

# Risk factors for coronary heart disease in Brazilian familial hypercholesterolemia subjects

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## Abstract

Heterozygous familial hypercholesterolemia (FH) is characterized by high LDL-cholesterol (LDL-C) levels and increased prevalence of premature coronary heart disease (CHD). However, despite elevated LDL-c the course of CHD manifestations in FH is variable. Our purpose was to evaluate clinical and nutritional parameters in FH subjects presenting or not CHD. Overall 110 consecutive FH patients were interviewed ( $48.9 \pm 16.2$  years, 62% females, LDL-c  $274 \pm 71$  mg/dL). CHD patients ( $n=30$ , 27%) were older ( $55.4 \pm 12.7$  vs  $46.5 \pm 16.8$  years;  $p=0.004$ ) and had a greater prevalence of male gender (60% vs 30%;  $p=0.004$ ), hypertension (90% vs 40%;  $p=0.001$ ), ex-smokers (40% vs 16.2%;  $p=0.008$ ); metabolic syndrome (53.3% vs 27.8%  $p=0.013$ ), low HDL-c (53.3% vs 15% ;  $p=0.001$ ), and sibling history of myocardial infarction (50 % vs 25%,  $p=0.012$ ). No differences were found regarding LDL-c levels, body mass index, waist circumference, food intake quality, and physical activity between the groups. After multivariate analysis the independent determinants of coronary artery disease (CAD) were low HDL-c (OR 8.4; CI 95% 2.7–27.6), male gender (OR 7.3; CI 95% 2.1–24.7), sibling history of myocardial infarction (OR 3.4; CI 95% 1.1–10.5), and age (OR 1.06; CI 95% 1.02–1.1). In spite of its severely increased levels LDL-c was not independently associated with CHD risk in our population. Low HDL-c, male gender and sibling history of CHD were the most important determinants of CHD in our population.

Key words: Heart disease; HDL-cholesterol; Gender; Familial history of myocardial infarction

## Introduction

Heterozygous familial hypercholesterolemia (FH) is characterized by an accelerated atherogenic process with high prevalence of premature coronary heart disease (CHD) and life expectancy reduction<sup>1-3</sup>. However, the course of CHD manifestations in FH is variable with some patients developing events earlier than others notwithstanding similar increased LDL-cholesterol (LDL-c) levels. Therefore other factors might play a role in CHD risk in these subjects. Previous studies in European and North-American populations have shown the influence

of risk factors like age, smoking and hypertension in FH subjects<sup>3</sup>. Furthermore, intra-abdominal visceral fat accumulation and low concentrations of HDL-c and high triglycerides<sup>1,3,7</sup> might also have a role in the early CHD risk. However, the influence of these risk factors characterizing the metabolic syndrome<sup>2</sup> in CHD manifestations in FH is not yet determined.

In addition to these factors, there is a positive relationship between saturated and trans fatty acids as well as cholesterol intake and increase of LDL-cholesterol concentrations<sup>8</sup>. On the other hand mono- and polyunsaturated

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fats as well as increased dietary fiber are related to the reduction of such concentrations<sup>3,8</sup>. The identification of such clinical and nutritional risk factors are fundamental because patients with identical genetic mutations may present different clinical manifestations in different ages<sup>1,3-7</sup>.

Due to the shortage of information on this interaction in Latin American populations especially the Brazilian population, the objective of our study was to evaluate clinical and nutritional profile of patients with FH with or without CHD.

## Methods

This is a cross-sectional study conducted between November 2003 and May 2005 that was approved by the Ethical and Scientific Commission of the Heart Institute (InCor - HC/FMUSP) of the University of Sao Paulo Clinics Hospital. An informed consent was obtained from all participants.

We evaluated 110 FH patients aged over 18 years, diagnosed according to the Dutch Lipid Clinic Network criteria<sup>9</sup> that had being followed-up at the Lipid Clinic of the InCor. Patient characteristics as well as laboratory values were ascertained by both medical record evaluation and interviews. Patients were divided according to the presence ( $n=30$ , 27%) or not of CHD ( $n=80$ , 63%) defined as previous myocardial infarction (MI), coronary artery bypass grafting surgery (CABG) or angioplasty. CHD was considered premature if occurred before 55 years for men and 65 years for women<sup>10</sup>. The metabolic syndrome was diagnosed according to the ATP III criteria<sup>2</sup>. Smoking habit was considered present if the patient smoked a cigarette within the last six months<sup>11</sup>. The diagnosis of diabetes and hypertension were extracted from patient's records. We also considered the average blood pressure measurements of the last 3 medical consultations available at the medical records. Laboratory examinations (fasting plasma lipids and glucose) were obtained from patient's medical records. For each individual, baseline (before the beginning of statin treatment) as well as current examinations (the last ones available at the time of the interview) were registered. Physically active individuals were considered the ones that practiced any type of physical activity for at least 45 minutes, three times a week<sup>12</sup>.

