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Risk factors for atherosclerosis in children and adolescents with family history of premature coronary artery disease

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Abstract

Objectives: To identify the prevalence of dyslipidemia in a group of 109 children and adolescents with a family history of premature coronary artery disease and to investigate the association between dyslipidemia and other risk factors for atherosclerosis.

Methods: Total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, body mass index, blood pressure, physical activity, smoking, *per capita* income and maternal schooling were investigated.

Results: Total cholesterol and LDL-C levels were higher than desirable in 27.5% and 19.3%, respectively, of our patients; 13.8% had lower HDL-C values and 13.0% presented hypertriglyceridemia. Obesity and excess weight were observed in 25.7% of the cases. Out of these, 57.1% had abnormal lipid values. Dyslipidemia was observed in 38.5%, either alone or in combination with other risk factors. Smoking was observed in 3.6%, hypertension in 2.7% and physical inactivity in 72.5%. There was no relationship between dyslipidemia and *per capita* income, maternal schooling and physical inactivity. However, obesity and excess weight were identified as significantly associated with the occurrence of dyslipidemia (p = 0.02; odds ratio = 2.82, 95% CI = 1.6-6.81).

Conclusion: In children and adolescents with a family history of premature coronary artery disease, early identification of the risk factors for atherosclerosis is essential to allow the implementation of preventive measures.

J Pediatr (Rio J). 2004;80(2):135-40: Hypercholesterolemia, dyslipidemia, coronary artery disease, atherosclerosis, lipoproteins.

Introduction

Coronary artery disease (CAD), secondary to atherosclerosis stands out as the primary cause of morbidity and mortality in modern industrialized societies. In the United States it was responsible for a third of all deaths in 1998.[1] Brazilian data reveals that the situation in our country is similar. In the same year, 32.6% of deaths from known causes were the result of diseases of the circulation.[2]

Clinical manifestations of coronary artery disease, such as myocardial infarction, stroke and peripheral vascular disease generally have onset from middle age onwards. However, studies indicate that the atherosclerotic process begins to develop during childhood. Fatty streaks, precursors to atherosclerotic plaques, begin to appear on the *tunica intima* of the aorta at three years of age[3] and on the coronary arteries during adolescence, progressing significantly during the thirties and forties.[4] Development of symptomatic CAD has been correlated with atherosclerosis risk factors. Among the most important of these factors are a family history of CAD, dyslipidemia, arterial hypertension, diabetes mellitus, obesity, smoking and a sedentary lifestyle.[5,6]

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Research has documented the association between a family history of CAD and the presence of atherosclerosis risk factors in children and adolescents.[7-9] It is believed that the occurrence of CAD in ancestors younger than 55 or 65 for men and women respectively, termed premature CAD, confers a significant risk for the disease.[10,11]

Dyslipidemia is a condition in which there are abnormal lipid or lipoprotein concentrations in the blood and is a risk factor for the development of atherosclerosis complications. The correlations between elevated serum total cholesterol (TC) levels, particularly low density lipoproteins (LDL-C) and CAD have been well documented for foreign populations, as has the association between reduced high density lipoprotein concentrations and CAD.[12,13] Many different studies have related childhood cholesterol concentrations with those found in adultyhood.[14,15]

In our country there have been few studies[16-18] discussing the association between dyslipidemia prevalence and other atherosclerosis risk factors in children and adolescents with family histories of premature CAD. This being the case we performed assays of the serum concentrations of TC, LDL-C, HDL-C and triglycerides (TG) from a sample of children and adolescents with family histories of CAD manifesting before 55 for men and 65 for women and evaluated their relationship with CAD risk factors.

Patients and methods

During the period between March 1998 and February 2000 109 children and adolescents were studied. They were all registered at the of the Instituto da Criança Nutrition and Metabolism Unit at the Hospital das Clínicas (HC) of the Medical Faculty of the Universidade de São Paulo (FMUSP) and had been referred from the Instituto do Coração at the HC of the FMUSP as belonging to a high-risk group for atherosclerosis, having ancestors who had contracted premature CAD.

Children and adolescents, resident in the city of São Paulo, older than two years and younger than twenty and whose parents or grandparents had undergone myocardial revascularization surgery, at ages below 55 for men and 65 for women, at the Instituto do Coração of the HC at the FMUSP were included in the study.

