Atherosclerosis risk factors in children and adolescents with or without family history of premature coronary artery disease

Roya Kelishadi, Sarraf Zadegan, Gholam Naderi, Sedigueh Asgary, Nasrollah Bashardoust,

Summary:
Background: Although coronary artery disease (CAD) becomes symptomatic much later in life, the early identification and modification of risk factors may reduce its later incidence.
Material/Methods: 100 subjects 2–18 years old, evenly divided by sex, were randomly selected from among children of patients suffering from premature myocardial infarction (<55 years); the controls were 100 age- and sex-matched subjects without a similar family history. In the Pediatric Preventive Cardiology Clinic at the Isfahan Cardiovascular Research Center, the subjects completed a special questionnaire consisting of anthropometric data, blood pressure, skinfold thickness, rate of physical activity, and active or passive cigarette smoking. Fasting venous blood was analyzed for serum lipids, lipoproteins fibrinogen, and apolipoproteins A1 and B100. The data were analyzed with SPSS V6.0/WIN using the independent t-test, Kruskal-Wallis, chi-squared, and standard linear multiple regression tests.
Results: The data showed higher prevalence of some major and new risk factors in the experimental group than in the controls. The mean total cholesterol, LDL-C, TG, fibrinogen and Apo B100 were significantly higher in the experimental group, while the mean values of HDL-C and Apo A1 were significantly lower. The differences in terms of Body Mass Index, percentage body fat, rate of regular physical activity, and active and passive smoking were not significant between groups.
Conclusion: Major and new CAD risk factors should be identified and modified as early as possible in children with high family risk by screening and health education at an early age.

key words: premature coronary artery disease • major & new risk factors • children

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Comments
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Roya Kelishadi, Nizal Sarrafzadegan, Gholam Ali Nadery, Sedigheh Asgary, Nasrollah Bashardoust

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BACKGROUND

Risk factors for certain chronic diseases, such as coronary artery disease (CAD), may be observed during childhood. Both unmodifiable (e.g., heredity, race, age, sex) and modifiable (e.g., serum lipids, obesity, physical inactivity, smoking) CAD risk factors are etiologically related to atherosclerosis and may contribute to CAD in adults. Therefore, preventive measures adopted in early life may help reduce the prevalence of the disease in adulthood. The control of risk factors is an effective strategy for preventing atherosclerotic disease [1-7].

This is especially important for those having a family history of premature CAD or cerebrovascular or occlusive peripheral vascular disease (defined as onset before the age of 55 years in a sibling or parent). A family history of premature CAD predicts cardiovascular risk in the next generation. The early detection and treatment of youth at risk for premature CAD is shown to provide the greatest opportunity to decrease morbidity and mortality [8-10].

Although family history is an important predictor of CAD, this relation, in large part, is not explained by the currently accepted risk factors (termed as major). New risk factors, such as fibrinogen, apolipoproteins, homocysteine and lipoprotein a (Lpa) have been identified and are under further investigation [11-14]; the identification and possible modification of these could prove to be effective CAD prevention in childhood.

In recent years, the prevalence of CAD has increased in Iran, and the mean age of its incidence has decreased [15]; concurrently, an increasing trend in risk factors for atherosclerosis has been shown in the children and adolescents of our population [16]. The aim of the present study, performed for the first time in our country, was to characterize the risk factor profile of children and adolescents with a family history of premature CAD.

MATERIAL AND METHODS

The population studied as the experimental group consisted of 100 subjects (50 girls, 50 boys), 2-18 years old, randomly selected from among the children of patients suffering from premature myocardial infarction hospitalized in the coronary care units (CCU) of the hospitals related to the Isfahan University of Medical Sciences.

The control group consisted of age- and sex-matched children randomly selected from the neighbors of the experimental group, with equivalent socioeconomic status as in the experimental group, but without a family history of CAD.

Written informed consent was obtained from the parents of the subjects after a full explanation of the procedures involved. Data was collected in the Pediatric Preventive Cardiology Clinic at the Isfahan Cardiovascular Research Center.

The age of each subject (accurate to 1 month) was recorded. Weight was measured to the nearest 0.5 kg (Seca Beam Balance), with the subjects lightly dressed and barefoot. Standing height to the nearest 0.5 cm (Seca stadiometer) was also recorded.

A mercury sphygmomanometer with suitable cuff size for each subject was used to record the sitting and supine blood pressure, following WHO criteria. The mean of two measurements of Korotkoff phase I and the mean of two values of phase IV were recorded for systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively.

Percentage body fat was calculated from the average of two measurements of skin fold with a standard caliper using Lohman’s formula [17].

For the assessment of physical activity, a valid physical activity recall questionnaire was used. Active and/or passive smoking was ascertained by means of a confidential questionnaire.

