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DOI: 10.1590/1806-9282.65.1.3

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# Prevalence, treatment, and control of dyslipidemia in diabetic participants of two Brazilian cohorts: a place far from heaven

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<http://dx.doi.org/10.1590/1806-9282.65.1.3>

## SUMMARY

**OBJECTIVE:** Diabetes is one of the leading causes of cardiovascular mortality. Over the last years, mortality has decreased significantly, more in individuals with diabetes than in healthy ones. That is mostly due to the control of other cardiovascular risk factors. The objective of our study was to analyze the dyslipidemia control in two diabetes cohorts.

**METHODS:** Patients from two distinct cohorts were studied, 173 patients from the BHS (Brasília Heart Study) and 222 patients from the BDS (Brazilian Diabetes Study). The data on dyslipidemia control were studied in both different populations. All patients had diabetes.

**RESULTS:** There are significant differences concerning comorbidities between the LDL-C and BDS groups. The average glycated hemoglobin is of 8.2 in the LDL-C > 100 group in comparison with 7.7 and 7.5 in the 70-100 and < 70 groups, respectively ( $p = 0.024$ ). There is a higher percentage of hypertensive patients with LDL between 70-100 (63.9%), when comparing the < 70 and > 100 groups (54.3% and 54.9%, respectively;  $p = 0.005$ ). Diastolic pressure is higher in the group with LDL > 100, with an average of 87 mmHg, in comparison with 82.6 mmHg and 81.9 mmHg in the 70-100 and < 70 groups, respectively ( $p = 0.019$ ). The group with LDL > 100 has the greatest percentage of smokers (8.7%) in comparison with the groups with LDL between 70-100 and < 70 (5.6% and 4.3%, respectively;  $p = 0.015$ ). There is also a difference in the previous incidence of coronaropathy. In the group with LDL < 70, 28.3% of patients had already experienced a previous infarction, compared with 11.1% and 10.6% in the 70-100 and > 100 groups, respectively ( $p < 0.001$ ).

**CONCLUSIONS:** The data in our study have shown that the dyslipidemia control in diabetic patients is inadequate and there is a tendency of direct association between lack of blood glucose control and lack of dyslipidemia control, in addition to the association with other cardiovascular risk factors, such as diastolic hypertension and smoking. This worsened control might be related to the plateau in the descending curve of mortality, and investments in this regard can improve the cardiovascular health in diabetic patients.

**KEYWORDS:** Dyslipidemias. Diabetes mellitus. Risk factors. Targets.

DATE OF SUBMISSION: 16-Oct-2018

DATE OF ACCEPTANCE: 26-Oct-2018

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## INTRODUCTION

Diabetes is a huge cause of morbidity, mortality and economic impact. It affects 415 million individuals worldwide<sup>1</sup>, with an increase in prevalence over the past years, going from 4.7% in 1980 to 8.5% in 2014, most significantly in countries with low and medium income<sup>2</sup>. In Brasil, the estimated prevalence is of 8.1%. It is the direct cause of 6% of all deaths in the country, in addition to contributing to 31% of deaths attributed to cardiovascular disease<sup>3</sup>.

Over the last 30 years, cardiovascular mortality was substantially reduced, more so in diabetic individuals than in healthy ones, reaching a plateau after 2008-2010.<sup>4,5</sup> In large part, this more favorable evolution of the cardiovascular prognosis in diabetic patients was due to an improved response to acute cardiovascular care in this population and also the

improvement in the treatment of comorbidities such as hypertension and dyslipidemia.