Exclusion criteria were diabetes mellitus, hypothyroidism, nephrotic syndrome, chronic renal failure, chronic cholestatic liver diseases or use of corticosteroids, beta-blockers, anabolic steroids or contraceptives.[11]

This was a cross-sectional study evaluating socio-economic variables (number of years the mother spent at school and family income), physical activity, smoking, weight, height and arterial blood pressure.

Each child or adolescent's body mass index (BMI), expressed in kg/m^2, was calculated. Using the National Center for Health Statistics (NCHS)[19] BMI for age and sex curves as reference values, we investigated obesity (BMI equal to or greater than the 95th percentile), overweight (BMI equal to or greater than the 85th percentile but less than the 95th), normal weight (BMI greater than or equal to the 5th percentile and below the 85th percentile) and underweight (BMI less than the 5th percentile). We defined both overweight and obesity as excessive weight.

Systolic and diastolic pressures were considered normal when below the 95th percentile, in accordance with the Report of the Second Task Force on Blood Pressure Control in Children (1987).[20]

Venous blood samples were collected after a minimum of 12 hours fasting for serum concentrations of TC, LDL-C, HDL-C and TG to be tested. Assays were performed at the Central Laboratory Central of the HC at the FMUSP following routine procedures. Reference values were taken from the National Cholesterol Education Program[10] recommendations as referred to be the Third Brazilian Directives on Dyslipidemia[11] (Table 1). In cases of abnormal results tests were repeated and an average taken of the two results.

Table 1 - Reference values for lipids of children and adolescents between 2 and 19 years old[20]

Lipids	Age (years)	Values (mg/dl) Normal	Threshold	Abnormal
TC *	2–19	< 170	170–199	≥ 200
LDL-C †	2–19	< 110	110–129	≥130
HDL-C ‡	< 10	≥ 40		
	10–19	≥ 35		
TG §	< 10	≤ 100		> 100
	10–19	≤ 130		> 130

* TC = total cholesterol.
† LDL-C = low density lipoprotein cholesterol.
‡ HDL-C = high density lipoprotein cholesterol.
§ TG = triglycerides.

Depending on laboratory results, dyslipidemia was classified as: 1) isolated hypercholesterolemia (elevated TC only, generally due to increased LDL-C); 2) isolated hypertriglyceridemia (elevated TG values only); 3) mixed hyperlipidemia (elevated TC and TG values); 4) reduced HDL-C in isolation or in association with increased LDL-C and/or TG.[11]

The physical activity variable was divided into the following categories: daily physical activity, twice or thrice a week, occasionally and no physical activity whatsoever. Adolescents that reported smoking at least five cigarettes per day were classed as smokers.[16] Family income was measured in multiples of the national minimum salary *per capita* per month. Maternal education was split into two categories: those who had not passed

the seventh grade and those who had completed from the eighth grade onwards.

Either Fisher's exact test or the chi-square test were applied, as appropriate, to measure the associations between variables. Risk was estimated using odds-ratios, taking dyslipidemia as the dependant variable. Significance was set at 5% ($p < 0.05$). All calculations were performed using GraphPad InStat version 3.01 for Windows 95 by GraphPad Software Inc. (San Diego, CA, USA).

The research project was approved by the institution's Research and Ethics Commission. All parents or legal guardians of participating children and adolescents signed an informed consent form having been instructed on the objectives and methods of the study and the laboratory tests involved.

Results

Forty-seven point seven percent of the 109 participating children and adolescents were male while 52.3% were female. Their ages varied from 2.1 to 19.6 years, giving a mean average of 12.2 years±4.9 years and a median of 12 years.

