Is There a Clear Threshold for Fasting Plasma Glucose That Differentiates Between Those With and Without Neuropathy and Chronic Kidney Disease?

The Singapore Prospective Study Program

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Recent studies suggest that no distinct glycemic threshold consistently differentiates individuals with or without retinopathy. The authors sought to determine whether the same was true for other microvascular complications. They studied 5,094 participants with fasting plasma glucose values and concurrent microvascular complications from 4 previous cross-sectional surveys carried out in Singapore (1982–1998) who attended a follow-up examination in 2004–2007. Peripheral neuropathy was diagnosed based on abnormal responses to a 10-g monofilament or neurothesiometer test. Chronic kidney disease was defined in various ways by using albuminuria (urine albumin: creatinine ratio >30 μg/mg) and estimated glomerular filtration rate, alone and in combination. Prevalence of peripheral neuropathy was 7.5%. For chronic kidney disease, prevalence of albuminuria only was 10.5%, estimated glomerular filtration rate of <60 mL/minute per 1.73 m² only was 4.1%, and both was 2.1%. Prevalence of peripheral neuropathy and chronic kidney disease gradually increased in relation to fasting plasma glucose, beginning at levels below the existing diagnostic threshold for diabetes mellitus of 7.0 mmol/L (126 mg/dL). For chronic kidney disease, these associations persisted after adjustment for age, gender, ethnic group, and hypertension. Current diagnostic thresholds for diabetes mellitus have limited sensitivity for identifying individuals with these microvascular complications. Ascertaining these individuals may require development and application of novel screening strategies.

Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia. In 1997, the American Diabetes Association Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recommended that fasting plasma glucose (FPG) testing should be the preferred method for diagnosing diabetes (1). They further recommended a reduction in the diagnostic threshold for FPG from 7.8 mmol/L (140 mg/dL) to 7.0 mmol/L (126 mg/dL). This threshold was established primarily on the basis of 3 studies showing that the prevalence of retinopathy increased dramatically above this level of FPG (2–4). In 2003, a follow-up report on the diagnosis of diabetes mellitus addressed the question as to whether this diagnostic threshold should be changed, citing a study showing that the prevalence of retinopathy in Pima Indians increased at FPG levels above 5.8–5.9 mmol/L (104 mg/dL–106 mg/dL) (5). At that time, however, the committee’s conclusion was that, “in the absence of supporting data from additional populations, no new cut point can be recommended” (5, p. 3161).

Since then, an analysis of retinopathy data from 3 large population-based studies that included more than 10,000...
individuals found little evidence of a clear glycemic threshold for retinopathy that was consistent across the 3 populations (6). Instead, a more gradual increase in retinopathy prevalence with FPG was observed, which strongly suggests a continuous relation, similar to the one between glycemia and cardiovascular disease (7).

The microvascular complications of chronic hyperglycemia are not limited to retinopathy and include chronic kidney disease and peripheral neuropathy. Evidence that the relation between glycemia and these other complications also shows a pattern similar to that observed for retinopathy would provide further motivation to reexamine the basis by which the diagnostic threshold for diabetes mellitus has been established. The aim of our current study was to examine the relation between FPG and the prevalence of chronic kidney disease and peripheral neuropathy in a large population spanning the full range of glucose tolerance.

MATERIALS AND METHODS

Study design and population

We invited 10,445 subjects from 4 population-based, cross-sectional surveys conducted in Singapore (1982–1998) to participate in a repeat examination from 2004 to 2007. The 4 studies include the Thyroid and Heart Study 1982–1984 (8), the National Health Survey 1992 (9), the National University of Singapore Heart Study 1993–1995 (10), and the National Health Survey 1998 (11). Briefly, all studies included a random sample of individuals from the Singapore population, with disproportionate sampling stratified by ethnicity to increase the number in the minority ethnic groups (Malays and Asian Indians). Subjects deceased at the time of follow-up (as shown by data linkage to the Registry of Births and Deaths) were excluded (n = 517). Also excluded were 6 subjects who had emigrated and 85 who had errors in the records regarding their identity card number.

Subjects were contacted to obtain an appointment for investigators to administer the questionnaire at a subject’s home. Three home visits were made on 3 different occasions, including one weekend and weekday, before a subject was deemed noncontactable. After this procedure was completed, 2,673 subjects were noncontactable. Of those subjects who could be contacted, 30 (0.3%) refused to participate. All subjects were invited to attend a health examination for additional tests and collection of biologic specimens shortly after the home visit. A total of 7,742 (74.1% response rate) subjects completed the questionnaire; 5,157 of them (66.6% of those who completed the questionnaire or 49.4% of all eligible subjects) also attended the health examination (Figure 1).

Ethics approval was obtained from 2 institutional review boards (the National University of Singapore and the Singapore General Hospital). Informed consent was obtained before the study was conducted.

