Genetics, Obesity, and Environmental Risk Factors Associated with Type 2 Diabetes

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Aim
To determine the association between consanguineous marriages, obesity, and environmental risk factors associated with type 2 diabetes, in the adult Qatari population.

Methods
The case-control study was carried out among diabetic patients and healthy subjects at the Primary Healthcare Clinics (PHCs) and the survey was conducted from February to November 2003. The study included 338 cases (with diabetes) and 338 controls (without diabetes). Face-to-face interviews were based on a questionnaire that included variables such as age, gender, socioeconomic status, parity, income level, cigarette smoking, physical activity, body mass index (BMI), obesity, and lifestyle. Their health status was assessed by medical conditions, family history, physical examination, blood pressure, blood glucose, blood count, lipid profile, cholesterol total, HDL, LDL, and triglycerides analysis.

Results
The mean age (in years ± standard deviation) of cases versus controls was 45.5 ± 8.9 vs 42.4 ± 8.0, P < 0.001. The study revealed that there were statistically significant differences between diabetic and control subjects with respect to body mass index, low educational level, consanguineous marriage, and number of children (P < 0.001). The obesity was considerably more frequent among diabetes subjects (P < 0.001). Self reported family history (in first degree relatives) of diabetes (62.1% vs 44.4%, OR = 2.06, 95% confidence interval (CI) = 1.49-2.83) P < 0.001) was prominent among diabetic subjects. The diabetes was significantly common among the consanguineous marriages of the first degree relatives compared with the control group (33.1% vs. 24.6%, OR = 1.59, 95% CI = 1.11-2.29), P = 0.008). Systolic blood pressure (P = 0.023) and glucose fasting (P < 0.001) levels were significantly higher in diabetic patients than in control subjects. The logistic regression model showed that smoking (OR = 2.42 95% CI = 1.66-3.54, P < 0.0001); degree of consanguinity (OR = 1.38 95% CI = 1.13-1.69, P = 0.002), BMI (OR = 1.41 95% CI = 1.12-1.76, P = 0.003), level of education (OR = 1.23 95% CI = 1.04-1.45, P = 0.017), number of children (OR = 1.34 95% CI = 1.02-1.77, P = 0.037), and systolic blood pressure (OR = 1.01 95% CI = 1.00-1.02, P = 0.044) were considered as associated risk factors for diabetes.

Conclusion
The present study revealed that obesity, consanguinity, blood pressure, total cholesterol, HDL-cholesterol, and triglycerides were more prevalent in diabetic patients. The characterization of these factors will contribute to defining more effective and specific strategies to screen for and control diabetes and cardiovascular disease in a developing country.

Qatar, like many other developing countries, has witnessed a rapid change in many aspects of life during the last two decades. There has been a dramatic improvement of the national economy in terms of per capita income. These dramatic changes have had a great impact on urbanization and lifestyle of the Qatari community and as a result, diabetes mellitus has become the main public health problem.

The prevalence of type 2 diabetes has been rising worldwide (1). In particular, epidemics of this disorder have taken place in developing so-
cieties (2), with the highest prevalence recorded among the Pima Indians of Arizona, USA (3). In the developed and rapidly modernizing countries, there has been an increasing concern about the impact of type 2 diabetes on health services (4-8). The increasing prevalence of this disorder in the modern world has been attributed to an unmasking of genetic defects by environmental factors brought about by changes in lifestyle (9-12). Type 2 diabetes mellitus is a common multifactorial genetic syndrome, which is determined by several different genes and environmental factors (8-12). From a metabolic viewpoint, the most accepted model for the development of type 2 diabetes involves an interaction of insulin resistance with hyposecretion of insulin (13), but which abnormality comes first is still a matter of debate (14). Most investigators, however, believe that insulin resistance plays a predominant role in the pathogenesis of type 2 diabetes (15). In some populations, however, the role of insulin resistance has been questioned when high insulin sensitivities were found in a large proportion of subjects with type 2 diabetes (16). Another common belief is that type 2 diabetes is only one component of a more generalized metabolic syndrome (Syndrome X, ref. 17) which is caused by insulin resistance and/or hyperinsulinemia, and encompasses hypertension, dyslipidemia, and susceptibility to coronary heart disease (18). This viewpoint however, may not be true in all populations (19). In addition, a significant correlation between hyperinsulinemia and hyperuricemia does exist (19-22). The rising prevalence of non-insulin-dependent diabetes mellitus in developing societies has been attributed to an unmasking of genetically determined insulin resistance by a modern lifestyle.

