Use of statins and the risk of developing pre-diabetes and diabetes: a longitudinal study in individuals aged 40 years or older

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Summary

Background: Statins are the main therapeutic option for the control of dyslipidemias and cardiovascular prevention. However, studies indicate the possibility of the use of statins cause increases in blood glucose levels. **Aim:** The aim of the study was to analyze the use of statin and the risk of developing pre-diabetes (DM) or DM. **Methods:** This was a cohort study conducted with individuals aged 40 years or older, living in a medium-sized municipality in the north of Paraná, Brazil. Data were obtained through individual interviews and laboratory tests in the years 2011 (baseline) and 2015 (follow-up). Dependent variables were the development of DM (yes; no) and the development of pre-DM or DM (yes; no). The independent variable was the use of statins (no use; use only in 2011; use only in 2015; use in 2011 and 2015). Poisson (loglinear) regression analysis was used to calculate the relative risk (RR) and 95% confidence intervals (95% CI) in generalized linear models. **Results:** An association was observed between the use of statins and the incidence of DM (RR 2.89, 95% CI: 1.59-5.24) and the incidence of pre-DM or DM (RR 2.01, 95% CI: 1.39-2.92) for the group of individuals who used statins only in 2015. **Conclusions:** The present study identified an association between the use of statins and the incidence of pre-DM and DM only for those who used them exclusively in 2015.

Key words: Diabetes mellitus, statins, adverse drug reactions.

Resumo

Uso de estatina e risco de desenvolver pré-diabetes e diabetes: um estudo longitudinal em pessoas com 40 anos ou mais

Introdução: As estatinas são a principal opção terapêutica para o controle de dislipidemias e prevenção cardiovascular. No entanto, estudos indicam a possibilidade do uso de estatinas causar aumentos nos níveis de glicose no sangue. **Objetivo:** O objetivo do estudo foi analisar o uso de estatina e o risco de desenvolver pré-diabetes (DM) ou DM. **Métodos:** Estudo de coorte realizado com indivíduos com 40 anos ou mais de idade, residentes em um município de médio porte no norte do Paraná. Os dados foram obtidos por meio de entrevistas individuais e exames laboratoriais nos anos de 2011 (linha de base) e 2015 (acompanhamento). As variáveis dependentes foram o desenvolvimento de DM (sim; não) e o desenvolvimento de pré-DM ou DM (sim; não). A variável independente foi o uso de estatinas (sem uso; uso apenas em 2011; uso apenas em 2015; uso em 2011 e 2015). A análise de regressão de Poisson (log-linear) foi utilizada para calcular o risco relativo (RR) e os intervalos de confiança de 95% (IC95%) em modelos lineares generalizados. **Resultados:** Observou-se associação entre o uso de estatinas e a incidência de DM (RR 2,89, IC 95%: 1,59-5,24) e a incidência de pré-DM ou DM (RR 2,01, IC 95%: 1,39-2,92) para o grupo de indivíduos que usaram estatinas apenas em 2015. Conclusões: O presente estudo identificou associação entre o uso de estatinas e a incidência de pré-DM e DM apenas para aqueles que as usaram exclusivamente em 2015.

Palabras clave: Diabetes mellitus; Estatinas; Eventos adversos.

Resumen

Uso de estatinas y el riesgo de desarrollar prediabetes y diabetes: un estudio longitudinal en personas de 40 años o mayores

Introducción: las estatinas son la principal opción terapéutica para el control de la dislipidemia y la prevención cardiovascular. Sin embargo, los estudios indican la posibilidad de que el uso de estatinas pueda causar aumentos en los niveles de glucosa en sangre. Objetivo: analizar el uso de estatinas y el riesgo de desarrollar prediabetes (DM) o DM. **Métodos:** estudio de cohorte realizado con individuos de 40 años o más, que viven en un municipio de tamaño medio en el norte de Paraná, Brasil. Los datos se obtuvieron mediante entrevistas individuales y pruebas de laboratorio en los años 2011 (línea de base) y 2015 (seguimiento). Las variables dependientes

