Factors Predictive of Cardiovascular Disease in Patients With Type-2 Diabetes and Hypercholesterolemia. ESODIAH Study

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Introduction and objectives. We investigated the pattern of cardiovascular disease and the factors that predict such disease in outpatients with type-2 diabetes and hypercholesterolemia.

Methods. This prospective open observational study included outpatients of both sexes (mean age 62 [8] years) with type-2 diabetes and hypercholesterolemia. Clinical manifestations of cardiovascular disease (e.g., angina, myocardial infarction, stroke and peripheral arterial disease), glucose and HbA_{1c} levels, and cardiovascular risk factors were recorded every 4 months throughout the 2-year follow-up period. Overall, 838 patients completed follow-up.

Results. During follow-up, 81 patients (9.6%) presented with a cardiovascular event, nine of which were fatal. Cardiovascular events were more frequent in patients with a history of an ischemic condition than in those without: 58 of 258 (22.5%) and 23 of 579 (4%), respectively ($P<.01$). Previous angina or myocardial infarction was the strongest predictor of cardiovascular risk (relative risk [RR]=4.08, 95% confidence interval [CI] 2.39-6.95), followed by previous stroke (RR=2.96, 95% CI 1.26-6.93), high low-density lipoprotein (LDL)-cholesterol level ≥135 mg/dL (RR=2.79, 95% CI 1.56-5.01), peripheral arterial disease (RR=2.44, 95% CI 1.27-4.68), a high HbA_{1c} level (RR=2.08, 95% CI 1.22-3.57), and obesity (RR=1.69, 95% CI 1.0-2.86).

Conclusions. The incidence of cardiovascular disease in this southern European population of patients with type-2 diabetes and hypercholesterolemia was high. A history of an ischemic condition and a high LDL-cholesterol level during follow-up were the strongest predictors of cardiovascular disease.

Key words: *Diabetes mellitus. Cardiovascular disease. Hypercholesterolemia. Cardiovascular risk factors. Follow-up studies.*

Factores predictivos del riesgo de enfermedad cardiovascular en los pacientes con diabetes tipo 2 e hipercolesterolemia. Estudio ESODIAH

Introducción y objetivos. Evaluar el patrón y los factores predictivos de enfermedad cardiovascular (ECV) en los pacientes ambulatorios con diabetes tipo 2 e hipercolesterolemia.

Métodos. Estudio prospectivo, abierto y observacional en el que se incluyó a pacientes de ambos sexos (62 ± 8 años) con diabetes tipo 2 e hipercolesterolemia. Se registraron las manifestaciones clínicas de ECV, incluidos la angina, el infarto de miocardio, el ictus y la enfermedad arterial periférica; la glucosa, la hemoglobina glucosilada (HbA_{1c}) y los factores de riesgo cardiovascular se evaluaron cada 4 meses durante un período de seguimiento de 2 años, que fue completado por 838 pacientes.

Resultados. En total, 81 pacientes (9,6%) presentaron un episodio de ECV y 9 fallecieron durante el seguimiento. La ECV fue más frecuente en los pacientes con historia previa de enfermedad isquémica que en los pacientes sin ella (58 de 258 [22,5%] frente a 23 de 579 [4%], respectivamente; $p < 0,01$). La angina o el infarto de miocardio previos fueron los predictores más potentes del riesgo cardiovascular (riesgo relativo [RR] = 4,08; intervalo de confianza [IC] del 95%, 2,39-6,95), seguidos del ictus previo (RR = 2,96; IC del 95%, 1,26-6,93), el exceso de colesterol unido a lipoproteínas de baja densidad (cLDL) (≥ 135 mg/dl) (RR = 2,79; IC del 95%, 1,56-5,01), la arteriopatía periférica (RR = 2,44; IC del 95%, 1,27-4,68), el exceso de HbA_{1c} (RR = 2,08; IC del 95%, 1,22-3,57) y la obesidad (RR = 1,69; IC del 95%, 1,0-2,86).

