Statin Use Is Prospectively Associated With New-Onset Diabetes After Transplantation in Renal Transplant Recipients

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Statin Use Is Prospectively Associated With New-Onset Diabetes After Transplantation in Renal Transplant Recipients

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OBJECTIVE

New-onset diabetes after transplantation (NODAT) is frequent and worsens graft and patient outcomes in renal transplant recipients (RTRs). In the general population, statins are diabetogenic. This study investigated whether statins also increase NODAT risk in RTRs.

RESEARCH DESIGN AND METHODS

From a prospective longitudinal study of 606 RTRs (functioning allograft >1 year, single academic center, follow-up: median 9.6 [range, 6.6–10.2] years), 95 patients using statins were age- and sex-matched to RTRs not on statins (all diabetes-free at inclusion).

RESULTS

NODAT incidence was 7.2% (73.3% of these on statins). In Kaplan-Meier (log-rank test, $P = 0.017$) and COX regression analyses (HR 3.86 [95% CI 1.21–12.27]; $P = 0.022$), statins were prospectively associated with incident NODAT, even independent of several relevant confounders including immunosuppressive medication and biomarkers of glucose homeostasis.

CONCLUSIONS

This study demonstrates that statin use is prospectively associated with the development of NODAT in RTRs independent of other recognized risk factors.

The population of renal transplant recipients (RTRs) is increasing, and these patients frequently (up to 50%) develop new-onset diabetes after transplantation (NODAT), which is related to worse graft and patient outcomes (1,2). In the general population, statin use is associated with an increased risk for type 2 diabetes (3). Pathophysiologically, this finding has been attributed to statins increasing LDL receptor expression on β-cells and, consequently, the uptake of LDL resulting in cholesterol-induced dysfunction and damage (3). Somewhat counterintuitively, such a mechanism does not seem to be at work when PCSK9 levels are high (4). Kidney Disease Improving Global Outcomes guidelines recommend statins to be uniformly prescribed to RTRs (5). However, data on whether statin use is associated with NODAT incidence are currently limited. Therefore, this study aimed to prospectively investigate the association between statin use and NODAT in RTRs.

RESEARCH DESIGN AND METHODS

A detailed setup of this prospective longitudinal cohort study has been published (6). The protocol was approved by the local medical ethical committee (METc2001/039),

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every participant provided written informed consent. The study was carried out in accordance with the Declaration of Helsinki. Briefly, between August 2001 and July 2003, 606 RTRs were included who had at least 1 year of having a functioning allograft. Baseline laboratory values were determined at inclusion, and all follow-up data presented, including incident NODAT, are related to this time point of inclusion. Patients with systemic illnesses were excluded. Furthermore, 105 RTRs were excluded because of type 1 or 2 diabetes, impaired fasting glucose (defined by fasting plasma glucose levels between 100 mg/dL [5.6 mmol/L] and 126 mg/dL [7.0 mmol/L]), $HbA_{1c} \geq 6.5\%$, or use of glucose-lowering medication. A total of 92 patients were additionally excluded due to missing values, and 4 were excluded because they received a mixed kidney liver transplant.

In a first analysis, age emerged as a major potential confounder, with RTRs in the statin group being significantly older ($P < 0.001$). Therefore, 95 RTRs using statins were matched to nonusers with respect to sex and age (5-year age groups). The diagnosis of NODAT was defined according to expert panel recommendations based on the 2003 American Diabetes Association criteria (7) with the following requirements: fasting plasma glucose >126 mg/dL (7.0 mmol/L), nonfasting plasma glucose >200 mg/dL (11 mmol/L), $HbA_{1c} \geq 6.5\%$, and/or classic type 2 diabetes symptoms (polyuria, polydipsia, or unexplained weight loss). All relevant patient characteristics were obtained from the Groningen Renal Transplant Database, which includes medical records and outcomes of self-report questionnaires. There was no selection bias for the use of cyclosporin versus tacrolimus as the primary calcineurin inhibitor. Statistical analyses were performed using the SPSS version 25 (IBM). A P value <0.05 was considered significant. Baseline variables were screened for normal distribution. Significances between statin users and nonusers were tested utilizing Mann-Whitney U test for skewed data, t test for normally distributed data, and χ^2 test for categorical data. Kaplan-Meier curves were constructed, and significance was tested using a log-rank test. Furthermore, Cox proportional hazards regression analysis was performed with respective adjustments for potential confounders defined as variables having a significant association with NODAT in the univariate analysis.