fueron el desarrollo de DM (sí; no) y el desarrollo de pre-DM o DM (sí; no). La variable independiente fue el uso de estatinas (sin uso; uso solo en 2011; uso solo en 2015; uso en 2011 y 2015). El análisis de regresión de Poisson (log-lineal) se utilizó para calcular el riesgo relativo (RR) y los intervalos de confianza del 95% (IC del 95%) en modelos lineales generalizados. **Resultados:** Se observó una asociación entre el uso de estatinas y la incidencia de DM (RR 2,89, IC 95%: 1,59-5,24) y la incidencia de pre-DM o DM (RR 2,01, IC 95%: 1,39-2,92) para el grupo de individuos que usaron estatinas solo en 2015. **Conclusiones:** el presente estudio identificó una asociación entre el uso de estatinas y la incidencia de pre-DM y DM solo para aquellos que las usaron exclusivamente en 2015.

Palabras clave: Diabetes mellitus, estatinas, evento adverso.

Introduction

Chronic noncommunicable diseases, especially cardiovascular diseases, are the main cause of death in Brazil and worldwide [1]. Among the several factors that influence the occurrence of these diseases, increased levels of plasma lipids should be noted. Evidence consistently shows that lower levels of cholesterol, especially low-density lipoproteins (LDL), have a direct impact on the risk of cardiovascular complications and consequent mortality [2-4].

Currently, the use of statins is the main therapeutic measure, in addition to behavioral measures, to control dyslipidemias, and particularly to decrease LDL levels [3,4]. Statins are lipid-lowering drugs that act by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), a cholesterol-lowering rate-limiting enzyme in cholesterol biosynthesis [5]. The therapeutic use of statins has been validated by several studies that demonstrated the benefit of its use in prevention of cardiovascular events [6-8].

Although statins are effective agents for the treatment of dyslipidemia [5], studies have indicated that their use can be associated with an increased risk of developing type 2 diabetes mellitus (DM) [9-11]. Some studies further suggest that this association varies according to dose, with a higher risk at higher doses [12,13]. The increased incidence of DM is also evident in Brazil, with an expected increase of more than 30% in the next 30 years [14], which may be aggravated owing to the use of statins.

Considering the observations of the studies previously cited and the lack of studies analyzing the Brazilian population, the present study aimed to analyze the use of statin and the risk of developing pre-DM or DM.

Methods

The present study was a longitudinal, observational cohort study that is part of VigiCardio [15], a project examining individuals aged 40 years or older, living in the urban area of the municipality of Cambé, Paraná. This project was developed at two timepoints, 2011 (baseline) and 2015 (follow-up), for which data were collected through interviews and laboratory tests.

The sample of the VigiCardio study considered a margin of error of 3.0%, 95% confidence interval, prevalence of the outcome of 50.0% and increase for losses and refusals of 25.0%, resulting in 1322 people to be interviewed. All census tracts in the urban area of the study municipality were selected and the number of people to be interviewed in each sector was defined according to the proportional distribution of residents by sex and age group. Details of the sample calculation and interviewer selection process are found in another publication [15]. Data were obtained from home interviews. VigiCardio data collection occurred between February and June 2011, totaling 1,180 participants (baseline).

From the VigiCardio population sample, all individuals who were not classified as having DM at baseline (no use of antidiabetic drugs or serum glucose ≤125 mg/dL) [16] and for whom sufficient data were available to infer the presence or absence of pre-DM or DM at follow-up were included in the present study. The fasting blood glucose values proposed by the Brazilian Diabetes Society (pre-DM: fasting glycemia [FG] ≥100 mg/dL and ≤125 mg/dL; DM: FG ≥126 mg/dL) [16] were used to define individuals with pre-DM and DM at follow-up, and use of antidiabetic drugs or insulin was used to define individuals with DM.

