treatments significantly decreased LDL in comparison with the pretreatment plasma LDL levels (Figure 4).

DISCUSSION

The relationship of statin therapy to glucose intolerance or even diabetes remains uncertain. Recent reports confirmed that statin impaired glucose tolerance and might induce diabetes [28, 74, 75].

Table 2. Baseline versus post-treatment level in atorvastatin group.

Atorvastatin, n = 20	Basal	6-weeks treatment
Fasting Plasma Glucose mg/dl	124.5 mg/dl ± 1.381	107.6 mg/dl ± 1.326 ***
HbA1c %	6.413% ± 0.1277	5.616% ± 0.1039 ***
LDL mg/dl	191.7 mg/dl ± 3.678	145.6 mg/dl ± 6.552 ***

***p < 0.0001

Table 3. Baseline versus post-treatment level in rosuvastatin group.

Rosuvastatin, n = 15	Basal	6-weeks treatment
Fasting Plasma Glucose mg/dl	123.6 mg/dl ± 1.536	109.6 mg/dl ± 3.124 **
HbA1c %	5.925% ± 0.1548	5.075% ± 0.1181 **
LDL mg/dl	186.6 mg/dl ± 8.158	170.8 mg/dl ± 6.974 **

**p < 0.001
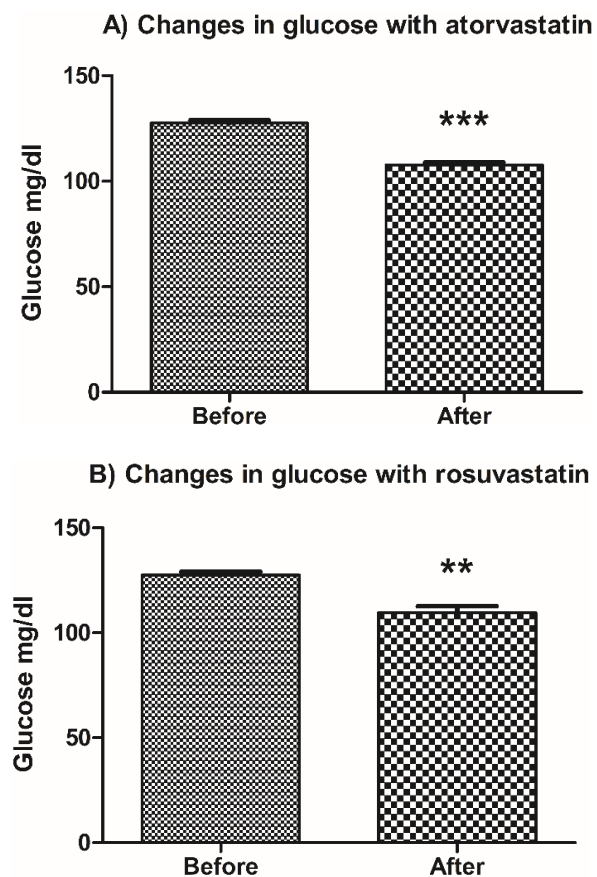
Figure 2. Effects of 6 weeks of treatment with A) atorvastatin and B) Rosuvastatin on glucose homeostasis. Data are expressed as the mean ± standard error. **P<0.01, ***P<0.001.
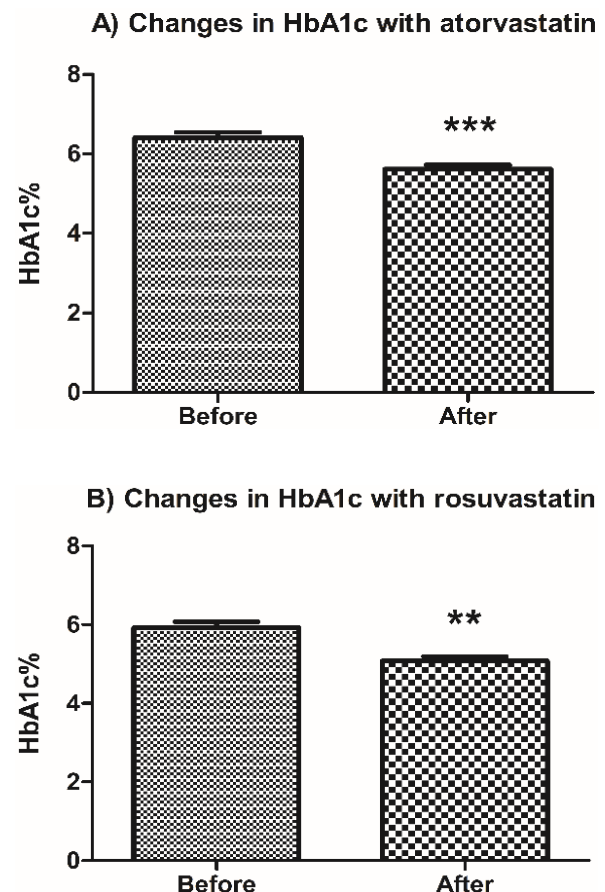
Figure 3. Effects of 6 weeks of treatment with A) atorvastatin and B) Rosuvastatin on HbA1c. Data are expressed as the mean ± standard error. **P<0.01, ***P<0.001.
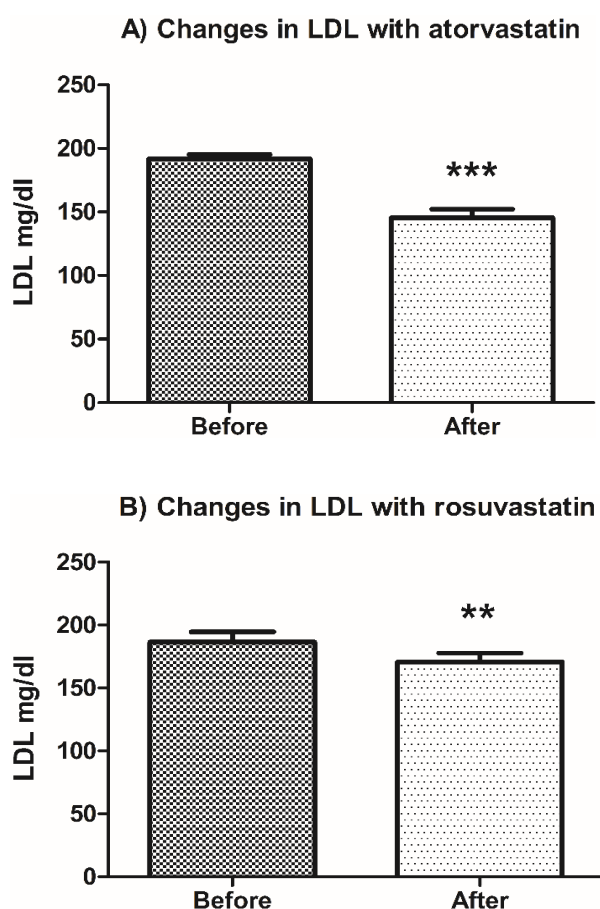
A) Changes in LDL with atorvastatin