The aim of this study was to determine the association between consanguineous marriages, lifestyle-habits, obesity, and environmental risk factors associated with type 2 diabetes in the adult Qatari population.

Subjects and Methods

This was a case-control study, designed to determine the relationship between type 2 diabetes, genetic factors, and life-style risk factors among the adult Qatari population between 25 and 65 years of age. The study was conducted in a period from February to November 2003.

Selection of Diabetic Subjects

Persons were classified as diabetics if their venous blood glucose values were ≥7.0 mmol/L or if they were currently taking diabetic medication (1). A total number of 338 diabetic Qatari patients aged 25-65 years was selected by a simple random method from Primary Health Care Centers. Their health status was assessed by recording previous medical conditions, family history, physical examination, blood pressure, blood glucose, blood count, cholesterol total, HDL, LDL, and triglycerides.

Selection of Control Subjects

Control subjects aged 25-65 years were identified from community as healthy if their venous blood glucose values were <6.1 mmol/L and if they had never received any diabetic medication. They were 344 healthy subjects who visited the PHC Centers for any reason other than acute or chronic disease. They were chosen randomly from the daily appointment list. The health status was assessed by recording previous medical conditions, family history, physical examination, blood pressure, blood glucose, blood count, cholesterol total, HDL, LDL, and triglycerides.

The study was approved by the Research Ethics Committee of Hamad General Hospital and Hamad Medical Corporation. Informed consent was obtained from each person who agreed to participate in this study, which was carried out in accord with the Helsinki Declaration. The survey was based on standardized interviews performed by trained health professionals and nurses. Patients were classified as physically inactive if they reported not participating in physical activities such as cycling or walking for at least 30 min/day.

Height and weight were measured using standardized methods; the participants wore light clothes and no shoes for this part of the examination. The BMI was calculated as weight in kilograms (with 1 kg subtracted to allow for clothing) divided by height in meters squared. Subjects were classified into three categories: acceptable weight, BMI<25; overweight, BMI 25-30; and obese, BMI>30 (8).

Blood pressure measurement was carried out by trained practical nurses according to World Health Organization (WHO) standardized criteria (18). The mean value obtained from the three readings was used in the analysis. Hyperten-
sion was defined according to WHO criteria as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication (18). Mean blood pressure was defined as 1/3 systolic pressure + 2/3 diastolic pressure. The pulse pressure was calculated as the difference between systolic and diastolic pressures. The fasting glucose test was performed according to the WHO recommendations (1). Plasma concentrations of glucose, insulin, triglycerides, total cholesterol, and HDL-cholesterol were determined in fasting blood samples (1).

**Clinical Investigation**

Samples for insulin were centrifuged and the serum was stored at -20 °C until assay. Serum insulin concentration were determined by a solid-phase 125I radio-immunoassay kit (DPC, Los Angeles, CA, USA). The intra- and interassay coefficients of variation were 5% and 10%, respectively. Serum glucose was determined by the glucose dehydrogenase method (Dimension clinical chemistry system, Dade International Inc., Deerfield, IL, USA). Total cholesterol and triglycerides were measured using enzymatic techniques on a Technicon Analyzer (Technicon Instruments, New York, NY, USA). Measurement of HDL-cholesterol was performed using the same technique following heparin-manganese precipitation of VLDL- and LDL-cholesterol. The level of LDL-cholesterol was calculated using the Friedewald formula (19).