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Conclusiones. La incidencia de ECV en esta población de pacientes del sur de Europa con diabetes tipo 2 e hipercolesterolemia es elevada. El hecho de haber presentado un episodio isquémico previo y el exceso de cLDL durante el seguimiento son los predictores más potentes del riesgo de presentar futuros episodios de ECV.

Palabras clave: *Diabetes mellitus. Enfermedad cardiovascular. Hipercolesterolemia. Factores de riesgo cardiovascular. Estudios de seguimiento.*

ABBREVIATIONS

HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
CI: confidence interval
RR: relative risk

INTRODUCTION

Diabetes mellitus affects approximately 100 million individuals worldwide and it is predicted that there will be an increase of 30% by 2025, due in particular to an increase in the prevalence of obesity and the progressive ageing of the population.[1] Cardiovascular disease is the main cause of morbidity and mortality in patients with type-2 diabetes.[2] In those patients, the risk of death due to ischemic heart disease or stroke is 2 to 3 times greater,[3] and that, along with the high incidence of other macrovascular complications such as ischemia of the lower limbs or amputations implies a significant health burden and an enormous cost to the health care system. Identification of predictors of increased cardiovascular risk in diabetic patients is of particular interest in order to establish more effective preventive strategies.

While it is accepted that diabetic microangiopathy is mainly associated with hyperglycemia, the role of factors associated with the disease is less well understood.[4-6] Thus, the cardiovascular risk attributable to hyperglycemia has yet to be determined and it is also unknown to what extent it is independent of other atherogenic factors.[7-9] Hypercholesterolemia plays a major role in the cardiovascular risk associated with these patients[10]; however, there are other anomalies of lipid metabolism that are more characteristic of diabetes, such as hypertriglyceridemia, high-density lipoprotein cholesterol (HDL-C) deficiency, and alterations in the composition of low-density lipoprotein (LDL) particles, which are smaller, have a higher density, and are more atherogenic.[11,12] It is also not known with any certainty which of these lipid abnormalities best predicts cardiovascular risk in diabetes. The principal aim of this project, which forms part of the ESODIAH study (observational study in diabetic patients with hypercholesterolemia), was to assess predictors of cardiovascular disease in a sample of Spanish diabetic patients with hypercholesterolemia over a 2-year follow-up period. The secondary aims were to describe the incidence of cardiovascular disease in that group and the prevalence of cardiovascular risk factors, along with the level of management of those factors.

METHODS

The ESODIAH study was proposed as a prospective, open, observational, naturalistic study. Between February 1999 and December 2002, 930 patients with type-2 diabetes and hypercholesterolemia were included in the study and followed for 2 years in 26 different hospital lipid and cardiovascular risk units (n=520, 55.9%) and primary care clinics (n=410, 44.1%) throughout Spain, with the exception of the Autonomous Regions of the Balearic Islands, Canary Islands, and Castile-La Mancha.

Inclusion criteria were as follows: type-2 diabetes diagnosed at least 6 months previously according to the criteria of the American Diabetes Association[13] and recorded concentrations in the last 2 years of LDL-C >135 mg/dL or total cholesterol >220 mg/dL when triglyceride concentrations were greater than 400 mg/dL. These lipid concentrations must have been confirmed 3 months after having received dietary advice. The exclusion criteria were as follows: type-1 diabetes, pregnancy, body mass index (BMI) ≥40, excretion of albumin in the urine >300 mg per 24 hours, serum creatinine >1.7 mg/dL, renal disease, severe hepatic disease, or other severe chronic diseases.

