Fasting Glucose and Cardiovascular Risk Factors in An Urban Population

R Gupta, M Sarna, Jyoti Thanvi, Vibha Sharma, VP Gupta

Abstract

Objective: To test the hypothesis that blood glucose levels in the range of normoglycemia are associated with increased cardiovascular risk we performed an epidemiological study in an urban population.

Methods: Randomly selected adults ≥ 20 years were studied using stratified sampling. Target sample was 1800 (men 960, women 840) of which 1123 subjects participated. Blood samples were available in 1091 subjects (60.6%, men 532, women 559). Measurement of anthropometric variables, blood pressure, fasting blood glucose and lipids was performed. Cardiovascular risk factors were determined using US Adult Treatment Panel-3 guidelines. Pearson's correlation coefficients (r) of fasting glucose with various risk factors were determined. Fasting glucose levels were classified into various groups as <75 mg/dl, 75-89 mg/dl, 90-109 mg/dl, 110-125 mg/dl and >126 mg/dl or known diabetes. Prevalence of cardiovascular risk factors was determined in each group.

Results: There was a significant positive correlation of fasting glucose in men and women with body mass index (r= 0.20, 0.12), waist-hip ratio (0.17, 0.09), systolic blood pressure (0.07, 0.22), total cholesterol (0.21, 0.15) and triglycerides (0.21, 0.25). Prevalence (%) of cardiovascular risk factors in men and women was smoking/tobacco use in 37.6 and 11.6, hypertension in 37.0 and 37.6, overweight and obesity in 37.8 and 50.3, truncal obesity in 57.3 and 68.0, high cholesterol ≥ 200 mg/dl in 37.4 and 45.8, high triglycerides ≥ 150 mg/dl in 32.3 and 28.6 and metabolic syndrome in 22.9 and 31.6 percent. In various groups of fasting glucose there was an increasing trend in prevalence of overweight/obesity, hypertension, hypercholesterolaemia, hypertriglyceridaemia, and metabolic syndrome (Mantel-Haenzel $X^2$ for trend, p<0.05) and fasting glucose <75 mg/dl was associated with the lowest prevalence of these risk factors.

Conclusions: There is a continuous relationship of fasting glucose levels with many cardiovascular risk factors and level <75 mg/dl is associated with the lowest prevalence.

INTRODUCTION

It has been consistently shown that escalating glycaemia in diabetes as measured by fasting or post-load glucose levels or glycated haemoglobin (HbA$_1$c) concentrations is associated with increasing cardiovascular risk. However, whether glucose levels less than diabetes threshold are associated with this risk is not clear. Many studies have reported that as the fasting blood glucose levels increase beyond 90 mg/dl the coronary risk escalates while some have failed to support these findings. The Whitehall study in Britain reported that there was a two-fold increase in coronary heart disease and stroke mortality in subjects whose 2-hour post-load capillary glucose was more than 97 mg/dl. The relationship of non-diabetic range hyperglycaemia and cardiovascular disease was also noted in the Rancho Bernardo study in North America. In a case-control study Gerstein et al reported that a fasting glucose of <88 mg/dl was associated with the lowest incidence of myocardial infarction and a 21 mg/dl increase in postprandial glucose was independently associated with an increase in odds of myocardial infarction of 1.58 in Indians. Coutinho et al performed a meta-analysis of twenty studies to examine relationship between glucose and incident cardiovascular events and concluded that as compared to fasting glucose of <75 mg/dl, a fasting glucose level of 110 mg/dl was associated with a relative cardiovascular event risk of 1.33. On the other hand, a prospective study from Japan reported that impaired fasting glucose is not a risk factor for cardiovascular disease compared to impaired glucose tolerance.

Escalating epidemic of diabetes in India and many developing countries has focused attention on various aspects of blood glucose levels. We reported that the prevalence of many cardiovascular risk factors in high in subjects with diabetes and insulin resistance syndrome diagnosed according to the US National Cholesterol...
Education Program (Adult Treatment Panel-3) (ATP-3) guidelines. To test the hypothesis that the blood glucose levels even below the diabetes and impaired fasting glucose levels are associated with increased coronary risk we analyzed data from an epidemiological study in an urban population in India.

METHODS

The study was approved by the institutional ethics committee. Detailed protocol of the study has been reported. History of major cardiovascular risk factors such as smoking, alcohol intake, amount of physical activity, diabetes and hypertension were inquired. The physical examination emphasized measurement of height, weight, waist, hip and blood pressure. Height was measured in meters and weight in kilograms using calibrated equipment. Supine waist girth was measured at the level of umbilicus with person breathing silently according to the World Health Organization (WHO) guidelines. Blood pressure was measured using standard mercury manometer. At least two readings at 5 minute interval were recorded and if a high blood pressure \(\geq 140/90\) was noted in either measurement a third reading was taken after 30 minutes. Lowest of the three readings was recorded. Fasting blood sample was obtained from all the individuals for estimation of glucose, total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol and triglycerides using previously reported techniques.