**Statistical Analysis**

Student t test was used to test the significance of differences between mean values of two continuous variables. Chi-square analysis was performed to test the differences in proportions of categorical variables between two or more groups. In 2×2 tables, the Fisher exact test (two-tailed) replaced the χ² test if the assumptions underlying χ² were violated, namely in case of small sample size or when the expected frequency was less than 5 in any of the cells. Odds Ratio (OR) and their 95% confidence intervals (CI) was calculated by the Mantel-Haenszel test. Multivariate logistic regression analysis was used to predict risk factors for di-

<table>
<thead>
<tr>
<th>Table 1. Socio-demographic data of diabetic cases (n=338) and non diabetic controls (n=338)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age group:</td>
</tr>
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</tr>
<tr>
<td>35-50</td>
</tr>
<tr>
<td>&gt;50</td>
</tr>
<tr>
<td>Gender:</td>
</tr>
<tr>
<td>female</td>
</tr>
<tr>
<td>male</td>
</tr>
<tr>
<td>Current marital status:</td>
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<tr>
<td>single</td>
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<tr>
<td>married</td>
</tr>
<tr>
<td>Education level:</td>
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<td>secondary</td>
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<td>&gt;5,000 QAR</td>
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<td>&gt;5</td>
</tr>
<tr>
<td>Type of residence:</td>
</tr>
<tr>
<td>villa</td>
</tr>
<tr>
<td>shabia (mud house)</td>
</tr>
<tr>
<td>apartment</td>
</tr>
<tr>
<td>No. of rooms:</td>
</tr>
<tr>
<td>≤5</td>
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<tr>
<td>&gt;5</td>
</tr>
<tr>
<td>No. of people living at home:</td>
</tr>
<tr>
<td>≤5</td>
</tr>
<tr>
<td>&gt;5</td>
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</table>

*Abbreviations: OR – odds ratio; CI – confidence interval; QAR – Qatar Riyals, 1US$=3.65QAR.
Results

The mean ± standard deviation age for cases versus controls was 45.5 ± 8.9 vs 42.4 ± 8.0 years, \( P < 0.001 \) (Student t test).

Significantly more diabetics had low educational level (35.8% vs 23.4%, \( P < 0.001 \)), and had more than 5 children (47.9% vs 38.2%, \( P < 0.001 \); Table 1). Significantly less diabetic subjects lived in houses with more than 5 rooms (39.1% vs 47.0%, \( P = 0.036 \)) in households of more than five members (80.5% vs 71.6%, \( P = 0.007 \); Table 1).

The basic lifestyle habits, genetic, and family history among diabetic and non-diabetic cases are shown in Table 2. The diabetes was significantly more frequent among the consanguineous group (OR = 1.47, 95% CI = 1.07-2.03 and \( P = 0.013 \)). Furthermore, among first degree consanguinity the chances of diabetes were even higher (OR = 1.59, 95% CI = 1.11-2.29, \( P = 0.008 \)). Obesity was more common among diabetic patients 53.8% vs 41.1% (OR = 2.48, 95% CI = 1.61-3.84, \( P < 0.001 \)). Consumption of salty food, vegetables, and red meat was similar in the two groups. Consumption of fruit was higher (\( P = 0.011 \)), whereas consumption of fish/chicken was significantly lower in diabetic subjects (\( P < 0.001 \)), since they are more aware of