Venous blood samples were taken from each subject following an overnight fast (12 hours). An Elan Autoanalyzer (Ependorf, Germany) was utilized for the determination of serum lipids and lipoproteins. Apolipoproteins were measured by spectrophotometry using the turbidimetry method. The quantitative determination of fibrinogen levels was performed by the clotting method in the laboratory of the Isfahan Cardiovascular Research Center, which is under external quality control by the Central Laboratory of St. Rafael University, Department of Epidemiology, Leuven, Belgium.

Statistical analysis

Statistical analyses were performed by the SPSS statistical package, version 10.0 for Windows, using chi-squared, Kruskall-Wallis and independent t-tests. Standard linear multiple regression analysis was also used in order to examine the relationships between variables. A p value less than 0.05 was considered to be significant.

RESULTS

The mean hospitalization period of the parents was 8 (± 3) days. The participation rate was 92% in the experi-

Table 1. Subjects Characteristics of the case and control groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case group N=100 (Mean±SD)</th>
<th>Control group N=100 (Mean±SD)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.7 (+0.4)</td>
<td>11.8 (+0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>140 (+0.5)</td>
<td>141 (+0.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>32 (+0.8)</td>
<td>32.5 (+0.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>24.1 (+7.8)</td>
<td>24.1 (+8.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Regular physical activity (%)</td>
<td>20.2 (+3.2)</td>
<td>19.7 (+2.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>3.1 (+0.7)</td>
<td>3.4 (+0.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Passive smoking in home (%)</td>
<td>17.7 (+5.9)</td>
<td>18.4 (+0.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>102.4 (+4.8)</td>
<td>103.6 (+4.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>59.4 (+6.7)</td>
<td>58.8 (+6.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

a) At least 3 times a week and at least 20 minutes per session
b) > 1 cigarette per day
c) Being exposed to smoking at home in last 2 years
The subjects' characteristics are shown in Table 1, which reveals no significant difference regarding regular physical activity, active smoking, passive smoking, weight, height and percentage of body fat between the groups. The difference between girls and boys was not significant except for smoking and regular physical activity (Table 2). Laboratory data are listed in Table 3. An important finding was that total cholesterol (T. Cho), low density lipoprotein-cholesterol (LDL-C), triglyceride (TG), apolipoprotein B100 (APO B100) and fibrinogen were significantly higher in the experimental group than in the controls (P<0.05). Some preventive factors, such as high density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (APO A1), were significantly lower in the experimental group (P<0.05).

These differences were also significant between the boys and the girls within the experimental group and within the control group (P<0.05) (Table 4).

No case of diabetes mellitus was found.

Mean systolic and diastolic blood pressure did not differ between the groups, but blood pressure was generally higher in the children of hypertensive parents in both groups (Table 5).

Standard linear multiple regression analysis of serum lipids, lipoproteins and the new CAD risk factors under study (apolipoproteins and fibrinogen) did not show any significant relationship (Table 6).

Table 2. Subjects Characteristics of the case and control groups according to sex.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case group (Mean±SD)</th>
<th>Control group (Mean±SD)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Girls (N=50)</td>
<td>Boys (N=50)</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>11.7±0.4</td>
<td>11.7±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>140±0.5</td>
<td>141±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>32±0.6</td>
<td>33±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>24.4±7.6</td>
<td>22.2±8.1</td>
<td>NS</td>
</tr>
<tr>
<td>Regular physical activity(1)(%)</td>
<td>18.1±4.2</td>
<td>22.2±2.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>2.1±0.6</td>
<td>5.2±0.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Passive smoking in home(2)(%)</td>
<td>17.1±0.4</td>
<td>18.2±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>102.1±5.2</td>
<td>104.1±4.4</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>51.2±6.2</td>
<td>33.4±7.1</td>
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</tr>
</tbody>
</table>

(1) At least 3 times a week and at least 20 minutes per session; 
(2) >1 cigarette per day; 
(3) Being exposed to smoking at home in last 2 years.

Table 3. Laboratory data in the case and control groups.

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>T. Cho</td>
<td>168.1±27.2</td>
<td>172.0±30.1</td>
<td>0.04</td>
</tr>
<tr>
<td>LDL-C</td>
<td>102.0±25.4</td>
<td>98.8±22.8</td>
<td>0.03</td>
</tr>
<tr>
<td>TG</td>
<td>144.0±37.4</td>
<td>121.2±38.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>234.2±22.2</td>
<td>208.0±25.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Apo B100</td>
<td>92.8±3.1</td>
<td>87.8±2.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Apo A1</td>
<td>118.2±5.4</td>
<td>121.5±5.4</td>
<td>0.02</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40.1±5.5</td>
<td>46.9±8.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 4. Laboratory data in the case and control groups according to sex.