The weight and height were measured by the Body Mass Index (BMI) calculation, for the classification of the nutritional condition<sup>13</sup>.

Waist circumference was measured by the height of the umbilical scar, being the values of normality divided, according to the risk of metabolic complications associated to obesity. The women with measures between 80 cm and 88 cm, and the men with measures between 94 cm and 102 cm were considered as *enhanced risk*. Women

with values  $>88$  cm and men  $>102$  cm were considered as *very much enhanced risk*<sup>2</sup>.

The food intake was evaluated by the food frequency questionnaire (FFQ)<sup>14</sup>, which is made up of foods rich in fats and dietary fibers. This questionnaire utilizes scores such as evaluation methods, and classifies the fat intake as minimum ( $\leq 17$ ), low (18–21), relatively high (22–24), high (25–27), and very high ( $>27$ ). The classification of the dietary fibers intake was defined as low ( $<20$ ), regular (20–29), and adequate ( $\geq 30$ ).

Obtained scores were converted into quantities of total fats (g and %), saturated fats (g), dietary cholesterol (mg), and food fibers (g), by means of equations which measure the daily food intake of such nutrients<sup>15</sup>.

Patients were asked about previous nutritional guidance, and registration of further consultations with dieticians was verified on patients' medical records.

Quantitative variables were described as minimum and maximum values, and the average of pattern diversions was calculated. For qualitative variables, absolute and relative frequencies were calculated.

In equality hypothesis analysis of average between the two groups, the Student's *t* test was used. When the supposition of normality of the data was rejected, Mann-Whitney's test was utilized<sup>16</sup>. In order to test homogeneity of the groups in relation to the proportions, the chi-square test was used, or Fisher's<sup>16</sup> exact test, when is indicated when expected frequencies lower than 5 occurred. A multivariate logistic model was used to evaluate the influence of risk factors other than LDL-c in the presence of CAD<sup>17</sup>.

## Results

One hundred ten heterozygous FH patients, 68 (61.8%) women, with  $48.9 \pm 16.2$  years-old, were studied. Table 1 shows the clinical characteristics of FH with and without CHD. Thirty (7.3%) individuals, had diagnosed CHD, being considered a premature event in 96.7% of the cases. Out of these patients, 21 (70%) suffered acute myocardial infarction (AMI) at  $41.8 \pm 8.6$  years ( $39.7 \pm 8.2$  years for men and  $45.0 \pm 8.8$  years for women), 17 (56.6%) underwent myocardial revascularization (MR) at  $47.4 \pm 9.6$  years of age, and angioplasty was conducted in 11 (36.6%) at  $43.6 \pm 8.5$  years.

Twenty two (73.3%) patients of CHD group and 45 (56.9%) patients without CHD ( $p=0.117$ ), had a family history of premature CHD. The mostly affected relatives were the relative (53.3% vs 48.7%;  $p=0.669$ ), but there was only difference related to the sibling history of AMI (50.0% vs 25.0%;  $p=0.012$ ).

Table 2 shows the laboratory values of individuals with

**Table 1. Clinical characteristics of the participants of the study with and without coronary heart disease (CHD).**

Variable	Group				P value
	With CHD (n=30)		Without CHD (n=80)		
	n	%	n	%	
Age (years)	55.4±12.7		46.5±16.8		0.004
Sex					
Male	18	60.0	24	30.0	
Female	12	40.0	56	70.0	0.004
Hypertension	27	90.0	32	40.0	0.001
SBP (mmHg)	132±14		136±17		0.188
DBP (mmHg)	82±7		86±10		0.007
Diabetes mellitus	8	26.6	9	11.2	0.072
Metabolic syndrome*	16	53.3	22	27.8	0.013
Smokers	4	13.3	9	11.2	0.748
Ex-smokers	12	40.0	13	16.2	0.008
Smokers + Ex-smokers	16	53.3	21	26.2	0.007
Low HDL-c (%)	16	53.3	12	15.0	0.001
Body mass index (BMI (kg/m <sup>2</sup> ))	27.5±4.0		26.9±4.8		0.514
Waist circumference (cm)	96.2±11.0		93.1±12.8		0.241
Regular practice of physical exercise	4	13.3	22	27.5	0.119

\*variable analysed in 109 patients due to unavailability of data.

