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Original Research

Effect of Atorvastatin on Pancreatic Beta-Cell Function and Insulin Resistance in Type 2 Diabetes Mellitus Patients: A Randomized Pilot Study

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ABSTRACT

Objective: Statins are commonly used for the management of dyslipidemia in type 2 diabetes mellitus patients. We hypothesized that atorvastatin could modulate the beta-cell function by altering the levels of proapoptotic and antiapoptotic lipoproteins and could also have an effect on insulin resistance. The aim of the present pilot study was to assess the effect of atorvastatin 10 mg on pancreatic beta-cell function and insulin resistance in patients with hyperlipidemia and type 2 diabetes by using the homeostasis model assessment-2 (HOMA2) index.
Methods: Fifty-one type 2 diabetes patients receiving oral antidiabetes drugs, not taking statins, with baseline low-density lipoprotein cholesterol between 2.6 mmol/L and 4.1 mmol/L were included. Forty-three patients (21 in placebo group and 22 in atorvastatin group) completed the study and were taken up for final analysis. Fasting blood samples were obtained at baseline and at 12 weeks to determine levels of blood glucose, lipid profile, insulin, C-peptide and glycosylated hemoglobin (A1C).
Results: Atorvastatin nonsignificantly increased fasting serum insulin (+14.29%, p=0.18), accompanied by marginal nonsignificant increases in fasting plasma glucose and A1C. There was a decrease in HOMA2 percent beta-cell function (−2.9%, p=0.72) and increase in HOMA2 insulin resistance (+14%, p=0.16) in the atorvastatin group as compared with baseline, but the difference was not statistically significant.
Conclusions: Atorvastatin in the dose used failed to produce significant change in pancreatic beta-cell function and insulin resistance in type 2 diabetes patients as assessed by the HOMA2 index. The possible explanations include absence of lipotoxicity at prevailing levels of dyslipidemia at baseline or inadequacy of statin dose used in the study. (Clinical Trials Registry-India: CTRI/2008/091/000099)

Mots clés :
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RÉSUMÉ

Objectif : Les statines sont fréquemment utilisées pour prendre en charge la dyslipidémie des patients souffrant de diabète sucré de type 2. Nous avons posé l'hypothèse que l'atorvastatine module le fonctionnement des cellules bêta en altérant les taux des lipoprotéines proapoptotiques et antiapoptotiques et qu'elle peut également avoir un effet sur l'insulinorésistance. Le but de cette étude pilote était d'évaluer l'effet de l'atorvastatine à raison de 10 mg sur le fonctionnement des cellules bêta du pancréas et de l'insulinorésistance chez les patients souffrant d'hyperlipidémie et de diabète de type 2 en utilisant l'indice HOMA2 (*Homeostasis Model Assessment2*).
Méthodes : Cinquante-et-un (51) patients souffrant de diabète de type 2 qui recevaient des antidiabétiques oraux, ne prenaient pas de statines, qui avaient un cholestérol à lipoprotéines de faible densité initial entre 2,6 mmol/l et 4,1 mmol/l ont été inclus. Quarante-trois (43) patients (21 du groupe qui prenait le placébo et 22 du groupe qui prenait l'atorvastatine) ont réalisé l'étude et ont été retenus pour l'analyse finale. Les échantillons de sang à jeun ont été prélevés au début et à la 12^{e} semaine pour déterminer la glycémie, le profil lipidique, les taux d'insuline, de peptide C et d'hémoglobine glyquée (A1c).
Résultats : L'atorvastatine a augmenté de manière non significative le taux sérique de l'insuline à jeun (+14,29 %, p = 0,18), et a montré des augmentations minimes non significatives de la glycémie à jeun et

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de l'A1c. Il y a eu une diminution du fonctionnement des cellules bêta HOMA2 % (−2,9 %, p = 0,72) et une augmentation de l'insulinorésistance HOMA2 (+14 %, p = 0,16) dans le groupe qui prenait de l'atorvastatine par rapport au début, mais la différence n'était pas statistiquement significative.
Conclusions : La dose d'atorvastatine utilisée n'a pas réussi à produire de changements significatifs du fonctionnement des cellules bêta du pancréas et de l'insulinorésistance chez les patients ayant le diabète de type 2 comme l'estimait l'indice HOMA2. Les explications possibles sont l'absence de lipotoxicité selon les dyslipidémies observées au début ou la dose inadéquate de statines utilisée durant l'étude (Registre des essais cliniques en Inde : CTRI/2008/091/000099).

Introduction

Type 2 diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to a combination of peripheral insulin resistance, impaired regulation of hepatic glucose production and decreasing pancreatic beta-cell function, eventually leading to beta-cell failure (1). Lipid abnormalities present in type 2 diabetes patients play a significant role in increasing the cardiovascular risk of these patients (2). Various primary and secondary prevention trials provide strong evidence that atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitor, decreases the risk of cardiovascular events in type 2 diabetes patients (3). In addition to lowering low-density lipoprotein cholesterol (LDL-C) levels, statins are known to contain the progression of atherosclerosis by their pleiotropic actions, including the antioxidant effect, improvement of vascular endothelial cell damage, anti-inflammatory action and stabilization of plaques (4).