The patients who met the criteria for inclusion were invited to participate in the ESODIAH study and signed an informed consent form. In all patients, clinical assessment and laboratory analyses were performed at the baseline visit (visit 1) and subsequently every 4 months over a period of 2 years (visits 2 to 7); 838 patients completed the follow-up period (Table 1). Ischemic manifestations of cardiovascular disease such as angina, symptomatic or silent (electrocardiographic findings) myocardial infarction, transient ischemic attack, stroke, and peripheral artery disease, which included intermittent claudication and revascularization or amputation procedures, were assessed. Recording of these manifestations included medical visits and review of patient charts. For recording of physical activity, patients were considered sedentary if they walked for less than 20 minutes per day, moderately active if they walked for 20 to 60 minutes per day, and active if they walked for more than 60 minutes per day or undertook other sporting activities. The other variables collected in the study were as follows: *a)* history of diabetes, hypercholesterolemia, or heart disease in first-degree relatives; *b)* date of appearance of diabetes and diagnosis

TABLE 1. **Baseline Patient Characteristics***

	Total (n=838)
Sex	
Men	430 (51.3%)
Women	408 (48.7%)
Age, y; n(%) >65 years	62 (8); 354 (42.4%)
Years since diagnosis of diabetes; n (%) ≥6 years	8.4 (7.7); 365 (52.1%)
HbA_{1C} (%); n (%) ≥7.5%	7.24 (1.58); 317 (40.6%)
Body mass index; n (%) ≥30	28.9 (4.0); 302 (36.3%)
Smoking	
Nonsmoker	558 (66.6%)
Smoker	99 (11.8%)
Ex smoker	181 (21.6%)
Physical activity	
Sedentary	265 (31.9%)
Moderate	502 (60.3%)
Active	65 (7.8%)
Systolic blood pressure, mm Hg; n (%) ≥130 mm Hg	145 (19.4); 706 (85.0%)
Diastolic blood pressure, mm Hg; n (%) ≥85 mm Hg	83 (11.4); 370 (44.5%)
Albuminuria, mg/24 h; n (%) ≥30 mg/24 h	41.6 (56.3); 216 (37.2%)
Total cholesterol, mg/dL; n (%) ≥200 mg/dL	246.4 (43.5); 706 (85.2%)
LDL-C, mg/dL; n (%) ≥135 mg/dL	159.6 (37.1); 583 (76.1%)
HDL-C, mg/dL; n (%) <40 mg/dL	49.7 (13.6); 192 (23.2%)
Total cholesterol/HDL-C; n (%) ≥5	5.29 (1.61); 437 (53.2%)
Non-HDL cholesterol; n (%) ≥165 mg/dL	196.8 (44.22); 627 (76.4%)
Triglycerides, mg/dL; n (%) ≥200 mg/dL	186 (148.6); 251 (30.1%)

*LDL-C indicates low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

of hypercholesterolemia; *c)* retinopathy; *d)* diabetic nephropathy; *e)* anthropometric variables (weight, height, waist circumference, and hip circumference), electrocardiogram, and resting systolic and diastolic blood pressure; and *f)* drug treatment at the beginning of the study. In terms of drug treatment at the beginning of the study, 54.9% of patients received hypolipidemic treatment and statins were the most commonly used drugs (47%). Antihypertensive treatment was used in 49.1% of patients, with angiotensin converting enzyme inhibitors the most frequently prescribed (27.8%). Oral antidiabetic treatment was used by 71.9% of patients. The study was approved by the ethics committee of Bellvitge University Hospital and conducted in accordance with the Declaration of Helsinki.

Laboratory analyses included glucose, glycosylated hemoglobin (HbA_{1C}), creatinine, transaminases, creatinine kinase, total cholesterol, HDL-C, LDL cholesterol (LDL-C), triglycerides, complete blood count, albumin excretion in urine, and urine culture and/or sedimentation. Excretion of albumin in urine was measured in 24-hour urine samples, or when such samples were unavailable, recent urine. Samples with positive findings in urine culture or abnormal urine sedimentation were excluded.

Statistical Analysis

An independent company was used to manage the data, which was subject to quality control checks.

Comparisons between patients with and without history of cardiovascular disease were made using the χ^2 test for qualitative variables and analysis of variance for quantitative variables. Bivariate Kaplan-Meier survival analysis was used to select variables for inclusion in a Cox regression model. A *P* value less than .05 was considered significant. Statistical analyses were performed using the statistical package SPSS 10.0 (1999 SPSS Inc, Chicago, Illinois, USA).