The study was designed to investigate people at random and to cover large and varied areas of Jaipur with a view to include persons from all walks of urban life. Randomly chosen locations from different regions of the city were identified so as to cover different socioeconomic groups. Details of the populations in these wards were available from the Voters’ lists. We randomly selected population proportionate sample of 300 persons (160 males, 140 females) from each locality and the total target study sample was 1800 (960 males, 840 females) who were invited for participation. This sample size was considered adequate for identification of major cardiovascular risk factors. The sample size in epidemiological studies is based on the estimate of disease prevalence in the population, usually taken from the previous work in the literature and should account for the \(\delta\)-factor (biologically relevant differences that the study seeks to detect), \(\alpha\) error (probability of the observed difference arising by chance, type 1 error usually set at 0.1 to 0.01), and \(\beta\) error (probability of missing a true difference or power of the study usually set at 0.80 to 0.95). An appropriate formula for calculation of sample size is: \(SE = \sqrt{pq/n}\), where \(SE\) = standard error, \(p\) = proportion affected, \(q\) = \((1-p)/SE\), \(n\) = number in sample. In comparisons between two groups the significance of differences between estimates is given with sufficient accuracy by: \((p_1 - p_2)/SE\) difference. If the estimated true rate (%) for \(p_1\) is 5.0 and \(p_2\) is 2.0 the required sample would be 670 subjects. These prevalence rates are taken from previous studies. This sample would have an 85% chance of recognizing a specified difference in rates (1-\(\beta\)) between two populations, significant at 5% level (two-tailed test). We chose a sample size of 1800 subjects, or three times the required sample, to decrease the SE of the estimate. This was also in view of the response rates that vary from 65-70% in previous epidemiological studies in this region. The study was preceded by meetings with local leaders who cooperated in identifying and ensuring participation of selected subjects.

The diagnostic criteria have been previously reported and are summarized below. Smokers in India consume tobacco in various forms, therefore, users of all type of tobacco products and present and past smokers were included in smoker category. Physical activity was measured by asking about both work-related and leisure time activities as per criteria defined by Paffenberger et al. Persons not engaged in either work-related or leisure-time physical activity were classified as sedentary. Body mass index (BMI) was calculated by dividing weight in kg by squared height in metres and overweight and obesity defined as BMI \(\geq 25\) kg/m\(^2\). Obesity was defined by BMI \(\geq 30\) kg/m\(^2\). Truncal obesity was diagnosed when waist:hip ratio (WHR) was >0.9 in men and >0.8 in women according to the US National Education Program guidelines. Hypertension was diagnosed when blood pressure was \(\geq 140/90\) or a person was known hypertensive. Normoglycaemia was defined as fasting glucose <75 mg/dl (Group 1) and hyperglycemia categorized into 75-89 mg/dl (Group 2) and 90-109 mg/dl (Group 3). Impaired fasting glucose (IFG) was defined when glucose level was 110-125 mg/dl (Group 4) and diabetes was diagnosed when there was a history of diabetes or fasting glucose was \(\geq 126\) mg/dl (Group 5). For calculation of correlation coefficients of fasting blood glucose with various risk factors in known diabetes group the fasting glucose was presumed to be 140 mg/dl if it was lower than this value, otherwise the observed value was recorded as reported in a previous study. Dyslipidaemia was defined by the presence of high total cholesterol \(\geq 200\) mg/dl, high LDL cholesterol \(\geq 130\) mg/dl, low HDL cholesterol <40 mg/dl or high triglycerides \(\geq 150\) mg/dl. Metabolic syndrome was defined when any three of the five diagnostic criteria (high blood pressure \(\geq 130/\geq 85\) mm Hg, waist circumference \(\geq 102\) cm in men and \(\geq 88\) cm in women, diabetes or fasting glucose \(\geq 110\) mg/dl, high triglycerides \(\geq 150\) mg/dl or low HDL cholesterol <45 mg/dl in men, <50 mg/dl in women) were present according to the US National Education Program criteria.