The contribution of free fatty acids in the development of type 2 diabetes has been reported widely (5), but there are not many clinical studies done to study the effects of lipoproteins on pancreatic beta-cell function. Dose-dependent increase in rate of apoptosis, induced by human purified very-low-density lipoprotein and LDL, has been demonstrated in an insulin-secreting beta-cell line, wherein high-density lipoprotein (HDL) was able to efficiently stop the cell death in the in vitro experiment (6). Also, mutation of adenosine triphosphate binding cassette transporter A1 (ABCA1) in pancreatic beta cells, a cellular cholesterol transporter, has resulted in accumulation of cellular cholesterol, causing, in turn, decreased insulin secretion from beta cells (7). That also highlights the role of high cholesterol in beta-cell dysfunction in the pathogenesis of type 2 diabetes. Although experimental studies suggest that the changes in lipid profile observed in type 2 diabetes could contribute to the progression of beta-cell dysfunction and failure (6–9), the direct action of statins on insulin sensitivity remains controversial, with data suggesting beneficial, indifferent or unfavourable effects of different statins on insulin sensitivity. Recently, a meta-analysis reported that statins do not demonstrate a "class effect" on insulin sensitivity in patients not having diabetes, with different statins showing different actions on insulin sensitivity (10).

We hypothesized that atorvastatin could modulate beta-cell function by altering the levels of proapoptotic and antiapoptotic lipoproteins and could also have an effect on insulin resistance. Hence, the present trial, a randomized controlled study, was conducted to assess the effect of atorvastatin 10 mg daily on pancreatic beta-cell function and insulin resistance in patients with hyperlipidemia and type 2 diabetes by using the homeostasis model of assessment-2 (HOMA2) index. The data collected from this pilot study could be used for planning other, larger multicentre trials.

Methods

Study population

The trial started in May 2008 and the last patient was enrolled in July 2009. A total of 51 patients were randomly allocated into 2 groups (25 in the placebo group and 26 in the atorvastatin group). The study population consisted of adult patients with type 2 diabetes diagnosed according to American Diabetes Association criteria, with disease duration <10 years, and treatment with either medical nutrition therapy (MNT) or oral antidiabetes agents for the management of hyperglycemia. The inclusion criteria included 1) being off statins for ≥3 months; 2) LDL-C ≥2.6 to ≤4.1 mmol/L if patient was receiving MNT or LDL-C ≥3.4 to ≤4.1 mmol/L if patient had not received MNT earlier; 3) taking either sulphonylureas (prescribed dose ≤50% of the maximum recommended dose) or biguanides or both, and 4) glycosylated hemoglobin (A1C) ≥6.5% to ≤10.0%. Such LDL inclusion criteria were chosen because MNT alone has been shown to reduce LDL by 0.8 mmol/L, and target LDL-C levels in type 2 diabetes patients is <2.6 mmol/L as recommended by the National Cholesterol Education Program Adult Treatment Panel III (11). The maximum prescribed dose of sulphonylureas was limited to ≤50% of the maximum recommended dose to ensure that enough pancreatic beta cells were present in patients to demonstrate the protective effect of atorvastatin on beta-cell mass.

The exclusion criteria were 1) insulin therapy or thiazolidinediones; 2) deranged liver function test (alanine aminotransferase >3 times upper normal limit); 3) serum creatinine >132.6 μmol/L; 4) clinically significant cardiovascular disease including history of myocardial infarction or heart failure (New York Heart Association functional class III or IV); 5) pregnancy; 6) lactation; 7) drugs that can increase the incidence of statin-induced myopathy and 8) drugs known to cause hyperglycemia.

In this pilot study, we tested the hypothesis that atorvastatin 10 mg per day could modulate the pancreatic beta-cell function by altering the levels of proapoptotic and antiapoptotic lipoproteins and could also have an effect on insulin resistance. It was decided to enrol at least 21 patients in each arm. The primary outcome measure was change in HOMA2 beta-cell function (HOMA2-%beta) as a measure of pancreatic beta-cell function and HOMA2 insulin resistance (HOMA2-IR) as a measure of insulin resistance in patients with hyperlipidemia and type 2 diabetes after receiving treatment for 12 weeks. The secondary outcome measures were the impact of atorvastatin therapy on the levels of A1C and on quality of life using the Audit of Diabetes Dependent Quality of Life Questionnaire–19 (ADDQoL-19) in type 2 diabetes patients.

Study design

This study was a randomized, double-blind, placebo-controlled trial involving patients with dyslipidemia and type 2 diabetes, conducted in collaboration with the department of pharmacology and the department of endocrinology and metabolism at the All India Institute of Medical Sciences (AIIMS), New Delhi, India. The detailed trial profile is shown in Figure 1. The study conformed to Good Clinical Practice guidelines and was done under the guidelines of the Declaration of Helsinki. The patients were enrolled and randomized after providing written informed consent. The study protocol and all subsequent amendments to it were reviewed and approved by the Institute Ethics Committee, AIIMS, New Delhi (A-54/23.01.2008).