Data collection

Data on demographic and lifestyle factors (alcohol consumption, smoking), as well as medical history (including physician-diagnosed hypertension, diabetes mellitus, and hyperlipidemia), were collected by using interviewer-administered questionnaires. For the health examination, participants were examined the morning following a 10-hour overnight fast. Venous blood was drawn and collected in plain and fluoride oxalate tubes and was stored at 4°C for a maximum of 4 hours prior to processing. A random urine specimen was also collected.

All biochemical analyses of blood were carried out at the National University Hospital Referral Laboratory, which is accredited by the College of American Pathologists. Serum total cholesterol, triglyceride, and high density lipoprotein cholesterol were measured by using an automated autoanalyzer (ADVIA 2400; Bayer Diagnostics, Tarrytown, New York). Low density lipoprotein cholesterol levels were calculated by using the Friedewald formula. Plasma glucose was also assayed with enzymatic methods (ADVIA 2400) by using blood collected in fluoride oxalate tubes. Plasma creatinine was measured by enzymatic methods (ADVIA 2400). The new National Institute of Standards and Technology Standard Reference Material (NIST SRM) 967, Creatinine in Frozen Human Serum, was developed in collaboration with the National Kidney Disease Education Program and the College of American Pathologists to meet the need for improved calibration of clinical instruments and procedures for measuring serum creatinine. The intraday and interday coefficients of variation for total cholesterol, triglyceride, high density lipoprotein cholesterol, plasma glucose, and creatinine were 0.80%–1.57% and 0.93%–1.15%, 0%–3.85% and 1.27%–3.40%, 0.56%–0.65% and 1.18%–2.00%, 0%–0.93% and 1.68%–1.83%, and 2.50%–6.60% and 5.60%–7.20%, respectively. Random urinary spot albumin and creatinine were measured by using commercial assays (Immulite; Diagnostic Products Corporation, Gwynedd, United Kingdom for urinary albumin and Roche Diagnostics GmbH, Mannheim, Germany for creatinine). The lower detection limits for urinary albumin and creatinine were 0.5 mg/L and 0.027 mmol/L, respectively.

Height was measured without shoes by using a wall-mounted stadiometer. Weight was measured in light clothing by using the same digital scale (SECA, model 782-2321009; Vogel & Halle, Hamberg, Germany) for all participants. Participants were instructed to remove any objects such as keys and mobile phones before measurement.

An automated blood pressure monitor (Dinamap Pro100V2; Criticon, Norderstedt, Germany) was used to take 2 blood pressure readings from participants after 5 minutes of rest. A third reading was performed if the difference between the 2 readings of systolic blood pressure was greater than 10 mm Hg or of diastolic blood pressure was greater than 5 mm Hg. Mean values of the closest 2 readings were calculated. The respective inter- and intraobserver coefficients of variation for systolic blood pressure were 0.51%–10.20% and 0%–2.5%, whereas they were 0.41%–7.50% and 0%–2.5% for diastolic blood pressure.

The vibration perception threshold was measured with a neurothesiometer (Horwell, Wilford Industrial EST, Nottingham, United Kingdom). The probe was applied to the apex of the big toe and medial malleolus of both feet. The voltage was gradually increased from zero until the subjects
indicated verbally that the vibrations could be felt, and then the reading was recorded. A Touch-Test Sensory Evaluator 5.07 (10-g) monofilament (North Coast Medical, Morgan Hill, California) was applied to 5 noncalloused plantar sites per foot. The test sites were the distal great toe, third toe, and fifth toe and the first and fifth metatarsal heads. The patients were asked to answer yes if they could feel the filament. The number of sites that they could feel was recorded for each foot. All neurologic examinations were performed by research assistants who underwent standardized training conducted by a consultant endocrinologist. These research assistants were nurses or medically qualified physicians. Over the course of the study, only 4 individuals were involved in making these measurements.

During the period April 2, 2005, to February 20, 2006, because of limited resources, neurologic examination of the feet was carried out for only every alternate Chinese participant but for all participants from other ethnic groups. Furthermore, approval and funding for the urine examination was obtained only after the main study had begun, which

Figure 1. Flow diagram of subjects considered for inclusion in the study of fasting plasma glucose and microvascular complications of diabetes mellitus, the Singapore Prospective Study Program, 2004–2007.
explains the smaller number of subjects available for analysis in relation to the measurement of plasma creatinine and urine albumin:creatinine ratio. For this study, we included only those participants with both urine albumin:creatinine ratio and plasma creatinine measurements in our assessment in relation to chronic kidney disease (Figure 1).