B) Changes in LDL with rosuvastatin

Figure 4. Effects of 6 weeks of treatment with A) atorvastatin and B) Rosuvastatin on HbA1c. Data are expressed as the mean ± standard error. **P<0.01, ***P<0.001.

Statin lipophilicity, as well as, statin efficacy to inhibit the target enzyme HMG-CoA reductase [39, 76] are both regarded as a predisposing factor for statin impact on carbohydrate metabolism [39, 50, 66, 77]. However, acute treatment may have different effects by affecting β-cell function, and the current study revealed that short term treatment with atorvastatin and rosuvastatin (20 mg/day) decreased fasting plasma glucose level, in addition to LDL reduction, in middle-aged patients with glucose intolerance and untreated mild dyslipidemia. Both treatments also reduced HbA1c levels as a sensitive indicator of ambient glycaemia. Although the effect of atorvastatin on glucose level, HbA1c and LDL was more prominent, no statistical difference was found between the two agents with the short-term treatment. Our study supports the

conclusion of Wang and collaborators that short term, 3-weeks, treatment with atorvastatin reduces fasting glucose in mice with hyperlipidemia [78]. Results in patients with metabolic syndrome have also shown that 6-week treatment with atorvastatin resulted in a significant improvement in glucose metabolism and insulin sensitivity [79, 80]. Moreover, rats treated with atorvastatin showed improved pancreatic function with subsequent reduction in blood glucose [81, 82]. Similarly, 12-week treatment with rosuvastatin in hypercholesterolemia patients has been shown to increase insulin secretion [83]. In fact, rosuvastatin could reduce blood glucose by raising glucose uptake [56, 84]. It is clearly known that glucose metabolism and ATP production control insulin secretion *via* inhibition of K_{ATP} channels [85, 86]; the latter induced electrophysiological changes of the pancreatic β-cell followed by activation of Ca^{2+} influx with resultant insulin release [87]. *In-vitro* patch experiments have shown that lipophilic statins, but not the hydrophilic statins, directly block K_{ATP} channels in pancreatic β-cells, which was confirmed with inside-out patch technique with around 1μM concentration [66]. The latter is expected to increase insulin secretion [84]. Similarly, lipophilic statins have been found to block K_{ATP} channels in vascular smooth muscle [65, 66, 88]. This effect is consistent with the results conducted by Koh *et al.*, who demonstrated that atorvastatin increases insulin in humans [43]. Similarly, the lipophilic simvastatin but not the water-soluble pravastatin significantly increased insulin levels after 2-month treatment in atherosclerotic patients from primary care units [52]. Another lipophilic statin, cerivastatin, also improved insulin secretion in mild hyperglycemia patients [89]. By contrast, treatment with the hydrophilic pravastatin significantly decreased LDL cholesterol with no effect on insulin resistance or glucose intolerance [90]. On the other hand, *in-vitro* incubation with the lipophilic statin induces detrimental effect on mitochondrial function. It is well known that mitochondria play a critical role in pancreatic β-cell function; thus direct inhibition of the pancreatic mitochondrial function would adversely interfere with insulin synthesis and release [91, 92]. However, results have shown that statin inhibition of mitochondrial