Statistical analysis: Continuous variables are reported as mean \(\pm 1\) SD. The prevalence rates are reported in percent. All statistical calculations were performed using SPSS V4.0.1 statistical package. Pearson’s correlation coefficients were determined using fasting blood glucose as independent variable and age, education years, smoking \((\text{no}=0, \text{chewing tobacco}=1, \text{smoking}=2)\), BMI, WHR, physical activity \((0=\text{no activity}, 1=\text{work related activity}, 2=\text{leisure time activity})\) systolic and diastolic blood pressure,
hypertension (normotension=0, pre-hypertension= 1, stage I hypertension= 2, stage II hypertension= 3, according to JNC-7 report\(^{16}\)), and lipid levels (mg/dl) as dependent variables. Variables have been compared using either analysis of variance (ANOVA) or \(X^2\) test as appropriate. For numerical variables the trends were examined by ANOVA test for linearity and for categorical variables by using Mantel-Haenzel \(X^2\) test for trend. P values <0.05 were considered significant.

**RESULTS**

1123 of 1800 eligible subjects were clinically examined. Fasting blood samples were available in 1091 subjects (response rate 60.6%) and these have been included in the present study. 523/960 men (55.4%) and 559/840 women (66.5%) were evaluated for presence of diabetes, impaired fasting glucose as well as other cardiovascular risk factors. Diabetes was present in 70 men (13.2%) and 64 women (11.5%). 42 men (60.0%) and 48 women (75.0%) were aware of the diabetes. The age-adjusted (for local population) prevalence of diabetes was 9.3% in men (95% confidence intervals (CI) 6.7-11.8), 8.1% in women (CI 5.8-10.4) and 8.6% overall (CI 6.9-10.3). Correlation of fasting blood glucose levels was calculated with various numerical variables. There was a significant positive correlation (r values) of fasting glucose in men and women with body mass index (0.20, 0.12), waist-hip ratio (0.17, 0.09), systolic blood pressure (0.07, 0.22), total cholesterol (0.21, 0.15) and triglycerides (0.21, 0.25) (p<0.01).

Prevalence of cardiovascular risk factors is shown in Table 1. There was a high prevalence of smoking, physical inactivity, overweight and obesity (BMI \(\geq\) 25), truncal obesity, hypertension and lipid abnormalities. Low HDL cholesterol was the most common lipid abnormality in this population. To determine prevalence of risk factors according to the fasting glucose levels, subjects were divided in various groups. In Groups 1 to 5 respectively of the 532 men there were 120 (22.5%), 171 (32.1%), 151 (28.4%), 20 (3.8%) and 70 (13.2%) subjects while of 559 women there were 66 (11.8%), 214 (38.3%), 190 (34.0%), 26 (4.7%), and 63 (11.3%) subjects. Prevalence of various risk factors in different groups are shown in Fig. 1. In men there is a significantly increasing trend in the prevalence of overweight and obesity, hypertension, high total cholesterol, high triglycerides, and metabolic syndrome with increasing glucose levels (p for trend <0.05). In women there is a significantly increase in the prevalence of smoking/tobacco use, obesity, hypertension, high total cholesterol, high triglycerides and metabolic syndrome (p for trend <0.05). There is also an increasing trend in mean systolic blood pressure, BMI, WHR, total cholesterol, LDL cholesterol and triglyceride levels with increasing fasting glucose (ANOVA test for linearity p<0.05) (Table 2). The risk factor levels are the least in Group 1 (fasting glucose <75 mg/dl) and progressively increase with escalating glucose levels.

**DISCUSSION**

![Table 1: Prevalence of Cardiovascular Risk Factors](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAQAAAAEDAwMBQAPSAAAABJRU5ErkJggg==)

This study shows that many cardiovascular risk factors increase linearly with increasing fasting glucose in Indian subjects. There is a significant positive correlation of fasting glucose with body mass index, systolic blood pressure,
total and LDL cholesterol and triglycerides. There is also a significantly increasing trend in the prevalence of obesity, hypertension, hypercholesterolaemia, hypertriglyceridaemia and the metabolic syndrome with increasing glucose levels. Fasting glucose levels <75 mg/dl are associated with the lowest cardiovascular risk.

Largely epidemiological studies have consistently shown that patients with diabetes have a two- to fourfold increased risk of cardiovascular disease relative to non-diabetic patients. Studies also suggest that in patients with diabetes the degree of glucose elevation is directly related to the cardiovascular risk. For non-diabetic subjects a critical overview of available epidemiological studies suggests that this continuous relationship extends below the diabetic threshold and includes mildly elevated glucose levels that are considered normal. This like LDL cholesterol and blood pressure, glucose appears to be a continuous cardiovascular risk factor.