RESULTS

Clinical baseline characteristics of 95 statin-using RTRs ($n = 50$ atorvastatin, $n = 26$ fluvastatin, $n = 14$ simvastatin, $n = 5$ pravastatin) compared with age- and sex-matched RTRs not using statins are shown in Supplementary Table 1. Overall, NODAT incidence was 7.2% (73.3% of these using statins). Statin users were significantly more former smokers ($P = 0.002$) with a higher BMI ($P = 0.009$) and a trend toward higher waist circumference ($P = 0.069$). Transplant history characteristics were comparable between groups, as were renal allograft function and systemic inflammation. Glucose homeostasis parameters did not differ between groups. However, patients receiving statins more frequently had a family history of diabetes ($P = 0.014$). In RTRs on statins, LDL cholesterol was lower ($P < 0.001$), and triglycerides were higher ($P = 0.002$), whereas HDL cholesterol levels were not different. A total of 84 patients were on single (44%) and 106 were on double (56%) immunosuppressive therapy. No differences in medication use were detected between the groups, including prednisolone. In the univariate analyses (Supplementary Table 2), sex ($P = 0.017$), BMI ($P = 0.002$), waist circumference ($P = 0.001$), time since renal transplantation ($P = 0.016$), fasted plasma glucose ($P = 0.003$), plasma insulin ($P = 0.001$), HbA_{1c} ($P = 0.033$), HOMA-IR ($P = 0.001$), family history of diabetes ($P = 0.008$), LDL cholesterol ($P = 0.017$), triglycerides ($P = 0.002$), and mycophenolic acid ($P = 0.029$) were significantly associated with NODAT. HDL cholesterol ($P = 0.069$) exhibited a trend toward significance. Kaplan-Meier curves (Fig. 1) showed a prospective association of statins with higher NODAT incidence (log-rank test, $P = 0.017$). Finally, the Cox regression analyses (Supplementary Table 3) demonstrated a significant association of statin use with incident NODAT in crude (model 1, $P = 0.026$) and age- and sex-adjusted models (model 2, $P = 0.022$). Adding BMI and waist circumference (model 3, $P = 0.025$), time since renal transplantation (model 4, $P = 0.039$), plasma LDL cholesterol and triglycerides (model 5, $P = 0.038$), HDL cholesterol (model 6, $P = 0.022$), blood glucose and HbA_{1c} (model 7, $P = 0.025$), plasma