The response to the lipid-lowering treatment has been widely demonstrated, and each reduction of 40 mg/dL (1 mmol/L) in LDL cholesterol translates into 20% less incidence of more serious cardiovascular events and 16% less cardiovascular mortality.<sup>6</sup> Interestingly, in a subanalysis of the Improve-IT study, only diabetic patients benefited from the addition of ezetimibe on top of the maximum dose of statin.<sup>7</sup>

Despite the relevancy of the subject, adherence to the lipid-lowering treatment is probably the most significant barrier and must represent part of the explanation for the plateau in the curve of mortality trend over the last decade. However, data on the control of LDL cholesterol in Brasil are very scarce and inconsistent. The most relevant data available on the subject comes from the Elsa study (Longitudinal Study of Adult Health) and suggests that the adequate con-

**TABLE 1:** CHARACTERISTICS OF PATIENTS ENROLLED IN THE BRAZILIAN DIABETES STUDY

	LDL-C, mg/dL			p
	>100	70-100	<70	
<b>N (222)</b>	104 (47%)	72 (32%)	46 (21%)	
<b>Demographics</b>				
Age, years	58.6±6.9	59.8±7.1	61.1±6.5	0.106
Schooling, years	10.8±4.1	10.61±4.7	9.96±4.5	0.538
Men, %	53.8	55.6	73.9	0.058
<b>Medical history</b>				
Previous AMI, %	10.6	11.1	28.3	<0.001
Smokers, % / Former smokers, %	8.7/31.7	5.6/30.6	4.3/28.3	0.015/0.011
Hypertension, %	54.8	63.9	54.3	0.005
<b>Hemodynamics</b>				
SBP, mmHg	149.47±22.0	143.75±20.4	145.71±20.6	0.177
DBP, mmHg	87.09±13.2	82.65±10.2	81.9±12.8	0.019
HR, bpm	78.13±12.5	75.01±11.53	74.33±11.0	0.114
ER, %	57.6±11.6	60.6±9.1	59.4±6.2	0.782
<b>Biochemistry</b>				
Blood glucose, mg/dL	172.6±69.6	163.8±58.4	159.1±54.8	0.439
HbA1c, %	8.2±2.0	7.7±1.4	7.5±1.3	0.024
Creatinine, mg/dL	0.89±0.22	0.88±0.18	0.94±0.20	0.316
HDL-C, mg/dL	42.5±12.4	44.2±13.4	43.0±14.3	0.681
LDL-C, mg/dL	135.4±32.1	88.1±8.0	58.0±10.5	<0.001
TG, mg/dL	234.5±138	158.7±92.6	153.7±156.5	<0.001
PCRus, mg/L	0.42±0.54	0.32±0.32	0.35±0.41	0.343
<b>Treatment</b>				
Simvastatin, %	21	38	53	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; HbA1C: glycated hemoglobin; TG: triglycerides; CRP: ultrasensitive C-reactive protein.

**TABLE 2:** CHARACTERISTICS OF PATIENTS ENROLLED IN THE BRASÍLIA HEART STUDY

	LDL-C, mg/dL			
	>100	70-100	<70	p
<b>N (173)</b>	113 (65%)	37(21%)	23 (13%)	
<b>Demographics</b>				
Age, years	62.24±9.9	64.51±11.4	61.48±10.8	0.441
Schooling, years	7.3±4	7.2±5	7.6±5	0.944
Men, %	67.3	64.9	73.9	0.759
BMI, kg/m <sup>2</sup>	27.7±4	28.2±6	27.4±4	0.726
<b>Medical history</b>				
Previous AMI %	12.4%	27.0%	21.7%	0.093
Smoker, %	69.9	67.6	69.6	0.964
Hypertension, %	29.2	18.9	30.4	0.442
<b>Hemodynamics</b>				
SBP, mmHg	137±30	141±36	128±26	0.317
DBP, mmHg	87±19	86±20	82±19	0.579
HR, bpm	81±17	80±16	72 ±18	0.099
<b>Biochemistry</b>				
Blood glucose, mg/dL	206±87	200±84	191±98	0.741
HbA1c, %	8.1±2.3	8.1±2.0	8.1±1.9	0.983
Cr, mg/dL	1.16±0.35	1.18±0.52	1.15±0.71	0.966
HDL-C, mg/dL	39.0±9.8	37.0±10.4	27.1±10.0	<0.001
LDL-C, mg/dL	140.7±34.9	88.3±8.0	56.7±13.8	<0.001
TG, mg/dL	166.7±73.2	142.2±90.8	175.4±130.1	0.247
PCRus, mg/L	1.39±2.25	2.45±4.04	2.26±4.20	0.120
<b>Treatment</b>				
Simvastatin, %	28.8	27.8	30.4	0.976

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; HbA1C: glycated hemoglobin; TG: triglycerides; CRP: ultrasensitive C-reactive protein.

trol of dyslipidemia in the general population is lower than 10%.<sup>8</sup> However, it is well known that the Elsa population had an educational background different from that of most of the Brazilian population (52.6% with complete higher education). In the diabetic population, data are even more scarce, which has limited the development of public policies that address this group of patients.