Mean averages, standard deviations, medians and limits of variance for the serum levels of TC, LDL-C, HDL-C and TG are laid out in Table 2. Table 3 shows the patient distribution according to reference values for TC, LDL-C, HDL-C and TG concentrations. Observe that 72.5%, 20.2% and 7.3% of the children and adolescents presented TC serum levels considered desirable, borderline and elevated, respectively. Low density lipoprotein levels were desirable in 80.7%, borderline in 12% and elevated 7.3% of cases. Two patients with elevated LDL-C levels exhibited values between 160 and 189 mg/dl, which is considered excessive for individuals more than 20 years old.[11] Desirable HDL-C levels were encountered in 86.2% of the sample and undesirable in 13.8%. Triglyceridemia was normal in 87.2% of cases and elevated in 12.8%, including four patients (3.6% of the sample) who exhibited levels above the level considered high-risk for adults ($\geq$ 200 mg/dl).[11]

Across the series as a whole, 20.1% of patients presented isolated hypercholesterolemia, 0.9% isolated hypertriglyceridemia, 3.7% mixed hyperlipidemia and 13.8 % had reduced HDL-C levels, in isolation or in combination with increased LDL-C and/or TG. Thus, of the total of 109 children and adolescents with family histories of premature CAD, 42 (38.5%) presented dyslipidemia (Figure 1).

An analysis of BMI values revealed that 10.1% of the children and adolescents were obese , 15.6% presented overweight, 66.9% had normal weight and 7.4% were underweight. Lipid abnormalities were present in 57.1% (16/28) of the excess weight cases (overweight and obese) and 32% (26/55) of those whose weight was normal or who were underweight. We observed a significant association between excess weight and dyslipidemia ($p = 0.02$; odds-ratio 2.82; 95% CI = 1.16-6.81).

Information on family income was forthcoming in 104 cases and revealed that 76% of the families earned less than two minimum salaries *per capita*, per month. Fifty-two percent of the mothers had not completed schooling beyond the seventh grade while 48% had completed at least the eighth grade. Only 27.5 % (30/109) of the children and adolescents practiced physical activity either daily or two or three times a week. No associations were observed between family income, maternal education or physical activity and dyslipidemia.

Three point six percent of the patients (4/109) had a smoking habit and 2.7% (3/109) systolic arterial hypertension. Since both the number of patients who smoked and the number with arterial hypertension were small, it was not possible to assess any possible association between these factors and dyslipidemia.

Table 2 - Lipid values of 109 children and adolescents with family history of premature CAD

Lipids	Mean±SD*	Median	Limits of variance
TC †	155.4±26.6	151	106–230
LDL-C ‡	92.0±24.7	92	45–184
HDL-C §	48.8±13.6	47	21–98
TG ¦	78.4±50.1	65	27–362

* SD = standard deviation.
† TC = total cholesterol.
‡ LDL-C = low density lipoprotein cholesterol.
§ HDL-C = high density lipoprotein cholesterol.
|| TG = triglycerides.

Table 3 - Distribution of percentage of 109 children and adolescents with family history of premature CAD according to the reference values for lipids of patients between 2 and 19 years old[20]

Lipids	Values (mg/dl)	n	%
TC *	Normal	79	72.5
	Threshold	22	20.2
	Elevated	8	7.3
LDL-C †	Normal	88	80.7
	Threshold	13	12.0
	Elevated	8	7.3
HDL-C ‡	Normal	94	86.2
	Elevated	15	13.8
TG §	Normal	95	87.2
	Elevated	14	12.8

* TC = total cholesterol.
† LDL-C = low density lipoprotein cholesterol.
‡ HDL-C = high density lipoprotein cholesterol.
§ TG = triglycerides.

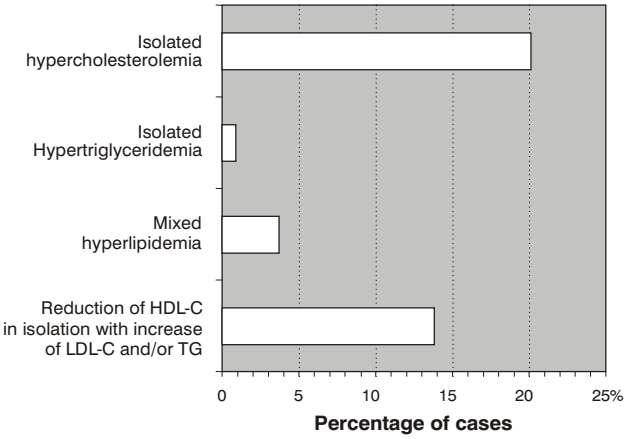

Figure 1 - Distributuin of percentage of children and adolescents with family history of premature CAD and lipid abnormalities according to the laboratorial classification of dyslipidemia[11]

Table 4 shows that 12.8% of the children and adolescents presented just one atherosclerosis risk factor and that 14.6%, 12.8% and 0.9% presented two, three and four factors, respectively, in combination with their family history of CAD. It was observed that the prevalence of dyslipidemia, in isolation or in combination with other risk factors was 38.5%.