**Table 2. Evolution of basal and current laboratory exams of study subjects with and without CHD.**

Parameter (mg/dL)		Group		P value
		With CHD	Without CHD	
Blood glucose	Basal	102±12	97±14	0.146
	Current	101±11	97±14	0.181
Total cholesterol	Basal	348±82	353±70	0.736
	Current	261±92	260±67	0.971
LDL-c	Basal	271±79	276±69	0.729
	Current	183±86	184±62	0.948
HDL-c	Basal	43±17	51±13	0.014
	Current	45±12	54±13	0.004
Triglycerides	Basal	181±97	131±55	0.011
	Current	160±80	111±53	0.008

and without CHD. Baseline values of glucose, total cholesterol, and LDL-c did not differ between the groups. CHD patients presented lower baseline and current concentrations of HDL-c and higher triglycerides levels.

The number of patients using lipid lowering drugs did not differ between the groups (96.6% vs 85.0%; p=0.109). Table 3 shows LDL-c goal attainment according to risk in both groups. Low proportions of subjects with LDL-c within recommended values were observed in both groups.

No differences in food intake assessed by means of scores was found between the groups, either for total fat intake (12.0±5.8 vs 13.4±6.7; p=0.391), or for the dietary fiber intake (22.0±5.3 vs 21.9±4.9; p=0.84). When the scores obtained were converted into the total quantity of fat consumed, the average intake was of 66.0±15.1 g for CHD patients and 72.7±16.0 g for no CHD (p=0.05) subjects, the percentages of fat intake were respectively 27.9% and 29.4% (p=0.07). The saturated fat intake was

**Table 3. Distribution of the participants of the study with and without CHD and targets of LDL-c reached.**

Group	Targets of LDL-c (mg/dL)									
	≤100		≤130		≤160		>160		Total	
	n	%	n	%	n	%	n	%	n	%
With CHD	2	8.0	6	24.0	6	24.0	11	44.0	25	30.5
Without CHD	1	1.7	12	21.0	13	22.8	31	54.4	57	69.5
Total	3	3.6	18	21.9	19	23.1	42	51.2	82	100

Value of p=0.577.

**Table 4. Odds ratio (OR) and Confidence Interval (CI 95%) for the presence of CHD.**

Variable	Univariate			Multivariate		
	OR	CI 95%	P value	OR	CI 95%	P value
Age	1.04	1.01–1.07	0.012	1.06	1.02–1.1	0.002
Male sex	3.50	1.46–8.38	0.005	7.3	2.1–24.7	0.001
Hypertension	13.50	3.78–48.26	<0.001	–	–	–
Diastolic blood pressure	1.50	0.64–3.52	0.351	–	–	–
Metabolic syndrome	2.96	1.24–7.07	0.014	–	–	–
Ex-tobacco smoking	3.21	1.34–7.69	0.009	–	–	–
Low HDL-c	6.48	2.52–16.65	<0.001	8.6	2.7–27.6	<0.001
Sibling with myocardial infarction	3.00	1.25–7.21	0.014	3.4	1.1–10.5	0.028

of  $18.5 \pm 5.4$  g vs  $18.7 \pm 6.4$  g ( $p=0.889$ ), and cholesterol was of  $200.5 \pm 52.9$  mg vs  $196.6 \pm 66.5$  mg ( $p=0.772$ ) for patients with or without CHD, respectively.

No significant differences were observed between the groups regarding quantity in grams of dietary fiber intake:  $23.1 \pm 4.9$  g vs  $22.8 \pm 4.1$  g;  $p=0.781$  respectively for CHD and non CHD subjects.

As far as previous nutritional guidance is concerned, 14 (46.7%) coronary patients, and 38 (47.5%) non-coronary ones had already received previous nutritional guidance. For both groups there was no correlation between fat intake and dietary fiber intake, and the consultation with a dietician.

Table 4 shows the parameters associated with the presence of CHD after multivariate logistic regression: age, male sex, diastolic blood pressure (DBP), metabolic syndrome (MS), ex-tobacco smoking, low HDL-c ( $<40$  mg/dL), and sibling history of AMI.

Arterial hypertension was associated with CHD in univariate analysis; however, due to problems in the sampling size, it had to be excluded from the multivariate logistic regression model. On account of this, this parameter was analyzed individually. The univariate analysis showed that hypertensive patients had 13.5 times more chance of pre-

senting CHD. Multivariate regression analysis showed that low HDL-c, male sex, sibling history of AMI, and advanced age were predictors of CHD.