The purpose of this study is to analyze data concerning the dyslipidemia control in diabetic patients using the population from two Brazilian cohorts.

## METHOD

The population of this study is composed of individuals from two distinct cohorts, with 173 patients from the BHS (Brasília Heart Study) and 222 patients from the BDS (Brazilian Diabetes Study). There were no patients who participated in both cohorts.

### Brasília Heart Study

The patients included in the BHS were consecutively enrolled provided they presented a diagnosis of infarction with ST-segment elevation admitted within 24 hours of the onset of pain at the Basic Hospital of the Federal District, the largest public hospital of the Federal Capital. A total of 173 patients admitted between 2006 and 2017 were included in the analysis. The inclusion criteria were: (i) less than 24 hours from the onset of the AMI symptoms; (ii) ST-segment elevation of at least 1 mm (frontal plane) or 2 mm (horizontal plane) in two contiguous leads; (iii) evidence of myocardial necrosis due to the rise in CK-MB and troponin; (iv) glycated hemoglobin > 6.5% or a previous diagnosis of diabetes with use of anti-diabetic medication; (v) absence of cognitive incompetence that prevents the verbal response to medical questionnaires or the return to medical consultations. During the evaluation, will be carried out: (i) anthropometry; (ii) analysis of dietary composition through a recall questionnaire; (iii) general medical records; (iv) blood samples for biochemical analysis and separation of plasma and DNA for freezing at -80°C. In the plasma biochemical analysis of the first evaluation will be measured: glycated Hemoglobin, insulin, C-peptide, blood glucose, total cholesterol, triglycerides, HDL cholesterol, high-sensitivity C-reactive protein, urea, and creatinine. This study was approved by the ethics committee of the Federal District Secretariat of Health, and all patients enrolled signed

an informed consent form authorizing the study.

### Brazilian Diabetes Study

The BDS is a cohort formed between 2016 and 2018 with diabetic patients admitted after a campaign in print media, radio, and television. Thus, the population studied is composed of voluntary diabetic individuals assessed in the Clinical Research Center (CPC) of the State University of Campinas (Unicamp). The inclusion criteria were: (i) patients with type 2 diabetes mellitus (DM2), (ii) between 40 and 70 years old, (iii) absence of cognitive incompetence that prevents verbal response to medical questionnaires and the informed consent form. The exclusion criteria were: (i) patients diabetes mellitus phenotypes other than DM2; (ii) insulin-dependent individuals. In the first assessment, the study was explained in detail to the patients, and the informed consent form was presented. Then, the patients' identification and contact information were collected, followed by the medical history and a complete physical examination; the arterial pressure measured while seating and standing, the abdominal circumference, height, and weight were recorded. Finally, the patient's pharmacological characterization was recorded, and a diabetic polyneuropathy assessment conducted, in addition to data concerning the socioeconomic conditions and lifestyle. The research ethics committee of Unicamp approved the study, and all the patients signed the informed consent form in order to be enrolled in the study.

### Statistical analysis

The quantitative data were presented as average +/- standard deviation. Comparison between the groups was carried out using the Student t-test for parametric continuous variables, the Mann-Whitey test for non-parametric continuous variables, and the  $\chi^2$  test for continuous variables. The statistical analysis was performed using the SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

In the Brasília Heart Study, there were no statistically significant differences in demographic factors between the groups with the best and worst dyslipidemia control (age, years of formal education, sex, and body mass index). The average of formal education in the cohort was 7.32 of studying. As for the dyslipid-

emia control, 21% of the patients reached LDL-C < 70 (good), 32% between 70-100 (intermediate) and 47% > 100 mg/dL (inadequate).