Table 4 - Risk factors of 109 children and adolescents with family history of premature CAD

Risk factor	n	%
Dyslipidemia	11	10.1
Arterial hypertension	1	0.9
Smoking	2	1.8
Dyslipidemia and lack of physical activity	13	11.9
Dyslipidemia and arterial hypertension	1	0.9
Dyslipidemia and overweight	2	1.8
Dyslipidemia, lack of physical activity and smoking	1	0.9
Dyslipidemia, overweight and e lack of physical activity	12	11.0
Dyslipidemia, overweight and smoking	1	0.9
Dyslipidemia, overweight, lack of physical activity and arterial hypertension	1	0.9
Total	45	41.1

Discussion

Atherosclerotic disease, with multi factor origins, is influenced by many different genetic and environmental variables. IN our study, the children and adolescents selected presented a genetic propensity to CAD. This is considered to be one of the most important factors indicating that children over two should have their lipids profiled.[9,10] It is also well established that dyslipidemia plays a significant role in the development of cardiovascular disease in adultyhood[21] and that reducing serum lipid concentrations leads to a significant reduction in both cardiovascular events and mortality.[22]

We observed that 27.5% and 19.3% of the sample under investigation presented, undesirable TC and LDL-C levels, respectively. In a different study, also performed in São Paulo, Forti et al.[16] found much higher frequencies. They studied children and adolescents from two to nineteen years of age, children of CAD patients younger than 55 who had been revascularized at the Instituto do Coração of the HC at the FMUSP, observing that 48.2% and 44.6% presented TC and LDL-C levels, respectively, above those considered ideal. In Campinas, Moura and Coronelli[17] working with a sample of schoolchildren from 7 to 10 years old, who presented TC values equal to or greater than 200 mg/dl, discovered a family history of cardiovascular disease in 53.5% of cases. An investigation performed in the South of the country by Gerber e Zielinsky[18] registered elevated TC values at a frequency greater than in this study. The authors of this study, in Bento Gonçalves, analyzed 1501 schoolchildren between 6 and 16 years (exclusive) detected that 38.3% had both a positive CAD family history and hypercholesterolemia. IN neither of these studies, however, was the age of CAD onset mentioned.

Research performed in other countries has reported percentages of schoolchildren with hypercholesterolemia who also had a family history of premature CAD varying from 14 to 21.5%.[23-25] A Danish study of children whose fathers had died of ischaemic heart disease younger than 45, found that just 6% presented elevated CT values.[26] Beigel et al.,[27] studying the descendents of CAD patients diagnosed at 40 years of age, did not find significant differences in TC or LDL-C serum concentrations in relation to a control group, but did find differences in apoproteins concentrations.

It is probable that the differences between the observed frequency of hypercholesterolemia among children and adolescents with family histories of CAD, in addition to genetic influences and biological variation, may also be determined by environmental factors, primarily family eating habits and the socio-economic variations between the populations of many different geographic regions.

In the sample currently in question, reduced HDL-C concentrations were detected in 13.8% of patients. This data is similar to that returned by another study in which reduced HDL-C values were found in 13.5% of children aged form 2 to 12 and in 14.2% of adolescents, both groups with family histories of premature CAD.[16] Research suggests that reduced HDL-C concentrations accelerate the progress of atherogenesis. Necropsy findings have revealed that HDL-C concentrations, prior

to death, were lower in cases that had presented atheromas when compared with cases not involving this type of lesion.[6] High density liporotein concentrations below the ideal are commonly associated with heredity, other atherogenic lipoproteins and obesity.[28] Within our sample six of the 11 obese children (54.5%) presented reduced HDL-C levels in association with elevated triglyceride levels. Of these six, three also presented undesirable TC and/or LDL-C levels.