RESULTS

Table 1 shows the baseline patient characteristics of the study group. Of all the patients included in the study, 320 (38.8%) had a family history of cardiovascular disease, 494 (58.9%) were hypertensive, 114 (13.8%) had a history of angina, 112 (13.5%) of acute myocardial infarction, 43 (5.2%) of stroke, 65 (7.9%) of peripheral artery disease, and 141 (16.8%) of retinopathy.

During the 2 years of follow-up, 81 patients presented an episode of cardiovascular disease, most as angina (n=33, 41%) or peripheral artery disease (n=21, 26%), and to a lesser extent, as myocardial infarction (n=14, 17%) or stroke (n=13, 16%). Nine of the 81 ischemic episodes were fatal, 8 due to ischemic heart disease and 1 due to stroke. Three patients who did not present an ischemic event died as a result of noncardiovascular disease.

Table 2 shows the baseline characteristics that were significantly different between patients who presented clinical signs of cardiovascular disease during follow-up and those who did not. The former included a higher proportion of individuals aged more than 65 years, with poor management of blood sugar, and the majority of the individuals were sedentary. Likewise, patients who developed ischemic episodes more often had a history of cardiovascular disease and had a higher prevalence of retinopathy and abnormal albuminuria. No significant differences were observed between the groups in terms of sex, obesity (BMI≥30), family history of cardiovascular disease, smoking, systolic and diastolic blood pressure, hypertension, number of years with diabetes (>6 years), cholesterol, LDL-C, HDL-C, ratio of total cholesterol to HDL-C (≥5), non-HDL cholesterol, or triglycerides.

Episodes of cardiovascular disease were more frequent in patients with a history of ischemia than in those

TABLE 2. **Variables for Which Significant Differences Were Observed Between Patients With or Without Episodes of Cardiovascular Disease During Follow-Up**

Baseline	With Cardiovascular Disease (n=81)	Without Cardiovascular Disease (n=757)	*P*
Age, y	63 (8.1)	62 (7.9)	.246
>65	45 (55.6%)	309 (41.0%)	.012
HbA_{1C}, %	7.65 (1.64)	7.20 (1.56)	.015
≥7.5	43 (53.8%)	274 (39.1%)	.011
Physical activity			
Sedentary	38 (46.9%)	227 (30.2%)	.017
Moderate	40 (49.4%)	462 (61.5%)	
Active	3 (3.7%)	62 (8.2%)	
Angina	28 (34.6%)	86 (11.5%)	<.001
Acute myocardial infarction	19 (23.5%)	93 (12.4%)	.006
Stroke	9 (11.1%)	34 (4.6%)	.012
Peripheral artery disease	19 (23.8%)	46 (6.2%)	.001
Retinopathy	22 (27.2%)	119 (15.7%)	.009
Albuminuria, mg/24 h	51.3 (52.7)	40.5 (56.6)	.166
≥30mg/24h	32 (55.2%)	184 (35.2%)	.003

TABLE 3. **Mean Values of Cardiovascular Risk Factors With Significant Differences Between Patients With and Without Episodes of Cardiovascular Disease During Follow-Up***

Follow-Up	With Cardiovascular Disease (n=81)	Without Cardiovascular Disease (n=757)	*P*
HbA_{1C}, %	7.52 (1.43)	7.08 (1.29)	.004
≥7.5%	42 (52.5%)	215 (30.3%)	<.001
Body mass index	29.6 (4.4)	29.0 (5.0)	.284
≥30	38 (46.9%)	263 (35.0%)	.034
Systolic blood pressure, mm Hg	142 (17.8)	142 (14.6)	.821
≥130 mm Hg	66 (81.5%)	624 (83.1%)	.715
Diastolic blood pressure, mm Hg	82 (13.2)	82 (7.5)	.718
≥85 mm Hg	32 (39.5%)	232 (30.9%)	.114
Total cholesterol, mg/dL	238.6 (45.7)	221.4 (29.1)	<.001
≥200 mg/dL	66 (81.5%)	579 (76.8%)	.339
LDL-C, mg/dL	152.2 (36.2)	138.4 (25.2)	<.001
≥135 mg/dL	54 (69.2%)	399 (54.3%)	.012
HDL-C, mg/dL	48.0 (10.3)	51.3 (12.2)	.021
<40 mg/dL	15 (18.5%)	122 (16.2%)	.589
Total cholesterol/HDL-C	5.13 (1.25)	4.53 (1.15)	.001
≥5	40 (49.4%)	230 (30.5%)	.001
Non-HDL cholesterol, mg/dL	190.6 (43.9)	170.2 (29.8)	<.001
≥165 mg/dL	58 (71.6%)	402 (53.3%)	.002
Triglycerides, mg/dL	180 (119.2)	166 (102.6)	.268
≥200 mg/dL	25 (30.9%)	166 (22.0%)	.073
Albuminuria, mg/24 h	66.2 (95.5)	52.7 (89.3)	.268
≥30 mg/24 h	33 (55.0%)	217 (36.9%)	.006