As for the prevalence of comorbidities between the LDL-C groups, there was also no statistically significant difference between the prevalence of chronic liver disease and hypertension, and the average glycated hemoglobin in the groups with LDL-C < 70, LDL-C = 70-100, and LDL-C > 100 mg/dL was of 8.1 ( $p = 0.966$ ), which suggests that the adequate control of LDL-C is independent from the adequate control of blood glucose targets.

In the Brazilian Diabetes Study (BDS), there were also no statistically significant differences between the LDL-C groups in comparison with demographic factors. There is a non-significant tendency of a greater number of men in the LDL-C < 70 (73.9%) group in comparison with the 70-100 and > 100 mg/dL groups (55.6% and 53.8%, respectively;  $p = 0.058$ ). Although the average formal schooling in this cohort (10.57 years of studying) is higher than in the BHS cohort, the dyslipidemia control was worse, with only 13% of patients reaching LDL-C < 70 (good), 21% between 70-100 (intermediate), and 65% > 100 (inadequate).

However, there are noteworthy statistically significant differences concerning comorbidities between the LDL-C groups. Concerning diabetes, there was a higher lack of blood glucose control in the group with a greater lack of dyslipidemia control. The average glycated hemoglobin is of 8.2 in the LDL-C > 100 group in comparison with 7.7 and 7.5 in the 70-100 and < 70 groups, respectively ( $p = 0.024$ ). There is a higher percentage of hypertensive patients with LDL between 70-100 (63.9%), when comparing the < 70 and > 100 groups (54.3% and 54.9%, respectively;  $p = 0.005$ ). Diastolic pressure is higher in the group with LDL > 100, with an average of 87 mmHg, in comparison with 82.6 mmHg and 81.9 mmHg in the 70-100 and < 70 groups, respectively ( $p = 0.019$ ). The group with LDL > 100 has the greatest percentage of smokers (8.7%) in comparison with the groups with LDL between 70-100 and < 70 (5.6% and 4.3%, respectively;  $p = 0.015$ ). There is also a difference in the previous incidence of coronary artery disease. In the group with LDL < 70, 28.3% of patients had already experienced a previous infarction, compared with 11.1% and 10.6% in the 70-100 and > 100 groups, respectively ( $p < 0.001$ ). Thus, it is reasonable to conclude that chasing more aggressive targets of LDL-C is more frequent for diabetic patients in secondary prevention than to those on primary prevention.

## DISCUSSION

Our work was one of the few in Brazil that proposed to evaluate the dyslipidemia control in diabetic populations. The results show that in both populations the control is beneath the desired (prevalence of adequate control of 32% in BHS and 13% in BDS) and that the prevalence of dyslipidemia is high.

A similar study was Elsa, composed of public servants from six institutions of higher education and research in Brazil. The prevalence of diabetes, however, was of only 19.1%, and the control with LDL < 70 was reached in 2.5% patients.<sup>8</sup> Another critical difference in this study is the level of formal education, with a greater prevalence of individuals with completed higher education. This suggests a higher socioeconomic level of the participants, with a likely prevalence of patients who already had medical follow-up by private or insurance medical professionals.

The difference in the prevalence of a previous coronary artery disease found in the BDS can be explained by the secondary prevention since patients with a previous ischemic event usually have a more intense and rigorous control of dyslipidemia.<sup>9</sup>

Other findings of the BDS are compatible with previous results in the literature: the patients with worst dyslipidemia control have a higher incidence of smoking<sup>10</sup> in this same population, present a higher diastolic pressure<sup>11-13</sup> and, lastly, which is the purpose of the research, a worse blood glucose control was found in patients with higher levels of LDL<sup>14,15</sup>.