Dependent variables were the development of DM (yes; no) and the development of pre-DM or DM (yes; no). The following criteria were considered: without DM in 2011 and classified as DM in 2015 (DM development); without DM or pre-DM in 2011 and classified as pre-DM in 2015 or without DM in 2011 and classified as DM in 2015 (development of pre-DM or DM).

The independent variable was the use of statins, categorized as (i) no use; (ii) use only in 2011; (iii) use only in 2015; (iv) use in 2011 and 2015. The following adjustment variables were used: sex (female; male), age (up to 59 years; 60 years or older), overweight, perception of health status, arterial hypertension, sedentary lifestyle, and increased abdominal circumference. For the overweight, arterial hypertension, sedentary lifestyle, and increased abdominal circumference variables, four categories of analysis were considered: no, only in 2011, only in 2015, and in 2011 and 2015.

The perception of health status was dichotomized as "very good/good" and "normal/bad/very bad," considering the years 2011 and 2015, as described for the previous variables. For the age variable, the data collected in 2011 were considered.

The blood pressure parameters proposed by the Brazilian Society of Cardiology (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) [17] or the use of anti-hypertensive drugs were used to classify individuals with arterial hypertension. At least three blood pressure measurements were performed and the mean of the last two measurements was considered. The cut-off values for abdominal circumference were ≥102 cm for men and ≥88 cm for women [18]. To classify overweight individuals, the cut-off value for body mass index (BMI) was ≥25 kilograms/square meters [19].

The present study was based on data obtained in the VigiCardio project, approved by the Research Ethics Committee of the State University of Londrina with number 0192.0.268.000-10 at baseline and number 39595614.4.0000.5231 at follow-up. All interviewed individuals signed the Informed Consent Form during the two phases of the project.

Statistical analysis

The data of 2011 were entered twice in a database created with the software Epi Info, version 3.5.4, with later corrections of discrepant information. For 2015, the data were partially entered into a Microsoft Excel spreadsheet (Excel version 2010) (entered twice). Some of the 2015 interviews were conducted by directly filling in a form developed exclusively for this collection on an electronic device (tablet). In the present study, the data were later analyzed using R software, version 3.2.3 [20]. The descriptive analysis was performed using absolute and relative frequencies, as well as measures of central tendency (mean and standard deviation [SD]). To calculate the relative risk (RR) and 95% confidence intervals (95% CI), Poisson regression (loglinear) analysis was used in generalized linear models.

Results

The first phase of the VigiCardio project (2011) (baseline) had 1,180 participants, of which only 885 were re-interviewed in 2015, in the second part of the project (follow-up), that is, there were 295 (25%) losses: 108 due to change without possibility of contact, 87 refusals, 51 individuals who died and 49 that were not found after 3 contact attempts on alternate days. In addition, 107 subjects were classified as having diabetes mellitus at baseline and 201 had no serum blood glucose values in 2011 (baseline) or in 2015 (follow-up), and 577 participants were eligible for this study.

A total of 577 eligible individuals were identified, with a mean age of 53.8 years (SD= 9.5) and a higher percentage of women (60.1%) than of men. The incidences of DM and pre-DM in the period of analysis (2011-2015) were 9.9% and 10.9%, respectively. The incidence of DM and pre-DM or DM in relation to the adjustment variables is shown in table 1.

Regarding the use of statins, frequencies of 8.2% (n=47) and 17.0% (n=98) were observed in 2011 and 2015, respectively. It was found that 5.4% (n=31) of participants used statins in 2011 and were still using them in 2015.

An association between the use of statins and the incidence of DM (adjusted RR: 2.89, 95% CI: 1.59-5.24) (table 2) and the incidence of DM or pre-DM (adjusted RR: 2.01, 95% CI: 1.39-2.92) (table 3) was observed, but only for the group of individuals who used statins only in 2015. A statistical power slightly below 80% was observed for analysis of the incidence of pre-DM or DM in individuals who used statins only in 2011 (78.0%) and who used them in 2011 and 2015 (37.0%). For the other groups, the statistical power was above 80.0%.