*HDL-C indicates high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

without (58 out of 258 [22.5%] vs 23 out of 579 [4%]; *P*<.01).

Table 3 shows the mean values for the main cardiovascular risk factors over the course of the follow-up period in patients with and without cardiovascular disease. LDL-C, total cholesterol, ratio of total cholesterol to HDL-C, non-HDL cholesterol, and HbA_{1C} were higher in patients with signs of cardiovascular disease, while HDL-C was lower in that group. A higher proportion of patients with cardiovascular disease had a BMI ≥30 and albuminuria ≥30 mg/24 h.

Table 4 shows the significant results obtained in the bivariate Kaplan-Meier analysis of time free of signs of cardiovascular disease. A history of cardiovascular disease or microangiopathy (retinopathy or abnormally high albuminuria) was associated with a shorter period free of disease. Poor control of blood sugar levels, obesity, sedentary lifestyle, hypercholesterolemia, hypertriglyceridemia, increased ratio of total cholesterol to HDL-C, and elevated non-HDL cholesterol during follow-up were also associated with reduced survival free of cardiovascular disease. No significant differences were observed in terms of sex, smoking, years with diabetes, hypertension, total cholesterol, low HDL-C (less then 40 mg/dL in men or less than 50 mg/dL in women), or systolic or diastolic blood pressure.

Cox regression analysis was performed with inclusion of those variables that had previously shown significant differences in the Kaplan-Meier analysis. That analysis revealed that history of ischemic heart disease (angina or infarction) was strongly associated with the risk of presenting an episode of cardiovascular disease and to a greater degree than other variables (relative risk [RR]=4.08; 95% confidence interval [CI], 2.39-6.95) (Table 5). History of stroke (RR=2.96; 95% CI, 1.26-6.93) and excess LDL-C (RR=2.79; 95% CI, 1.56-5.01) were also strongly associated with the risk of presenting ischemic episodes, as was also true, to a lesser extent, of peripheral artery disease (RR=2.44; 95% CI, 1.27-4.68), poor control of blood sugar levels (RR=2.08; 95% CI, 1.22-3.57), and obesity (RR=1.69; 95% CI, 1.002-2.86).

DISCUSSION

This prospective study performed in a group of Spanish diabetic patients with hypercholesterolemia shows that cardiovascular risk, that is, the risk of coronary heart disease, stroke, or peripheral artery disease, is strongly and independently associated with a history of ischemic disease, elevated LDL-C, poor management of hyperglycemia, and obesity.

TABLE 4. **Time Free of Episodes of Cardiovascular Disease by Bivariate Kaplan-Meier Analysis***