<table>
<thead>
<tr>
<th>Variable</th>
<th>all cases</th>
<th>controls</th>
<th>OR (95% CI)</th>
<th>( P )</th>
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<td>Consanguinity:</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>no</td>
<td>386 (57.1)</td>
<td>177 (52.4)</td>
<td>209 (61.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>yes</td>
<td>290 (42.9)</td>
<td>161 (47.6)</td>
<td>129 (38.2)</td>
<td>1.47 (1.07-2.03)</td>
</tr>
<tr>
<td>Degree of consanguinity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>386 (57.1)</td>
<td>177 (52.4)</td>
<td>209 (61.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>second degree</td>
<td>95 (14.1)</td>
<td>49 (14.5)</td>
<td>46 (13.6)</td>
<td>1.26 (0.78-2.02)</td>
</tr>
<tr>
<td>first degree</td>
<td>195 (28.8)</td>
<td>112 (33.1)</td>
<td>83 (24.6)</td>
<td>1.59 (1.11-2.29)</td>
</tr>
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<td>BMI group (kg/m²):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 (normal)</td>
<td>139 (20.6)</td>
<td>46 (14.2)</td>
<td>91 (26.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>25-30 (overweight)</td>
<td>216 (32.0)</td>
<td>108 (32.0)</td>
<td>108 (32.0)</td>
<td>1.90 (1.19-3.02)</td>
</tr>
<tr>
<td>&gt;30 (obese)</td>
<td>321 (47.5)</td>
<td>182 (53.8)</td>
<td>139 (41.1)</td>
<td>2.48 (1.61-3.84)</td>
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<td>Physical activity:</td>
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<tr>
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<td>321 (47.5)</td>
<td>180 (47.3)</td>
<td>141 (47.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>no</td>
<td>355 (52.5)</td>
<td>178 (52.7)</td>
<td>177 (52.4)</td>
<td>1.01 (0.74-1.38)</td>
</tr>
<tr>
<td>Smoking status:</td>
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<td></td>
<td></td>
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<tr>
<td>non smoker</td>
<td>526 (77.8)</td>
<td>288 (85.2)</td>
<td>238 (70.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>past smoker</td>
<td>74 (10.9)</td>
<td>29 (8.3)</td>
<td>45 (13.6)</td>
<td>0.50 (0.30-0.85)</td>
</tr>
<tr>
<td>smoker</td>
<td>76 (11.2)</td>
<td>22 (6.5)</td>
<td>54 (16.0)</td>
<td>0.34 (0.19-0.59)</td>
</tr>
<tr>
<td>Type of regular food intake:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Salty food:</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>322 (47.6)</td>
<td>172 (50.9)</td>
<td>150 (44.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>yes</td>
<td>354 (52.4)</td>
<td>166 (49.1)</td>
<td>188 (55.6)</td>
<td>0.77 (0.56-1.05)</td>
</tr>
<tr>
<td>Vegetables</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>yes</td>
<td>416 (61.5)</td>
<td>218 (64.5)</td>
<td>198 (58.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>no</td>
<td>290 (38.5)</td>
<td>120 (35.5)</td>
<td>140 (41.4)</td>
<td>0.78 (0.56-1.07)</td>
</tr>
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<td>Fruit:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>371 (54.9)</td>
<td>202 (59.8)</td>
<td>169 (50.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>no</td>
<td>305 (45.1)</td>
<td>136 (40.2)</td>
<td>169 (50.0)</td>
<td>0.67 (0.49-0.92)</td>
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<td>Red meat:</td>
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<tr>
<td>no</td>
<td>391 (57.8)</td>
<td>195 (57.7)</td>
<td>196 (58.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>yes</td>
<td>285 (42.2)</td>
<td>143 (42.3)</td>
<td>142 (42.0)</td>
<td>1.00 (0.73-1.37)</td>
</tr>
<tr>
<td>Fish/chicken:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>239 (35.4)</td>
<td>149 (44.1)</td>
<td>90 (26.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>yes</td>
<td>437 (64.6)</td>
<td>189 (55.9)</td>
<td>248 (73.4)</td>
<td>0.46 (0.33-0.64)</td>
</tr>
<tr>
<td>Family history in first degree relatives:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>hypertension:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>355 (52.5)</td>
<td>186 (55.0)</td>
<td>169 (50.0)</td>
<td>1.00</td>
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<tr>
<td>yes</td>
<td>321 (47.5)</td>
<td>152 (45.0)</td>
<td>169 (50.0)</td>
<td>0.82 (0.60-1.12)</td>
</tr>
<tr>
<td>heart attack:</td>
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<td></td>
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<td></td>
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<tr>
<td>no</td>
<td>515 (76.2)</td>
<td>251 (74.3)</td>
<td>264 (78.1)</td>
<td>1.00</td>
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<tr>
<td>yes</td>
<td>161 (23.8)</td>
<td>87 (25.7)</td>
<td>74 (21.9)</td>
<td>1.24 (0.85-1.79)</td>
</tr>
<tr>
<td>diabetes mellitus:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>316 (48.7)</td>
<td>128 (37.9)</td>
<td>188 (55.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>yes</td>
<td>360 (53.3)</td>
<td>212 (62.1)</td>
<td>152 (44.4)</td>
<td>2.06 (1.49-2.83)</td>
</tr>
</tbody>
</table>