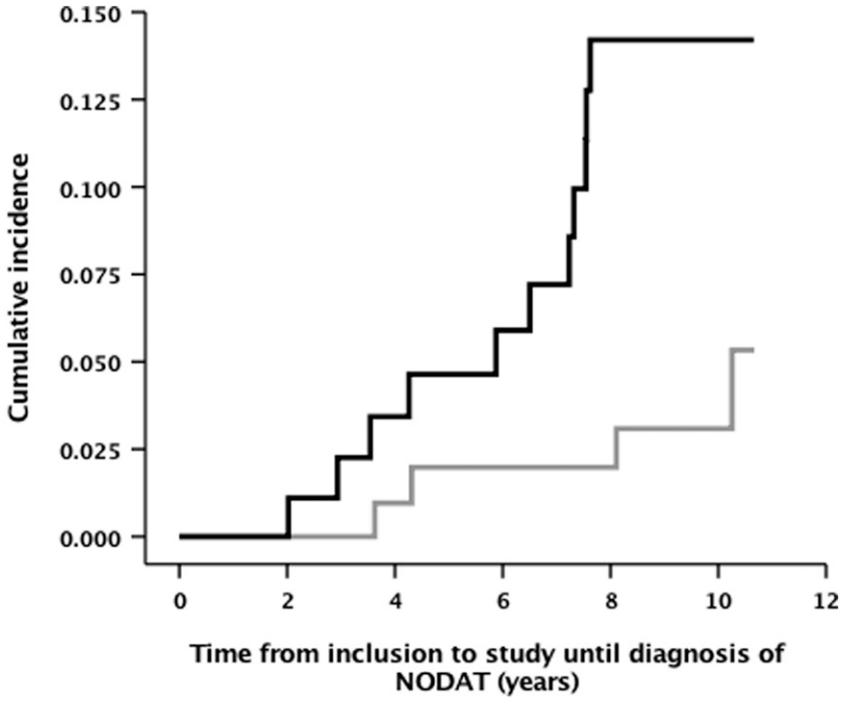

Figure 1—In age- and sex-matched analyses, (corresponding baseline data provided in Supplementary Table 1), statin use is associated with an increased incidence of NODAT in RTRs. Kaplan–Meier curves depicting NODAT incidence according to statin usage status in 95 statin users matched to nonusers for age and sex. Log-rank test, $P = 0.017$.

insulin and HOMA-IR (model 8, $P = 0.008$), family history of diabetes (model 9, $P = 0.036$), or use of immunosuppressive medication (model 10, $P = 0.027$) did not change this association.

CONCLUSIONS

In conclusion, this study demonstrates that statin use in RTRs is prospectively associated with an increased NODAT incidence. This is analogous to previous data reporting that statins are a risk factor for type 2 diabetes development in the general population (3). As NODAT is clearly related to increased graft failure and overall mortality (1,2), special attention seems to be required to screen for NODAT among RTRs using statins. Although current guidelines recommend statin administration to all RTRs to reduce incident cardiovascular disease (CVD) (5), literature supporting this advice is weak. Only one randomized controlled study, the Assessment of Lescol in Renal Transplantation (ALERT) trial, is available with respect to the topic. In ALERT, no significant association was found between statin use and the primary end point, i.e., first occurrence of a major CVD event (8). Post hoc subgroup analyses of ALERT showed a significant reduction in cardiovascular death or nonfatal myocardial infarction, particularly in nondiabetic patients. NODAT risk stratified by statin use was not evaluated (9). A 12-week treatment with rosuvastatin did not change glucose metabolism in a smaller group ($n = 20$) of low-risk RTRs (10). In a retrospective study of 303 RTRs (1-year follow-up; $n = 77$ on statins, $n = 37$ with NODAT) defining NODAT as blood glucose above 126 mg/dL without excluding patients based on HbA_{1c}, multivariate analyses also identified age as a strong NODAT risk factor, next to family history of diabetes, smoking habits, and diuretics (11). Statins were associated with NODAT only in the univariate analyses. Considering the diabetogenic risk of statins, more studies on this topic appear advisable in our view.

The current study is carried out in a large cohort of RTRs. However, it is still from a single center. Power was therefore limited to explore other aspects, e.g., whether a specific statin might confer a higher or lower risk compared with other members of the class. Inclusion began in 2001, which means that the shift in immunosuppression away from primarily using cyclosporin toward tacrolimus is not fully reflected in this study. However, our data might be valuable for current clinical decision making when patients are considered to be switched to cyclosporin due to, e.g., altered glucose metabolism. The inclusion in 2001 of formerly transplanted RTRs likely also explains the relatively high acute rejection rate that we report. Further, standard steroid dosages in our center were on the higher end of the spectrum, which could influence NODAT susceptibility. Additionally, because the prescription of statins was based on clinical grounds, a contribution of such a background risk of NODAT to our results cannot be fully excluded. Further, LDL cholesterol levels upon initiation of statins were not available in this cohort.

In conclusion, multicenter follow-up studies are recommended to confirm our findings and also to identify potential specific biomarkers allowing for an improved risk stratification of RTRs with respect to incident NODAT, specifically in the setting of statin use.

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