Table 1. Incidence of DM and pre-DM characterized according to demographic and health conditions (adjustment variables), Cambé, PR, 2011-2015.

Adjustment variables	DM	pre-DM or DM	Total
	n (%)	n (%)	n (%)
Sex			
Female	34 (9.80)	69 (19.88)	347 (60.14)
Male	23 (10.00)	51 (22.17)	230 (39.89)
Age			
Up to 59 years	40 (9.26)	83 (19.21)	432 (74.87)
60 or more	17 (11.72)	37 (25.52)	145 (25.13)
Overweight			
No (2011 and 2015)	2 (1.46)	12 (8.76)	137 (24.12)
Only 2011	1 (5.56)	2 (11.11)	18 (3.17)
Only 2015	3 (5.00)	11 (18.33)	60 (10.56)
In 2011 and 2015	48 (13.60)	89 (25.21)	353 (62.15)

(*Continued*)

Table 1. Incidence of DM and pre-DM characterized according to demographic and health conditions (adjustment variables), Cambé, PR, 2011-2015.

Adjustment variables	DM	pre-DM or DM	Total
	n (%)	n (%)	n (%)
Perception of health status			
Very good or good (2011 and 2015)	16 (6.67)	33 (13.75)	240 (41.74)
Normal, bad, or very bad (only 2011)	10 (11.76)	26 (30.59)	85 (14.78)
Normal, bad, or very bad (only 2015)	4 (5.13)	14 (17.95)	78 (13.57)
Normal, bad, or very bad (2011 and 2015)	27 (15.70)	45 (26.16)	172 (29.91)
Arterial hypertension			
No (2011 and 2015)	6 (3.64)	25 (15.15)	165 (28.80)
Only 2011	2 (5.56)	6 (16.67)	36 (6.28)
Only 2015	5 (4.17)	18 (15.00)	120 (20.94)
In 2011 and 2015	43 (17.06)	68 (26.98)	252 (43.98)
Sedentary lifestyle			
No (2011 and 2015)	7 (7.45)	16 (17.02)	94 (16.35)
Only 2011	6 (7.89)	14 (18.42)	76 (13.22)
Only 2015	11 (13.58)	19 (23.46)	81 (14.09)
In 2011 and 2015	33 (10.19)	69 (21.30)	324 (56.35)
Abdominal circumference			
No (2011 and 2015)	8 (3.62)	28 (12.67)	221 (38.57)
Only 2011	2 (7.14)	3 (10.71)	28 (4.89)
Only 2015	5 (7.04)	12 (16.90)	71 (12.39)
In 2011 and 2015	40 (15.81)	73 (28.85)	253 (44.15)

Table 2. Analysis of association between use of statins and development of DM. Cambé, PR, 2011-2015.

Use of statins	Development of DM		
	n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
No use (2011 and 2015)	6.69	1.00	1.00
Use only in 2011	18.75	2.80 (0.96-8.21)	1.23 (0.31-4.86)
Use only in 2015	28.36	4.23 (2.54-7.06)	2.89 (1.59-5.24)
Use in 2011 and 2015	12.90	1.93 (0.73-5.11)	1.53 (0.59-3.95)

RR= relative risk; CI= confidence interval. RR adjusted for variables: sex, age, overweight, perception of health status, arterial hypertension, sedentary lifestyle, and abdominal circumference.

Table 3. Analysis of association between use of statins and development of pre-DM or DM. Cambé, PR, 2011-2015.

Use of statins	Development of pre-DM or DM		
	n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
No use (2011 and 2015)	17.28	1.00	1.00
Use only in 2011	31.25	1.81 (0.85-3.84)	1.25 (0.53-2.95)
Use only in 2015	41.79	2.42 (1.71-3.42)	2.01 (1.39-2.92)
Use in 2011 and 2015	22.58	1.31 (0.66-2.58)	1.08 (0.56-2.08)

RR= relative risk; CI= confidence interval. RR adjusted for variables: sex, age, overweight, perception of health status, arterial hypertension, sedentary lifestyle, and abdominal circumference.