	Hazard Ratio	95% CI
Age ≤65 years >65 years	1.757	1.134-2.724
HbA_{1C}† <7.5% ≥7.5%	2.54	1.638-3.940
Obesity: BMI† <30 ≥30	1.633	1.056-2.527
Sedentary No Yes	2.011	1.300-3.111
Retinopathy No Yes	1.936	1.187-3.160
History of angina No Yes	3.798	2.401-6.008
History of infarction No Yes	2.079	1.243-3.477
History of angina and/or infarction No Yes	3.719	2.403-5.754
History of stroke No Yes	2.627	1.313-5.254
History of peripheral artery disease No Yes	4.353	2.600-7.287
LDL-C† <135 mg/dL ≥135 mg/dL	1.895	1.171-3.065
Triglycerides†, <200 mg/dL ≥200 mg/dL	1.648	1.029-2.641
Total cholesterol/HDL-C† <5 ≥5	2.185	1.413-3.378
Non-HDL cholesterol† <165 mg/dL ≥165 mg/dL	2.264	1.397-3.671
Albuminuria† <30 mg/24 h ≥30 mg/24 h	2.037	1.225-3.388

*HDL-C indicates high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CI, confidence interval; BMI, body mass index.
†Mean values during follow-up.

TABLE 5. **Predictors of Cardiovascular Disease by Cox Regression Analysis***

Variable	Exp(B) Relative Risk	95% CI or Exp(B)	*P*
History of angina or infarction	4.075	2.391-6.947	<.001
History of stroke	2.959	1.264-6.927	.012
LDL-C (≥135 mg/dL)†	2.794	1.559-5.008	.001
History of peripheral artery disease	2.439	1.272-4.675	.007
HbA_{1C} (≥7.5%)†	2.085	1.218-3.569	.007
Obesity (BMI ≥30)†	1.693	1.002-2.860	.049

*CI indicates confidence interval; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; BMI, body mass index.
The following variables that were not included in the Cox regression model as they were not statistically significant: triglycerides (≥200 mg/dL), total cholesterol/HDL-C (≥5), non-HDL cholesterol (≥165 mg/dL), albuminuria (≥30 mg/24 h), age (≥65 years), sedentary lifestyle, and history of retinopathy.
†Mean values during follow-up.

The high incidence of ischemic signs of cardiovascular disease in this population from the south of Europe, close to 20% over a period of 2 years, is notable as a result of being within the upper limits of that described in populations from the north of Europe.[14] In addition, this high incidence, which was observed in patients with or without prior history of ischemic episodes, occurred in a health care setting selected on the basis of ability to participate in epidemiologic studies, and therefore, with a quality of care that may have been slightly above average. In the group of patients without prior history of ischemia, 4% presented cardiovascular disease during the 2-year follow-up period. That rate corresponds to a 20% risk of coronary disease over 10 years, according to National Cholesterol Education Program (NCEP) criteria.[15] This finding may be explained by the advanced age of the population, which was selected according to presence of hypercholesterolemia, the relatively long period of time with diabetes, the high prevalence of atherogenic factors, and poor management of those factors. More than three quarters of the patients had increased systolic blood pressure, 76% had LDL-C concentrations greater than 135 mg/dL, a third were obese, and 41% had HbA_{1C} values clearly above the therapeutic range. These data show that, as in other geographic regions,[16] the control of atherogenic factors in diabetic patients is not strictly achieved and highlight the need for improved strategies to achieve the therapeutic targets recommended by the relevant scientific societies and expert panels.[17-19]

Prior history of ischemic heart disease was the strongest predictor of cardiovascular disease and was associated with a 4 times greater risk of presenting new ischemic episodes. Cerebrovascular disease and peripheral artery disease were also associated with increased cardiovascular risk, although to a lesser degree.

In agreement with our results, other studies undertaken in diabetic patients with a history of ischemia also showed increased morbidity and mortality.[20] This highlights the need for strict control of atherogenic factors in these patients.

A consensus is yet to be achieved on whether diabetic patients present an increased risk compared with ischemic patients who are not diabetic. Taking into account the data from various observational and follow-up studies performed in a Finnish population,[21] the guidelines of the NCEP indicate that the cardiovascular risk in patients with type-2 diabetes is equivalent to that of patients with ischemic heart disease,[15] and our results concur with that definition. However, in another study performed in a Scottish population, the patients with infarction presented a greater risk than diabetic patients,[22] a finding that was attributed to a longer period with diabetes than that observed in the patients from the Finnish study. Resolving

this apparent discrepancy is not easy and requires other prospective studies to be undertaken in patients recently diagnosed with type-2 diabetes and myocardial infarction, with adjustment for age and atherogenic factors.

