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Statin therapy with or without ezetimibe and the progression to diabetes

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OBJECTIVE: To assess the risk of progression from normoglycemia or prediabetes to overt diabetes among individuals treated with statins alone or in combination with ezetimibe.

METHODS: This was a retrospective study conducted in Greece including 877 subjects treated for dyslipidemia. We included individuals without overt diabetes at baseline and divided them in 2 subgroups according to their baseline fasting glucose: <100 (normal glucose) and 100 to 125 mg/dL (prediabetes). High and moderate-intensity statin therapy was defined according to the expected low-density lipoprotein cholesterol reduction (≥50% and 30 to <50%, respectively). We identified the predictors of incident diabetes and assessed the risk of new-onset diabetes among subgroups on various intensity statin or no statin treatment at all. Similar analyses were performed across different potency of statin monotherapy or combination of statin plus ezetimibe treatment.

RESULTS: A total of 877 subjects were eligible and followed-up for a median of 7 years. There were no differences between statins regarding diabetes development. However, a higher risk of incident diabetes was observed in prediabetic individuals receiving high-intensity statin therapy compared with those on moderate intensity (adjusted odds ratio [OR] = 2.12, 95% confidence interval [CI] = 1.06–4.24, $P < .05$) and those not taking a statin (adjusted OR = 4.90; 95% CI = 1.16–20.66, $P < .05$). The addition of ezetimibe to statin treatment did not increase the risk of incident diabetes in prediabetic individuals (adjusted OR = 0.89; 95% CI = 0.36–2.22, $P > .05$). Baseline fasting glucose, presence of metabolic syndrome, family history of diabetes, and follow-up duration were independent predictors of new-onset diabetes.

CONCLUSION: High-intensity statin treatment is associated with a higher risk of incident diabetes in prediabetic individuals, whereas the addition of ezetimibe to statin therapy has a neutral effect on glucose metabolism.

Introduction

Statins are the cornerstone of drug therapy for the reduction of cardiovascular (CV) risk.[1] Their principal mechanism of action is the reduction of low-density lipoprotein cholesterol (LDL-C) by inhibiting the 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, and they

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are generally considered as safe and well-tolerated drugs.[2] However, there has been recently a lot of debate regarding the relationship of statins with diabetes development.[3,4] In the JUPITER (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin) trial, individuals receiving rosuvastatin had a 25% higher risk for new-onset diabetes compared with those taking placebo.[5] Likewise, an increased risk for diabetes was also noticed in treatment with simvastatin or atorvastatin.[6–8] Recent meta-analyses have demonstrated a dose-dependent effect of statins on diabetes risk, meaning that a higher dose of the same statin increases the risk more for diabetes development. They also showed that across different statins, the more potent ones increase the risk more for diabetes compared with the less potent ones.[9,10] On the other hand, ezetimibe, which decreases the intestinal absorption of cholesterol by inhibiting the transport protein Nieman Pick C1 like 1 and is commonly used either in combination with statins or as an alternative lipid-lowering drug in statin-intolerant patients, has been reported to improve metabolic markers such as hepatic steatosis and insulin resistance.[11] Nevertheless, no adequate data exist regarding the use of ezetimibe and the development of diabetes.

The aim of the present study was to assess whether statin therapy with or without ezetimibe was associated with the development of diabetes in dyslipidemic individuals with normoglycemia or prediabetes at baseline visit who attended a University Hospital Lipid Clinic for an average of 7 years.

Subjects and methods

This was a retrospective observational study as previously described.[12] Briefly, we included dyslipidemic adults attending the Outpatient Lipid Clinic of the University Hospital of Ioannina in Greece and followed-up for at least 3 years. All participants had a complete assessment of concomitant diseases and their treatment. The study protocol was approved by the institutional ethics committee.

All subjects were of Greek origin (Caucasians). We excluded those with established diabetes at the baseline visit. The diagnosis of established diabetes was made (1) when fasting glucose levels were ≥126 mg/dL (6.9 mmol/L) in 2 separate past measurements before the baseline visit, (2) when glucose levels were ≥200 mg/dL (11.1 mmol/L) 2 hours after 75 g of oral glucose at the baseline visit,[13] or (3) when the individuals were already on antidiabetic therapy at the baseline visit. Demographic characteristics along with clinical data were recorded at baseline and at the most recent (final) visit. These included: (1) anthropometric indices (body mass index [BMI], waist), (2) age, follow-up duration, gender, and smoking status, (3) the presence of metabolic syndrome,[14] and (4) family history of diabetes. Laboratory data were also available, such as (1) blood pressure (BP) readings, (2) lipid profile, including total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), LDL-C, and (3) fasting glucose. In everyday clinical practice in our clinic, the physicians did not usually measure insulin, whereas glycated hemoglobin (HbA1c) was rarely measured before the diagnosis of diabetes because Greek guidelines for diabetes do not recommend HbA1c measurement for the diagnosis of diabetes. Thus, we could not investigate the impact of the intensity of statin therapy or ezetimibe on insulin resistance or HbA1c.

Concomitant medications were also recorded with particular emphasis on the lipid-lowering therapy, including the name and dose of each statin and other lipid-lowering drugs (i.e., ezetimibe, colesevelam, fibrates, and omega-3 fatty acids). In addition, the intensity of statin therapy was classified as "high", "moderate", and "low" on the basis of the average expected LDL-C lowering of ≥50%, 30 to <50%, and <30%, respectively.[15] Atorvastatin 80 mg was not available as a single pill in Greece and therefore was rarely prescribed. As a result, "high-intensity" treatment included atorvastatin 40 mg/day or rosuvastatin 20–40 mg/day. "Moderate-intensity" treatment included atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40 mg, and fluvastatin 80 mg daily. Simvastatin 10 mg, pravastatin 10–20 mg, and fluvastatin 20–40 mg daily were considered as "low-intensity" treatment.

We divided the subjects in 2 groups according to their baseline glucose values: (1) those with normal glucose levels (<100 mg/dL; 5.5 mmol/L) and (2) those with prediabetes (100 to 125 mg/dL; 5.5 to 6.9 mmol/L).[13] We assessed the risk of new-onset diabetes between: (1) various intensity statin treatment groups, (2) different statins (i.e., atorvastatin, rosuvastatin, simvastatin, and fluvastatin), and (3) combination treatment of statin plus ezetimibe as compared to statin monotherapy. These analyses were performed in individuals with normal fasting glucose compared with prediabetic individuals to evaluate whether there was any difference regarding diabetes development between these 2 subgroups.

Statistical analysis

Continuous variables were tested for normality by the Kolmogorov–Smirnov test, and logarithmic transformations were performed if necessary. Data are presented as mean ± standard deviation (SD) and median (interquartile range [IQR]) for normal and non-normal distributed data, respectively. Chi-square tests were performed for categorical values. The difference of variables between ≥2 groups was assessed by analysis of variance (ANOVA) and post hoc least significant difference tests were used for the comparison of variables or ratios of interest between the groups. The odds ratios (ORs) and 95% confidence intervals (CIs) for the development of new-onset diabetes were calculated on the basis of binary logistic regression. Univariate analyses were performed by binary logistic regression to define the predictors for incident diabetes (baseline age, BMI, waist, fasting glucose, lipid and BP levels, presence of metabolic syndrome, family history of diabetes, duration of follow-up, and concomitant therapy at the last visit). Multivariate