Thirteen percent of our patients had triglyceride levels above those considered ideal for their ages. This data is in agreement with other researchers who found elevated triglyceridemia in 14% of a group of children and adolescents with family histories of premature CAD.[15] Current thought entertains the hypothesis that certain triglyceride-rich lipoproteins may be independently involved in atherosclerosis development. Necropsy findings have shown an association between increased TG and very low density lipoprotein concentrations with fatty streaks and fibrous plaques in coronary arteries.[6]

Our study found dyslipidemia in 38.4% of cases (Table 4) and was unable to determine whether lipid abnormalities were dependent on genetic and/or environmental factors. Isolated hypercholesterolemia was the type of dyslipidemia most common. This is probably suggestive of the influence of family eating habits and lifestyle.

We observed that children and adolescents with excessive weight had a 2.8 times greater risk of dyslipidemia. This data agrees with Forti et al.[16] who found a significantly higher frequency of undesirably high TC values among children and adolescents with excessive weight and a family history of premature CAD. A longitudinal study performed in the city of Bogalusa[9] showed that the descendents of individuals who had presented CAD before reaching 50, were more obese than individuals with no family history and that this obesity had onset during early childhood. This being so weight control becomes extremely important during childhood and adolescence since obesity, in addition to being an independent risk factor for atherogenesis, can also be associated with a series of other atherosclerotic disease risk factors, such as arterial hypertension, diabetes mellitus type 2 and dyslipidemia.[5]

It did not prove possible to assess any possible association between dyslipidemia and arterial hypertension or smoking, considered significant risk factors for atherosclerosis, since only three and four cases, respectively, were identified.

We observed that there was no association between dyslipidemia and physical activity, family income or maternal education. One datum that attracted our attention was the fact that less than 30% of the children and adolescents regularly practiced physical activity. A sedentary lifestyle can contribute to obesity, arterial hypertension, low HDL-C concentrations and elevated TG, all of which are recognized as factors associated with atherosclerotic disease. Indeed, physical inactivity, when present during childhood tends to continue in adult life.[29]

This study identified 41% of the children and adolescents as presenting between one and four atherosclerosis risk factors in conjunction with a family history of premature CAD. In general, the larger the number or severity of the risk factors, the higher the probability of the disease. Furthermore, when more than one risk factor is present, their combined effects may be multiplied and not simply added.[30]

Our data suggests that lipid profiling, along with the investigation of other atherosclerosis risk factors, should always we performed for children and adolescents with family histories of premature CAD.

Concluding, we can state that atherosclerotic disease prevention must be started in early childhood and that pediatricians should be alert to its risk factors in order that they be identified early and intervention in the form of preventative health programs which would cover healthy eating habits and lifestyle.

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References

1. Centers for Disease Control and Prevention [homepage on the Internet]. Atlanta, GA: Centers for Disease Control and Prevention [updated 2001 Oct 12; cited 2004 March 16]. National Vital Statistics Report 2001;49(11):8. Available from: http://www.cdc.gov/nchs/data/nvsr/nvsr49/nvsr49_11.pdf.
2. Fundação Nacional da Saúde [site na Internet]. Ministério da Saúde; c1999-2003 [citado em 16 de março de 2004]. Disponível em: http://www.funasa.gov.br.
3. Holman RL, McGill Jr HC, Strong JP, Geer JC. The natural history of atherosclerosis. Am J Path. 1958;34:209-35.
4. Stary HC. The sequence of cell and matrix changes in atherosclerotic lesions of coronary arteries in the first forty years of life. Eur Heart J. 1990;11 Suppl E:3-19.
5. Kannel WB, Wilson PWF. An update on coronary risk factors. Med Clin North Am. 1995;79:951-71.
6. Tracy RE. Risk factors and atherosclerosis in youth autopsy findings of the Bogalusa Heart Study. Am J Med Sci. 1995;310 Suppl 1:37-41.
7. Burke GL, Savage PJ, Sprakfa JM, Selby JV, Jacobs DR Jr, Perkins LL, et al. Relation of risk factor levels in young adulthood to parental history of disease. The CARDIA Study. Circulation. 1991;84:1176-87.
8. Kaprio J, Norio R, Pesonen E, Sarna S. Intimal thickening of the coronary arteries in infants in relation to family history of coronary artery disease. Circulation. 1993;87:1960-8.
9. Bao W, Srinivasan SR, Valdez R, Greenlund KJ, Wattigney WA, Berenson GS. Longitudinal changes in cardiovascular risk from childhood to young adulthood in offspring of parents with coronary artery disease. The Bogalusa Heart Study. JAMA. 1997;278:1749-54.
10. National Cholesterol Education Program. Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics. 1992;89 Suppl:525-84.