A systematic review of all published cohort studies examining association of diabetes with cardiovascular risk in mainly non-diabetic population has been performed. This analysis describe studies with more than 1 million person years of follow-up and reported that the risk of cardiovascular diseases increased continuously with glucose levels above 75 mg/dl. This finding was supported by a recent prospective population-based study of 4662 men aged 45-79 followed for four years that found a continuous relationship between all-cause, cardiovascular, and coronary heart disease mortality and Hba1c throughout the entire population distribution with the lowest rates in those with Hba1c <5%. The present study shows that the cardiovascular risk is the least in those with blood glucose <75 mg/dl and there is a stepwise escalation in the risk as glucose levels increase. The study limitations include a small sample size and low response rate. However, the sample size has been derived using the WHO recommendations and appears appropriate for the study question. The number of subjects in Group 4 with impaired fasting glucose is small and less than the other groups but we have deliberately not divided the study groups according to mathematical quartiles as the present grouping is more clinically relevant.

Possible explanations for the glucose-cardiovascular disease relationship include direct toxic effect of glucose on cellular function and structure, indirect effects owing to insufficient insulin secretion to maintain normoglycaemia, and a long history of insulin resistance and hyperinsulinaemia prior to glucose elevations. This association could also be due to dysglycaemia being a marker of other known and unknown risk factors for cardiovascular disease such as hypertension, dyslipidaemia, abdominal obesity, renal damage and coagulation abnormalities. The present study shows that dysglycaemia (fasting glucose >75 mg/dl) is associated with multiple cardiovascular risk factors and could be a simple marker of increased risk. Large prospective studies are needed to confirm the present study findings.

**Table 2 : Blood glucose levels and cardiovascular risk factors**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men (n=532)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbers</td>
<td>120</td>
<td>171</td>
<td>151</td>
<td>20</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>21.5 ± 5</td>
<td>24.7 ± 6</td>
<td>23.8 ± 5</td>
<td>22.8 ± 6</td>
<td>25.9 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.89 ± 0.1</td>
<td>0.92 ± 0.1</td>
<td>0.92 ± 0.1</td>
<td>0.94 ± 0.1</td>
<td>0.95 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP mm Hg</td>
<td>121.4 ± 21</td>
<td>121.9 ± 27</td>
<td>120.8 ± 25</td>
<td>115.5 ± 23</td>
<td>128.6 ± 21</td>
<td>0.076</td>
</tr>
<tr>
<td>Cholesterol mg/dl</td>
<td>182.4 ± 37</td>
<td>190.7 ± 39</td>
<td>205.8 ± 46</td>
<td>190.2 ± 37</td>
<td>200.3 ± 47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol mg/dl</td>
<td>116.0 ± 36</td>
<td>122.9 ± 37</td>
<td>133.1 ± 39</td>
<td>118.9 ± 36</td>
<td>129.1 ± 45</td>
<td>0.005</td>
</tr>
<tr>
<td>HDL cholesterol mg/dl</td>
<td>39.5 ± 8</td>
<td>40.0 ± 9</td>
<td>39.3 ± 8</td>
<td>42.5 ± 9</td>
<td>37.8 ± 7</td>
<td>0.182</td>
</tr>
<tr>
<td>Triglycerides mg/dl</td>
<td>134.6 ± 55</td>
<td>139.2 ± 73</td>
<td>166.6 ± 93</td>
<td>143.8 ± 57</td>
<td>167.5 ± 91</td>
<td>0.005</td>
</tr>
</tbody>
</table>

| **Women (n=559)**  |         |         |         |         |         |             |
| Numbers             | 66      | 214     | 190     | 26      | 63      |             |
| BMI kg/m²           | 26.9 ± 7| 24.4 ± 5| 23.9 ± 5| 25.6 ± 6| 29.0 ± 6| <0.001      |
| Waist-hip ratio     | 0.84 ± 0.1| 0.83 ± 0.1| 0.83 ± 0.1| 0.99 ± 0.7| 0.86 ± 0.1| <0.001      |
| Systolic BP mm Hg   | 120.5 ± 21| 117.6 ± 20| 119.4 ± 22| 129.4 ± 23| 142.9 ± 26| <0.001      |
| Cholesterol mg/dl   | 187.2 ± 39| 190.9 ± 40| 205.8 ± 39| 209.7 ± 39| 203.0 ± 44| <0.001      |
| LDL cholesterol mg/dl | 124.2 ± 40| 124.1 ± 40| 137.4 ± 37| 139.3 ± 36| 129.9 ± 42| 0.007       |
| HDL cholesterol mg/dl | 37.4 ± 8| 40.8 ± 9| 39.5 ± 9| 40.4 ± 12| 39.0 ± 7| 0.020       |
| Triglycerides mg/dl | 127.8 ± 52| 128.5 ± 53| 143.9 ± 58| 150.2 ± 67| 170.4 ± 96| <0.001      |

BMI = body mass index, BP = blood pressure, LDL = low density lipoprotein, HDL = high density lipoprotein

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