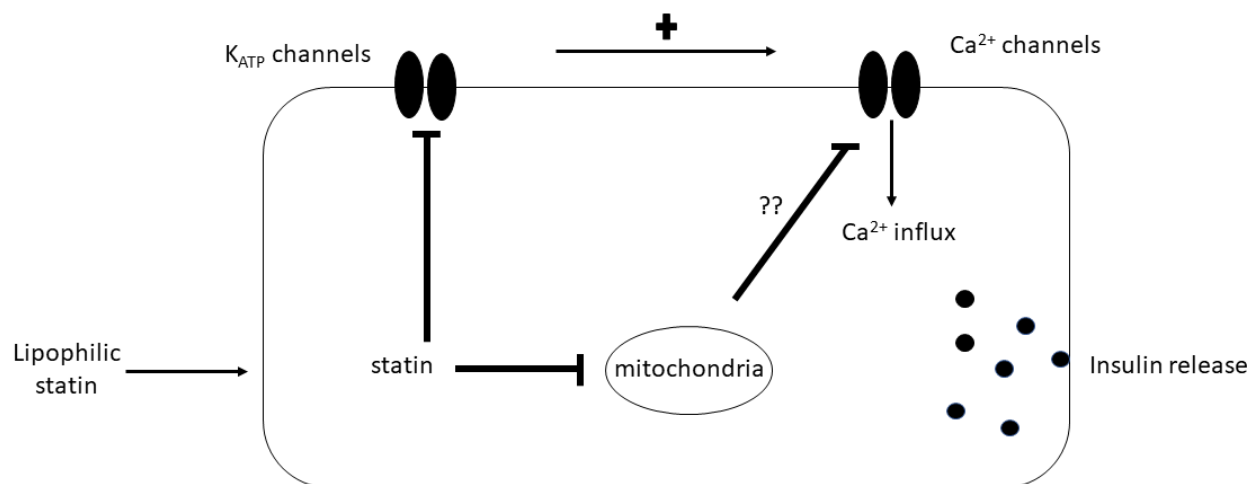
Figure 5. Acute effects of statin on pancreatic β-cell function: the lipophilic statins are suggested to block K_{ATP} channels acutely with subsequent insulin release and glucose reduction; statin also is proposed to induce mitochondrial depolarization.

function is usually induced by relatively higher concentration than those required for K_{ATP} channel inhibition. Interestingly, patch experiments also revealed that the lipophilic statins 10 μM, but not 1μM, could block Ca^{2+} channel secondary to mitochondrial inhibition and ATP reduction (Figure 5). Such mechanism has been described in pancreatic β-cell as a protective mechanism to limit Ca^{2+} overload [93], the latter obviously should inhibit insulin section with relatively high concentrations [27, 63, 64, 75, 94]. These two actions on K_{ATP} and Ca^{2+} channels clearly have a contradictory effect on glucose homeostasis and may be related to statin physiochemical properties, i.e., hydrophilic or hydrophobic, concentration of the drug used and to the duration of treatment. Such discrepancy could provide support to the hypothesis that small doses of certain statins (especially the lipophilic ones) could block K_{ATP} channels and increase insulin secretion with subsequent reduction in glucose level [78, 84] (Figure 5). Collectively this suggests that the beneficial effects of statins start before the metabolic disturbances; thus the patients should be informed about the potential risk of glucose intolerance when using a high dose of statins. Finally, there are some limitations of the study including small number of patients included in the study, as well as non-inclusion of measurement of

insulin release with insulin sensitivity due to technical issues.

Statins are generally well tolerated agents, and their ability to reduce cardiovascular events is well documented. However, statin therapy can lead in some conditions to metabolic side effects, for example interference with insulin secretion and/or sensitivity especially those induced by the lipophilic statins i.e., atorvastatin, simvastatin and lovastatin [40].

CONCLUSION

Short-term treatment with rosuvastatin and atorvastatin has a potential effect in reducing glucose level. Further and more powered studies are recommended to confirm the observation, as well as to consider a longer treatment period. Moreover, these findings need to be confirmed with another hydrophilic statin (pravastatin) to provide concrete evidence about the aforementioned study.

ETHICAL APPROVAL

All the experimental procedures were approved by the medical ethics committee of College of Pharmacy, University of Mosul. A consent form was collected from each subject included in the study after full explanation of the patient medical diagnosis, the purpose of the prescribed treatment,

atorvastatin or rosuvastatin, the beneficial outcome of drug therapy in addition to the possible side effects.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

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