<table>
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<tr>
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<th>Case group (Mean±SD)</th>
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</tr>
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</table>
The atherogenic process begins in childhood, when fatty streaks in the intima of arteries and the degree of atherogenesis is related to measurable risk factors. Several investigations have concluded that screening the progeny of patients suffering from early incidence of CAD is highly productive in the identification of young people at increased risk for future CAD. Because of the geographic and ethnic predisposition to CAD in different populations [1-10], this study of major and new CAD risk factors was performed for the first time in an Iranian population.

The prevalence of CAD risk factors in children of patients with premature CAD has been evaluated in comparison to controls by several investigators. Widhalm et al. reported a significant difference between at-risk and non-risk groups of children regarding HDL-C, TotG/HDL-C as well as LDL-C/HDL-C [18]. Barth et al. showed significantly higher values of total cholesterol and LDL cholesterol in children with a positive family history of premature CAD [19]. Sniderman et al. reported significantly higher lipid and lipoprotein levels, except for HDL-C, in the premature offspring of MI patients [20]. Beigel et al., however, did not find any significant difference in the concentrations of lipids and lipoproteins between children of high-risk families and controls [21]. Our study shows higher levels of total cholesterol, total triglycerides, and LDL-C, and lower levels of HDL-C in the children of parents with premature CAD.

Regarding apolipoproteins, Widhalm et al. showed them to be of considerable importance as risk indicators between offspring who might be at higher risk for later CAD, even in childhood and younger adolescence [18]. Sniderman et al. reported a higher Apo B100 level in the children of high risk families for CAD [20], Beigel et al. [21] and Islam et al. [22] showed a higher level of Apo B100 and lower level of Apo A1 in the children of patients with premature MI. Consistent with the findings of these studies [18,20-22], the present study shows higher levels of ApoB100 and lower levels of ApoA1 in children of patients with premature CAD, as well as low Apo A1, high ApoB100 level and low LDL-C/Apo B100 ratio in a significant direct relationship to family history of premature CAD.

Male sex is a known risk factor for CAD, and the findings of the present study tend to confirm that the boys of high-risk families are more likely to have elevated serum lipids and apolipoproteins. This supports the findings reported by Widhalm et al. [18], Barth et al. [19], and Beigel et al. [21], but contradicts the conclusions reached by Islam et al. [22].

The present study shows the importance of screening serum lipid, lipoprotein, and apolipoproteins in children of high-risk families, especially boys.

The mean SBP and DBP values were not significantly different between the two studied groups, a finding which is supported by the results of several other research groups [18-21]. The data in the present study regarding higher mean SBP and DBP in the children of hypertensive parents are in line with many other reports, such as the studies by Richard et al. [23] and Havlich et al. [24]. Thus it would be advisable to track childhood blood pressure, especially in the offspring of hypertensive adults [23-25].

Although our study did not show any significant difference between the mean BMI, percentage body fat, or the prevalence of obesity between the children of at-risk families and controls, which is consistent with the findings reported by other studies [18-21], still, given that the mortality of obese adolescents and children is higher than that of the general population [1] and that childhood obesity predisposes to adult obesity [26], we recommend prevention and control of this major CAD risk factor in childhood, especially in those with high family risk for CAD.

Our data did not show any significant difference in the rate of regular physical activity between the two groups. This was also found in the review by Vaccaro et al. [27]. However, a physically active lifestyle has been shown to be a crucial factor for health benefits among persons of all ages, since habits of regular physical activity acquired at an early age have been shown to persist through adolescence into adulthood [28], while the preventive benefits of regular physical activity on lowering the risk of CAD is well known. Thus regular physical activity should be emphasized, particularly in children from high risk families for CAD.

Passive smoking has many side effects on different body organs and serum lipids. It increases serum total cholesterol, LDL-C, and the Chol/HDL ratio, and decreases antioxidant capacity. This alters systemic oxygen transport and lipoprotein composition. These abnormalities are worse in active smokers [29]. The side effects in question are more hazardous for children with a family history of premature CAD [30]. The dangers of smoking and passive smoking should be particularly emphasized to these children.

The data obtained in our research do not show constant direct correlation between major and new CAD risk factors. Previous studies have likewise concluded that apolipoproteins are independent risk factors for CAD, and their predictive value for the incidence of CAD is higher than serum lipids [14-22]. We therefore recom-
mend that these new risk factors be measured at-risk children, in addition to the major risk factors.

CONCLUSIONS

Children and adolescents with a positive family history of premature CAD may benefit from the early detection and control of its modifiable major and new risk factors in childhood.

Regarding the importance of 'healthy lifestyles', particularly for those children at higher risk of CAD, it is advised that effective guidelines be developed, compatible with the socio-cultural milieu and sensitive to local variability in availability of resources and activities.

REFERENCES: