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Hyperinsulinemia and Dyslipidemia in Non-Obese, Normotensive Offspring of Hypertensive Parents in Northern India

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Insulin resistance contributes to initiation and acceleration of hypertension and atherosclerosis. This study attempted to detect occurrence of pre-hypertensive metabolic abnormalities, including hyperinsulinemia, in the offspring of hypertensive patients. Thirty-eight healthy offspring of hypertensive parents (group I, mean age 23.6±3.7 years) and 18 control offspring of normotensive parents (group II, mean age 24.2±2.8 years) were clinically examined, subjected to oral glucose tolerance test (OGTT), and the samples were analysed for blood glucose, insulin and lipid profile. Subjects in group I with fasting serum insulin < 90 nmol/L constituted group Ia (n = 23, 62%) and those with > 90 nmol/L constituted group Ib (n = 15, 38%). Both groups consisted of non-obese and normotensive subjects matched for body mass index and waist-hip ratio. There were no statistically significant differences in blood glucose levels between groups Ia, Ib and II during OGTT. Serum insulin levels during OGTT in group I were significantly higher than in group II (p<0.05), except at 30 min. Fasting insulin and 2 h post-OGTT insulin in group Ib were significantly higher than the other groups. Serum triglyceride levels, though within normal range, were higher in group I than group II (p<0.01). Similarly, high-density lipoprotein cholesterol levels in groups Ia and Ib were lower than those observed in group II (p<0.01). In conclusion, non-obese, normotensive offspring of hypertensive parents were observed to be hyperinsulinemic and dyslipidemic at an early age. These metabolic abnormalities may be associated with hypertension, glucose intolerance and accelerated atherosclerosis in adulthood. Key words: atherosclerosis, dyslipidemia, hyperinsulinemia, hypertension, insulin resistance, northern India, offspring of hypertensive parents.

INTRODUCTION

Essential hypertension is often associated with metabolic abnormalities such as impaired glucose tolerance (IGT), increased very low-density lipoprotein cholesterol (VLDL-c), decreased high-density lipoprotein cholesterol (HDL-c) and abdominal obesity. Coexistence of all these conditions in the same individual is termed Insulin Resistance Syndrome (IRS) [1]. Insulin resistance may be important in the pathogenesis of hypertension, glucose intolerance and atherosclerosis. Studies document significant insulin resistance in immigrant [2–5] as well as in native Indian [6–8] populations.

Both systolic and diastolic blood pressures show continuous, graded and independent correlation to all these diseases. Risk has been noted in both sexes and throughout the entire adult range [9]. While substantial benefit to the hypertensive patients may accrue from reduction of blood pressure, treatment of insulin resistance and co-morbid factors may be required to reduce the overall risk from the complications of atherosclerosis [9]. It is rational to target high-risk groups such as the offspring of hypertensive parents for prevention and detection of hypertension and other associated metabolic abnormalities. Some of these offspring may be in a stage of “pre-hypertension”, having only asymptomatic biochemical abnormality such as hyperinsulinemia.

The aim of the current study was to estimate pre-hypertensive metabolic abnormalities in the normotensive offspring of patients with essential hypertension.

MATERIALS AND METHODS

Subjects

The subjects were recruited from the Cardiology and Medicine outpatient clinics and wards. Thirty-eight offspring of hypertensive parents were recruited for the study. Entry criteria for the parent included one hypertensive parent above the age of 40 years, either male or female, diagnosed as having essential hypertension. Criteria for the diagnosis of hypertension in the parents were as follows: (i) hypertensive patients on therapy, diagnosed by a physician on the basis of repeated
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Table I. Clinical characteristics. All variables expressed as mean ± SD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I* (n = 38)</th>
<th>Group II** (n = 18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.6 ± 3.7</td>
<td>24.2 ± 2.8</td>
<td>NS</td>
</tr>
<tr>
<td>(male:female ratio)</td>
<td>32:6</td>
<td>15:3</td>
<td>NS</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>22.74 ± 3.95</td>
<td>21.83 ± 3.59</td>
<td>NS</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.87 ± 0.06</td>
<td>0.90 ± 0.06</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Study group.
** Control group.

Oral glucose tolerance test (OGTT) was performed according to the criteria established by WHO [10]. It was done in the morning after a 12-h overnight fast, preceded by an unrestricted diet for 3 days containing more than 150 g carbohydrate daily and usual physical activity. Smoking was not permitted during the test. After baseline fasting samples, subjects were given 75 g of glucose mixed in 200 ml water orally over 5–10 min. Venous blood samples were collected half hourly for serum insulin and blood glucose in plain test tubes and oxalate vials, respectively.

Blood was analysed for glucose, insulin and lipid profile. A modification of the Asatoor and King micro-method was used for blood glucose estimation [11]. Estimation of total cholesterol (TC), serum triglycerides (TG), and high-density lipoprotein cholesterol (HDL-c) was performed on the sample drawn after the 12-h overnight fast. TC was estimated with the ferric chloride method [12]. The method described by Rosenberg & Gottfried [13] was used for the determination of TG. After precipitation of VLDL-c and low-density lipoprotein cholesterol (LDL-c) from the serum by phosphotungstic acid and magnesium chloride, supernatant was taken and HDL-c estimation performed by the method described for TC. The value of LDL-c was calculated using Freidwald’s equation. Lipid levels were defined as abnormal by the criteria laid down by the National Cholesterol Education Program, Adult Treatment Panel II [14].

Serum insulin assay was done by double antibody radioimmunoassay using standard insulin: MRC (Human), anti-pork insulin guinea pig antibody (first antibody), anti-guinea pig gammaglobulin rabbit serum (second antibody) and radioimmunoassay buffer. Iodination of insulin was done by chloramine-T method. The I²⁵ insulin bound to the antibody was counted in Multiprias-II (Packard) Gamma Counter. Sensitivity of insulin assay was assessed by a 10% fall from zero binding achieved by 10 nmol/L of insulin, which is less than the lowest concentration of the standard used. All the samples were analysed in one assay. Hence there was no inter-assay variation. The low, medium and high coefficients of variation were <10%. Non-specific binding was 2.7%, whereas zero binding was 29%.

Statistical analysis

Mean and standard deviations (SD) were computed for all the compared parameters. One-way analysis of variance (ANOVA) was applied to assess the significance of the difference between the means of the three groups. For parameters where a significant difference had been found, Student-Newman-Keul multiple range test was applied to assess the significance of the difference among various groups.
Table II. Blood pressure values (mmHg). All variables expressed as mean ± SD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n = 38)</th>
<th>Group II (n = 18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine SBP</td>
<td>115 ± 4.5</td>
<td>115 ± 4.3</td>
<td>NS</td>
</tr>
<tr>
<td>Standing SBP</td>
<td>114 ± 5.8</td>
<td>116 ± 5.8</td>
<td>NS</td>
</tr>
<tr>
<td>Supine DBP</td>
<td>76 ± 4.8</td>
<td>76 ± 4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Standing DBP</td>
<td>78 ± 5.8</td>
<td>78 ± 3.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Group I: Study group. Group II: Controls.

SBP = systolic blood pressure, DBP = diastolic blood pressure.

Table III. Serum insulin levels (nmol/L). All values expressed as mean ± SD

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Group Ia</th>
<th>Group Ib</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>57.7 ± 20.9</td>
<td>132.6 ± 29.6</td>
<td>38.8 ± 15.5</td>
</tr>
<tr>
<td>30</td>
<td>281.4 ± 99.6</td>
<td>322.2 ± 88.3</td>
<td>277.2 ± 88.6</td>
</tr>
<tr>
<td>60</td>
<td>198.6 ± 75.9</td>
<td>235.5 ± 55.1</td>
<td>130.3 ± 59.1</td>
</tr>
<tr>
<td>90</td>
<td>159.9 ± 67.9</td>
<td>199.6 ± 57.5</td>
<td>115.9 ± 63.4</td>
</tr>
<tr>
<td>120</td>
<td>107.3 ± 51.9</td>
<td>169.8 ± 62.1</td>
<td>79.05 ± 33.69</td>
</tr>
</tbody>
</table>

Group I: Study group. Group II: Controls.

$^*$ p < 0.01 in group I vs group II at all time intervals except at 30 min.
$^*$ p < 0.001 (Ia vs Ib). $^{**}$ p < 0.01 (Ia vs Ib), $^*$ p < 0.01 (Ia vs II), $^{**}$ p < 0.05 (Ia vs II), $^{++}$ p < 0.001 (Ib vs II), $^{++}$ p < 0.05 (Ib vs II).

RESULTS

Forty-two subjects were screened for recruitment in the study group (group I). Of these, four subjects were excluded when OGTT revealed a previously undiagnosed diabetic state. Eighteen subjects were taken as controls (group II). Group I was further sub-classified into groups Ia and Ib based on fasting serum insulin levels. Subjects having fasting serum insulin < 90 nmol/L constituted group Ia (n = 23, 62%), and those with > 90 nmol/L constituted group Ib (n = 15, 38%).

Demographic, anthropometric, and clinical profile

The mean age of patients in group I was 23.6 ± 3.7 years (Table I). There was significant male preponderance in both the groups. There was no significant difference in the smoking, alcohol intake or pattern of physical activity between the two groups, though non-vegetarian subjects were significantly higher in group I. Six subjects (13.6%) of group I had a family history of CHD compared to only one subject (5%) in group II ($p < 0.05$). BMI and W-HR were similar in the two groups (Table I). Subjects in both the groups were normotensive (Table II).

Table I. Demographics, anthropometry, and clinical profile

DISCUSSION

Epidemiological data [15–18] showing the association between hypertension and insulin resistance has been supported by cellular and biochemical studies [19–22]. Several studies report development of insulin resistance during childhood and adolescence [16, 23, 24].

Offspring of hypertensive parents have been investigated for hyperinsulinemia and insulin sensitivity. Widgren et al. [25] reported hyperinsulinemia in 16
men with positive family history of hypertension. However, in this study hyperinsulinemia could also be attributed to the ageing process, since the subjects recruited in this study were middle-aged (38 ± 6 years). Compared to the mean age of subjects recruited by Widgren et al. [25], subjects in the current study were younger (23.6 ± 3.7 years), closely approximating the age of the subjects in the studies of Ferrari et al. [26] and Allenman et al. [27].

The influence of heredity is operative in the offspring of hypertensive parents. This could be due to inherited obesity, especially abdominal, or genetic propensity to develop IRS. On the other hand, shared environmental factors and dietary pattern may influence both hypertension and atherosclerosis [28, 29]. Of note, Allenman et al. report that abdominal fat mass in the offspring of hypertensive parents is positively correlated with fasting plasma insulin [27]. Widgren et al. further reported positive correlation of W-HR to baseline blood pressure, insulin and TC, whereas BMI was positively associated with the insulin response to oral glucose [25]. In the present study, both groups showed similar BMI, abdominal fat distribution and activity patterns. Absence of overweight in the subjects of group I in the present study negates it as an important cause of observed hyperinsulinemia.

Our findings of normal blood pressure in offspring of hypertensive parents is in contrast to previous observations where subjects with a positive family history had statistically higher blood pressure levels [25–27, 30], exhibiting close correlation with insulin sensitivity. [25–27, 31, 32]. Of note, Beatty et al. observed comparable insulin-mediated glucose disposal in test and control groups after adjustment for blood pressure [30].

Statistically significant hyperinsulinemia in normotensive offspring in this study is notable. Also of note is the fact that earlier studies did not show fasting hyperinsulinemia in the offspring of hypertensive parents, although it is clearly observable in group Ib in the present study. Post-OGTT insulin levels at 90 min were significantly higher in subjects with positive family history of hypertension in the study of Widgren et al. [25]. However, insulin sensitivity was estimated by the minimal model method in the other two trials [26, 27]. Of note, subjects in group I were normoglycemic on OGGT, and this could be due to a compensatory increase in insulin secretion to maintain blood glucose within the normal range. These subjects are at highest risk of developing glucose intolerance once beta cell exhaustion sets in. Widgren et al. noted that blood glucose levels at 90 and 120 min after oral glucose were already abnormal in middle-aged patients with parental history of hypertension [25].

The significantly increased TG and decreased HDL-c recorded in group I indicate the beginning of a dyslipidemic state in the offspring. Lower serum concentration of HDL-c was the only significant abnormality observed by Beatty et al. [30]. Further, Widgren et al. [25] observed that middle-aged offspring of hypertensive parents, besides being obese and hypertensive, had hypercholesterolemia. This could mean that if young offspring of hypertensive parents with hyperinsulinemia in the present study continue in a persistent insulin-resistant state, hyperlipidemia, hypertension and obesity are likely to ensue in adulthood.

Increased insulin levels, in contrast to catecholamines and angiotensin II, do not acutely increase blood pressure [33]. Structural and functional derangement in the vasculature due to hyperinsulinemia is subtle and occurs over a long period. Structural alterations of the vessel wall have been identified in the offspring of hypertensive parents [34]. Vascular hyper-reactivity to norepinephrine [35] and impaired vasodilator response to acetylcholine [36] have been observed as well, suggesting initiation at an early age of endothelial dysfunction involving an arginine-nitric oxide pathway. In addition, there is augmentation of the sympathetic responsiveness and endothelin levels to stress in such subjects [37]. An absence of renal functional reserve and an increase in microalbuminuria have also been observed [38].

In summary, non-obese, normotensive offspring of hypertensive parents were a distinct subgroup (n = 15, 38%) showing fasting and post-glucose load hyperinsulinemia while they were normoglycemic. They also had mild dyslipidemia in the form of higher TG and lower HDL-c values as compared to offspring from normotensive families.

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