In the Elsa study, it was found that the prevalence, awareness, and control of dyslipidemia were higher in men, black, and with less formal education.<sup>8</sup> In the populations studied in our work, however, we found a higher dyslipidemia control in patients with lower levels of formal education. Again, the greater prevalence of patients with a higher socioeconomic level among the group with higher formal education might suggest a follow-up by private or insurance doctors. In this sense, the guidelines by the Brazilian Society of Endocrinology and Metabolism proposes to identify the cardiovascular risk for each patient, considering that each diabetic individual has a unique risk and, thus, rejecting the theory that everyone has a high cardiovascular risk. In contrast, the guidelines by the Brazilian Society of Cardiology (SBC) suggests strict targets for LDL-C, at < 70 for everyone with high cardiovascu-

lar risk - a group that includes diabetic individuals. This recommendation is based on studies that show a decrease in cardiovascular events in diabetic patients undergoing a strict control of lipids<sup>16-18</sup>.

As limitations, we can mention the small sample of patients in each of the cohorts used in our work in comparison with the Elsa study, for example. Besides, there were no statistically significant associations between the groups of patients of the BHS. Lastly, the inclusion criteria in the cohorts usually selects patients with specific profiles; thus, the data found are not representative of the general diabetic population in Brasil.

In conclusion, there are few data on the dyslipid-

emia control in the Brazilian population, especially in people with diabetes. The data in our study shows that the control is inadequate and that there is a tendency of direct association between the lack of blood glucose control and the lack of dyslipidemia control, in addition to the association with other risk factors, such as diastolic hypertension and smoking. The limited control of dyslipidemia might be related to the plateau in the curve of mortality trend for diabetic individuals over the last decade. Investing in the control of comorbidities, such as dyslipidemia, can potentially prolong survival and translate into improved cardiovascular health for diabetic individuals.

## RESUMO

**OBJETIVO:** O diabetes é importante causa de mortalidade cardiovascular. Nos últimos anos, a mortalidade diminuiu substancialmente, mais em diabéticos do que em não diabéticos, em grande parte devido ao controle de outros fatores de risco cardiovasculares. Nosso estudo tem como objetivo analisar o controle de dislipidemia em duas coortes de diabéticos.

**MÉTODOS:** Foram estudados pacientes de duas coortes distintas, sendo 173 pacientes do BHS (Brasília Heart Study) e 222 pacientes do BDS (Brazilian Diabetes Study). Os dados sobre controle de dislipidemia foram estudados nas duas populações diferentes. Todos os pacientes eram diabéticos.

**RESULTADOS:** Há diferenças significativas em relação às comorbidades entre os grupos de LDL-C no BDS. A média de hemoglobina glicada é de 8,2 no grupo com LDL-C > 100, comparado com 7,7 e 7,5 nos grupos 70-100 e < 70, respectivamente ( $p = 0,024$ ). Há maior porcentagem de pacientes hipertensos com LDL entre 70-100 (63,9%), quando comparado aos grupos < 70 e > 100 (54,3% e 54,9%, respectivamente;  $p = 0,005$ ). A pressão diastólica é mais elevada no grupo com LDL > 100, com média de 87 mmHg, comparado com 82,6 mmHg e 81,9 mmHg nos grupos 70-100 e < 70, respectivamente ( $p = 0,019$ ). O grupo com LDL > 100 tem maior porcentagem de tabagistas (8,7%) quando comparado aos grupos com LDL entre 70-100 e < 70 (5,6% e 4,3%, respectivamente;  $p = 0,015$ ). Há, também, diferença na incidência prévia de coronariopatia. No grupo com LDL < 70, 28,3% dos pacientes já apresentaram infarto prévio, comparados com 11,1% e 10,6% nos grupos 70-100 e > 100, respectivamente ( $p < 0,001$ ).

**CONCLUSÃO:** Os dados do nosso estudo mostram que o controle de dislipidemia em diabéticos é inadequado, e há uma tendência de associação direta entre descontrole glicêmico e descontrole de dislipidemia, além de associação com outros fatores de risco cardiovascular, como hipertensão diastólica e tabagismo. Esse pior controle pode estar relacionado ao platô no descenso da curva de mortalidade, e o investimento nesse quesito pode melhorar a saúde cardiovascular dos diabéticos.

**PALAVRAS-CHAVE:** Dislipidemias. Diabetes mellitus. Fatores de risco. Metas.

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