Prior history of microangiopathy, including diabetic retinopathy or pathologic albuminuria, was more common in patients who presented an episode of cardiovascular disease during follow-up. However, microangiopathy was not found to be an independent predictor in the multivariate analysis, in which the remaining cardiovascular risk factors were included. This lack of predictive power has been observed in other studies[23] and may be attributable to the strong association between other atherogenic factors, particularly hyperglycemia, and microangiopathy, a finding that would indicate that it is more a consequence than a cause of arterial disease.

There is increasing evidence, based on pathophysiology and epidemiology as well as clinical trials, indicating that hyperglycemia plays an important role in the origin of cardiovascular disease in diabetic patients.[10,24,25] In addition, in these recent studies it has been demonstrated that HbA_{1C} is an independent predictor of cardiovascular risk, even within concentration ranges that could be considered normal or slightly elevated.[26] In this study, high concentrations of HbA_{1C}, both at baseline and during follow-up, were more common in patients who presented an episode of cardiovascular disease, and values greater than or equal to 7.5% were associated with a 2-fold greater risk of presenting such events. On the other hand, it has been observed that management of hyperglycemia, expressed by a reduction in HbA_{1C} levels, reduces cardiovascular risk.[7,27] In the United Kingdom Prospective Diabetes Study, it was demonstrated that for each 1% reduction in HbA_{1C} the incidence of myocardial infarction or stroke in patients with type-2 diabetes was reduced by 14% and 12%, respectively.[23]

The patients in this study who presented excess LDL-C (≥135 mg/dL) during follow-up had a 3-fold higher risk of presenting an ischemic episode than those with lower concentrations. LDL-C was the lipid variable that showed the greatest predictive power for cardiovascular disease. Triglycerides, HDL-C, the ratio of total cholesterol to HDL-C, and non-HDL cholesterol were not independently associated with cardiovascular risk when LDL-C was included in the statistical model. The predictive power for cardiovascular disease of the triglycerides is disputed, probably as a result of the high within-individual variability and the strong inverse correlation with HDL-C concentration.[28] There is greater consensus on the role of HDL-C and the ratios that relate cholesterol associated with these lipoproteins to total cholesterol[29] as predictors of cardiovascular disease. Two recent studies highlighted the role of the ratio of total cholesterol to HDL-C and of non-HDL cholesterol in the prediction of cardiovascular disease in the diabetic population,[30,31] particularly in patients with hypertriglyceridemia. The third report of the NCEP recognized the significance of non-HDL-C in diabetes and considered it to be a secondary therapeutic target[15]; nevertheless, LDL-C is defined as the main therapeutic target in the management of diabetic dyslipidemia. Increasing amounts of data have demonstrated the benefit of reducing LDL-C through the use of statins in the diabetic population,[29,32,33] even in those individuals with cholesterol levels that are slightly elevated or fall within the reference values. These findings have led to treatment with statins being recommended in all diabetic patients with increased cardiovascular risk, even in the absence of elevated concentrations of cholesterol.[18] In contrast, although hypertriglyceridemia and low HDL-C are more common than excess LDL-C in the diabetic population,[34] less data is available on their predictive power in relation to cardiovascular disease[35,36] or on the benefit of their treatment.[37]

Obesity is a risk factor for the presentation of diabetes and increases the severity of the disease in individuals who are already diabetic, while weight loss improves the management of hyperglycemia.[38-40] The data from this study confirm the importance of obesity as a risk factor for cardiovascular disease in patients with type-2 diabetes, since its predictive power is independent of other atherogenic factors.

CONCLUSIONS

The diabetic population studied presented a high level of short-term cardiovascular morbidity and mortality. The main predictors of presenting the disease were history of ischemia, particularly in the coronary arteries, and excess LDL-C. The high prevalence and inadequate control of hypercholesterolemia and atherogenic factors highlight the need to improve measures to prevent cardiovascular disease in this population.

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