Discussion

In the present study, an association was observed between the use of statins and the development of DM. However, this association was only statistically significant for the group of individuals who used statins in the follow-up period, but not at baseline (adjusted RR= 2.89, 95% CI 1.59-5.24). A statistical association was not observed in the other two groups that used statins. This situation was also observed for the development of pre-DM/DM (adjusted RR= 2.01, 95% CI 1.39-2.92).

The observed association between the use of statins only in 2015 with the development of pre-DM and DM indicates that glycemic changes should be detected early

in these individuals, especially for a potentially reversible pre-DM condition [21]. As the possible hyperglycemic actions of statins are related to the dose and potency of the drug [22], it is understandable that the association observed among individuals who did not use statins at the end of the follow-up period (2015) was weaker. Among the individuals who used statins during the entire period, however, the non-statistically significant observed association may be due to the low statistical power, since the individuals included in this group are very small (n= 31).

Studies by Rha *et al.* [23] and Yoon *et al.* [10] identified a lower risk of developing DM in three-year (RR 1.99, 95% CI 1.36-2.92) and eighteen-year (RR 1.87, 95% CI 1.43-2.44) study cohorts, respectively. In an additional six-year cohort study, a higher adjusted risk was found for the development of DM (RR 3.31, 95% CI 2.56-4.30) [24]. However, most studies designed to analyze the association between the use of statins and the development of DM have identified lower risks [11, 25] than the afore mentioned ones, including the present study. Yoon *et al.* [10] suggested that the risk of developing DM due to the use of statins may differ in different populations, with a higher risk in Asian and Eastern than Western individuals. However, a study by Currie *et al.* [24], conducted in New Zealand, found a higher risk among New Zealanders. Considering these findings, the different results observed in the present study could be associated with the population (Brazilian), which may have different characteristics from the populations analyzed in previous studies.

Other differences are also observed according to study type. In a population-based study, the occurrence of DM after the use of statins was higher than that in clinical studies that analyzed the action of statins on cardiovascular outcomes, for which the diabetes-promoting effect of these medications may have been underestimated [26]. Meta-analyses have indicated that the incidence of diabetes in individuals who use statins ranged from 9 to 18%, influenced by the differences in types of statins and doses used [12, 27].

Besides the predominance in Asians, it is recognized that the diabetes-promoting action of statins is more pronounced in some risk groups, such as obese and elderly individuals, women, and patients with metabolic syndrome [28]. Therefore, the present analysis was adjusted using a relevant set of variables to minimize their impact on the results obtained.

Although the mechanisms by which statins influence the development of type 2 DM have not been fully elucidated, some studies suggest that the drugs impact insulin sensitivity and pancreatic beta cell function [28]. Given the study results, the possibility should be considered that even individuals who are diagnosed with diabetes or pre-diabetes and require statins could have impaired glycemic control.

The inclusion of pre-DM as an outcome for the use of statins should be noted, as this factor had previously been poorly studied by the authors. Moreover, the analysis of the association in a population-based study in a Brazilian urban population qualifies the results found and permits extrapolation to other similar populations. One limitation of the study was that it did not allow analysis of the exposure period, or of the dose and type of statin used. These variations could influence the diabetogenic effect of the lipid-lowering agents. In addition, as the subgroups exposed to statins were reduced, especially those who used them in 2011 and 2015, the risk measures used did not present the expected results, not confirming the temporal relationship between use of statins and development of pre-DM or DM.

Conclusions

With the results presented in this study, it is possible to conclude that there is an association between the use of statins and the development of pre-DM and DM only among those who used them exclusively in 2015. Still, patients who use these drugs should be closely monitored, with periodic evaluation of serum glucose and, as required, glycated hemoglobin; especially by statins are important pharmacological strategies for the treatment of numerous diseases, especially those related to cardiovascular diseases. However, additional studies, particularly in the Brazilian population and with larger populations, including the type of statin and its dose, are required to confirm such an association in this specific population, especially in a longitudinal design.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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