11. III Diretrizes brasileiras sobre dislipidemias e diretriz de prevenção da aterosclerose do Departamento de aterosclerose da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2001;77 Suppl III:1-48.
12. Castelli WP, Garrison RJ, Wilson PWF, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA. 1986;256: 2835-8.
13. Menotti A, Lanti M, Puddu PE, Kromhout D. Coronary heart disease incidence in northern and southern European population: a reanalysis of seven countries study for a European coronary risk chart. Heart. 2000;84:238-44.
14. Lauer RM, Clarke WR. Use of cholesterol measurement in childhood for the prediction of adult hypercholesterolemia. The Muscatine Study. JAMA. 1990;264:3034-8.
15. Webber LS, Srinivasan SR, Wattigney WA, Berenson GS. Tracking of serum lipids and lipoproteins childhood to adulthood: the Bogalusa Heart Study. Am J Epidemiol. 1991;133:884-99.
16. Forti N, Giannini D, Diament J, Issa J, Fukushima J, Bó CD, Barretto ACP. Fatores de risco para doença arterial coronariana em crianças e adolescentes filhos de coronariopatas jovens. Arq Bras Cardiol. 1996;66:119-23.
17. Coronelli CLS, Moura EC. Hipercolesterolemia em escolares e seus fatores de risco. Rev Saúde Pública. 2003;37:24-31.
18. Gerber ZRS, Zielinsky P. Fatores de risco de aterosclerose na infância. Um estudo epidemiológico. Arq Bras Cardiol. 1997;69: 231-6.
19. Centers for Disease Control and Prevention [homepage on the Internet]. Atlanta, GA: Centers for Disease Control and Prevention National Center for Health Statistics [updated 2002 Dec 30; cited 2004 March 16]. Available from: http://www.cdc.gov/growthcharts.
20. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Pediatrics. 1996;98:649-58.
21. O'Keefe JH Jr., Lavie CJ Jr., McCallister BD. Insights into the pathogenesis and prevention of coronary disease. Mayo Clin Proc. 1995;70:69-79.
22. Robinson JC, Leon AS. The prevention of cardiovascular disease. Med Clin North Am. 1994;78:69-99.
23. Gluek CJ, Fallat RW, Tsang RC, Buncher CR. Hyperlipidemia in progeny of parents with myocardial infarction before age 50. Am J Dis Child. 1974;127:70-5.
24. Hennekens CH, Jesse MJ, Klein BE. Cholesterol among children of men with myocardial infarction. Pediatrics. 1976;58:211-17.
25. Sveger T, Flodmark C-E, Nordborg K, Nilsson-Ehle P, Borgfors N. Hereditary dyslipideamias and combined risk factors in children with a family history of premature coronary artery disease. Arch Dis Child. 2000;82:292-6.
26. Andersen GE, Hejl M, Christensen NC, Bott H, Lous P, Friis-Hansen B. Hyperlipemia among 1407 Danish children whose fathers have died from ischemic heart disease before age 45. Acta Paediatr Scand. 1981;70:843-9.
27. Beigel Y, George J, Leibovici L, Mattityahu A, Sclarovsky S, Blieden L. Coronary risk factors in children of parents with premature coronary artery disease. Acta Paediatr. 1993;82: 162-5.
28. Flodmark CE, Svenger T, Nilsson-Ehle P. Waist measurement correlates to a potentially atherogenic lipoprotein profile in obese 12-14-year-old children. Acta Paediatr. 1994;83:941-5.
29. Gidding SS. Preventive Pediatric Cardiology. Pediatr Clin North Am. 1999;46:253-62.
30. Fletcher RH, Fletcher SW, Fletcher EH. Risco. In: Fletcher RH, Fletcher SW, Fletcher EH, editores. Epidemiologia Clínica. 2ª ed. Porto Alegre: Artes Médicas; 1991. p. 126-44.

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