*Abbreviations: BMI – body mass index; OR – odds ratio; CI – confidence interval.*
Table 3. Baseline physical and metabolic characteristics (mean± standard deviation) in cases (n=338) and controls (n=338)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, BMI (kg/m²)</td>
<td>30.5±4.8</td>
<td>28.6±5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132.0±15.8</td>
<td>128.9±16.8</td>
<td>0.023</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82.2±9.2</td>
<td>81.0±9.6</td>
<td>0.098</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>98.8±9.8</td>
<td>96.9±10.7</td>
<td>0.035</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>49.8±13.9</td>
<td>47.9±13.4</td>
<td>0.071</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5.4±1.1</td>
<td>4.6±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>1.4±0.3</td>
<td>1.0±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>3.7±0.9</td>
<td>3.2±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>1.8±1.1</td>
<td>1.1±0.7</td>
<td>0.050</td>
</tr>
</tbody>
</table>

*Student t test.

Table 4. Multivariate logistic regression analysis for diabetes as dependent variable and lifestyle and genetic factors as independent variables*

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Smoking</td>
<td>2.42 (1.66-3.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Degree of consanguinity</td>
<td>1.38 (1.13-1.69)</td>
<td>0.002</td>
</tr>
<tr>
<td>Body mass index, BMI (kg/m²)</td>
<td>1.41 (1.12-1.78)</td>
<td>0.003</td>
</tr>
<tr>
<td>Level of education</td>
<td>1.32 (1.04-1.69)</td>
<td>0.017</td>
</tr>
<tr>
<td>Number of children</td>
<td>1.34 (1.02-1.77)</td>
<td>0.037</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.01 (1.00-1.02)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

*Abbreviations: OR – odds ratio; CI – confidence interval.

Discussion

To the best of our knowledge, there are no population-based studies that have examined the prevalence of diabetes and associated risk factors in Qatar. In the present study, smoking, consanguineous marriages, number of people living in the same household, and number of children were positively associated with diabetes.

Many risk factors have been identified which influence the prevalence or incidence of diabetes. Factors of particular importance are family history of diabetes mellitus, age, overweight, increased abdominal fat, hypertension, lack of physical exercise, and ethnic background (11).

In our study, low educational level, smoking, obesity, and systolic blood pressure were associated risk factors. This is consistent with previous studies (3-8,17). One study reported relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians (17). The high prevalence of diabetes in the Qatari population appears to be related to the interaction of environmental factors, such as obesity, with a diabetic genotype. The results confirm the possible detrimental effects of developing society on native populations. These findings are consistent with previous reports showing an association between diabetes’ socioeconomic status, lifestyle habits, obesity, and cardiovascular risk factors (3-8,17,20). In Japan, type 2 diabetes is an increasingly important problem as a lifestyle related disease, as the total diabetic population is estimated at approximately 7 million (21).

In the present study, most patients with type 2 diabetes mellitus were found to be obese. This complements other recent studies (4,5,8,11,17,20). The association between type 2 diabetes mellitus and obesity is probably the result of multiple mechanisms, including rises in plasma free fatty acids and tumor necrosis factor alpha released from “full” adipocytes (11). More recently, it has been shown that in the Indian population, general and central obesity were associated with a family history of diabetes (20).

A family history of diabetes may increase the risk of hypertension and hyperlipidemia indirectly through its connection to BMI (8-10). Furthermore, lack of physical exercise is also associated with diabetes mellitus, which led to the finding that exercise enhances the action of insulin, although the present study did not confirm it. Glucose tolerance test data on 794 first-degree relatives of diabetics in pedigrees ascertained through non-insulin dependent diabetes mellitus were used to identify risk factors for diabetes in southeastern Michigan (20). In the Michigan study, the general risk factors, age and obesity, were important in predicting diabetes at the initial visit, although the predicted risk curves were very...
different for men and women. Our study in Qatar showed that diabetes was more common among first degree relatives in addition to obesity and environmental factors influencing glucose tolerance among siblings.

In summary, the present study was directed at determining the effect of consanguineous marriages, obesity, and environmental risk factors of diabetes in the adult population of Qatar. The characterization of these factors will contribute to defining more effective and specific strategies to screen for and control diabetes mellitus in this developing country. From a lifestyle modification perspective, the importance of body weight control by diet and exercise as well as refraining from excessive smoking and avoiding consanguineous marriages should be emphasized.

Acknowledgement

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