## Discussion

Heterozygous FH is a disease characterized by high LDL-c and early onset of CHD. In addition to high LDL-c values, other risk factors play an important role in the development of atherosclerosis in this population. The course of CHD is variable and can be influenced by the type of genetic mutation, gender, classical risk factors, and risk markers for atherosclerosis<sup>6</sup>. Our study showed that hypertension, low HDL-c, male sex, sibling history of myocardial infarction, and advanced age were predictors of CHD in Brazilian FH subjects.

CHD prevalence found in our population (27.3%) was similar to the US FH population (26%)<sup>10</sup>. Studies developed in Canada<sup>6</sup>, Holland<sup>5,18</sup>, and England<sup>19</sup> showed a higher prevalence of CHD. The association of older with CHD was noticed by other authors<sup>5,18,19</sup>, however, since sudden death at an early age can be the first manifestation of CHD in FH subjects, the importance of other risk factors in CHD development might have been underes-

estimated. In our population, just like in other studies<sup>10,18,19</sup>, male sex was considered a determining risk factor for the development of CHD.

There was a high prevalence of family history of CHD in our population. Family history of premature CHD was similar between the CHD groups and non-CHD groups. The most frequent type of event was myocardial infarction in both groups. The presence of siblings who presented a myocardial infarction was an independent risk marker for CHD. This condition enhanced CHD risk almost 3.5 times. Recently, Nasir et al.<sup>20</sup> showed that the presence of CHD in siblings was the major determinant for the identification of subclinical atherosclerosis in non-FH subjects. The sibling to sibling relationship, for a number of coronary risk factors, is greater than the parents-children relationship, since, in addition to common genetic factors, there are some environmental aspects involved in these relationships between closer siblings.

Similarly to our results, the positive association between hypertension and development of CHD in individuals with FH has been observed<sup>5,18</sup>. However, the prevalence of hypertension in the Dutch population was of only 17%<sup>18</sup>, against 90% in our study. There is some evidence that hypercholesterolemia might predispose to hypertension, since it modifies endothelial function. We have previously shown that hypercholesterolemia leads to an increase of blood pressure in normotensive young FH subjects submitted to isocapnic hypoxia<sup>22</sup>; however, this response is abolished after the LDL-c lowering with the use of high doses of simvastatin<sup>23</sup>. Sposito et al.<sup>24</sup> demonstrated that cholesterol reduction potentiates the hypotensive effect of angiotensin-converting enzyme inhibitors.

Smoking is frequently seen in FH subjects<sup>6,10,18,19,25</sup>. However, in the present study, as well as in the study of De Sauvage Nolting et al.<sup>5</sup>, no significant correlation was found between tobacco smoking and the presence of CHD. This can be related to the lack of statistical power by the reduced number of smokers in the CHD group<sup>18</sup>.

There is evidence that FH individuals with CHD manifestation frequently present significantly reduced HDL-c levels and high triglycerides<sup>5,6,10,18,27</sup> as seen in our study. Defecting removal from plasma of chylomicron and VLDL remnants particles can directly influence the HDL-c concentrations in this population<sup>27</sup>. Higher concentrations of CETP (*Cholesteryl Ester Transfer Protein*) have also been associated with low HDL-c and higher triglycerides in FH subjects<sup>28</sup>.

Obesity, especially visceral obesity, is strongly associated with atherosclerosis<sup>2</sup>. However, we did not find difference in BMI between CHD and non-CHD groups. Furthermore no differences were found in visceral fat dis-

tribution between the groups. Differently, Hopkins et al.<sup>10</sup> found higher waist values in US FH subjects presenting CHD in comparison with non-CHD subjects. Whether this is due to ethnic differences between Brazilian and US population remains to be determined<sup>29</sup>.

Previous studies have already correlated increased saturated fat consumption with the presence of CHD<sup>8</sup>. Also, a reduced intake of fruits and vegetables, foods rich in dietary fibers, has been inversely associated with the risk of myocardial infarction<sup>30</sup>. The fat and dietary fiber intake of the studied population was considered satisfactory, being in accordance with the nutritional recommendations for this population<sup>2,3</sup>. However, one important limitation of our study was that almost half of the patients had already received nutritional guidance prior to this study, a finding that might have influenced in the food choices of the population.

The greatest limitation of this study was its retrospective nature, a finding that might explain the lack of association between smoking and CHD in our population, however this was the first report correlating risk factors other than increased LDL-c levels with the presence of CHD in Brazilian FH subjects. Risk factors other than LDL-C mainly, male gender, low HDL-c, history of CHD in a sibling and hypertension must alert for a higher risk subject. Further prospective studies are necessary in the Brazilian population.

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