Definitions

Diabetes mellitus was defined as FPG of $\geq 7.0$ mmol/L (126 mg/dL) or a known history of diabetes mellitus (both types 1 and 2, but a large majority was type 2) and current use of antidiabetic agents. Hypertension was considered a systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg or a history of hypertension or current use of antihypertensive medications. Peripheral neuropathy was defined as either a neurothesiometer reading of greater than 25 V (12) at any site, as described above, or monofilament sensory test of fewer than 4 of 5 points in either foot (13). A urine albumin:creatinine ratio of $30 \mu g/mg$ or above was taken to indicate the presence of albuminuria. This ratio was measured from a single urine sample obtained from subjects during the health examination. Estimated glomerular filtration rate (eGFR) was

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**Table 1.** Characteristics of Participants Who Completed Only the Questionnaire Compared with Both the Questionnaire and the Health Examination, a the Singapore Prospective Study Program, 2004–2007

<table>
<thead>
<tr>
<th></th>
<th>Questionnaire Only (n = 2,585)</th>
<th>Both the Questionnaire and Health Screening (n = 5,157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49.3 (13.8)</td>
<td>49.9 (11.8)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45.6</td>
<td>48.1</td>
</tr>
<tr>
<td>Female</td>
<td>54.4</td>
<td>51.9</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>60.7</td>
<td>66.6</td>
</tr>
<tr>
<td>Malay</td>
<td>21.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Asian Indian</td>
<td>14.4</td>
<td>13.9</td>
</tr>
<tr>
<td>Other</td>
<td>3.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Age group, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>28.2</td>
<td>19.3</td>
</tr>
<tr>
<td>40–49</td>
<td>28.4</td>
<td>33.5</td>
</tr>
<tr>
<td>50–59</td>
<td>20.9</td>
<td>28.2</td>
</tr>
<tr>
<td>$\geq$60</td>
<td>22.4</td>
<td>19.0</td>
</tr>
<tr>
<td>History of hypertension$^b$</td>
<td>23.4</td>
<td>21.8</td>
</tr>
<tr>
<td>History of diabetes$^c$</td>
<td>12.5</td>
<td>9.3</td>
</tr>
<tr>
<td>Current smoker$^d$</td>
<td>15.1</td>
<td>12.2</td>
</tr>
<tr>
<td>Alcohol consumption$^e$</td>
<td>16.7</td>
<td>24.7</td>
</tr>
</tbody>
</table>

$^a$ Data are expressed as mean (standard deviation) or % (proportion of the group). The $\chi^2$ test was used for categorical variables to compare differences between the 2 groups. No statistical difference was noted between the 2 groups.

$^b$ Derived from participants who answered yes to the question, Has a physician, a nurse, or other healthcare professional told you that you have high blood pressure? or Are you currently taking antihypertension medications?

$^c$ Derived from participants who answered yes to the question, Has a physician ever told you that you have diabetes? or Are you currently taking antidiabetic agents?

$^d$ Defined as a yes response to the questions, Have you ever smoked cigarettes? and Do you smoke now?

$^e$ Defined as a yes response to the question, Have you consumed alcohol within the past 3 months?

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**Table 2.** Demographic Characteristics of Participants Eligible for the Analysis of Each Microvascular Complication of Diabetes Mellitus, a the Singapore Prospective Study Program, 2004–2007

<table>
<thead>
<tr>
<th></th>
<th>Peripheral Neuropathy (n = 3,957)</th>
<th>Chronic Kidney Disease (n = 4,512)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49.7 (11.6)</td>
<td>49.7 (11.8)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48.4</td>
<td>48.0</td>
</tr>
<tr>
<td>Female</td>
<td>51.6</td>
<td>52.0</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>59.1</td>
<td>66.8</td>
</tr>
<tr>
<td>Malay</td>
<td>18.5</td>
<td>15.1</td>
</tr>
<tr>
<td>Asian Indian</td>
<td>17.1</td>
<td>13.7</td>
</tr>
<tr>
<td>Other</td>
<td>5.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Age group, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>19.2</td>
<td>20.0</td>
</tr>
<tr>
<td>40–49</td>
<td>34.5</td>
<td>33.5</td>
</tr>
<tr>
<td>50–59</td>
<td>28.3</td>
<td>28.1</td>
</tr>
<tr>
<td>$\geq$60</td>
<td>18.0</td>
<td>18.4</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>24.2 (5.1)</td>
<td>24.0 (4.4)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>132.3 (20.8)</td>
<td>132.2 (20.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>78.0 (10.7)</td>
<td>77.9 (10.9)</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>5.2 (1.6)</td>
<td>5.1 (1.5)</td>
</tr>
<tr>
<td>Hypertension$^b$</td>
<td>41.2</td>
<td>40.9</td>
</tr>
<tr>
<td>Diabetes mellitus$^c$</td>
<td>11.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Current smoker$^d$</td>
<td>12.3</td>
<td>12.1</td>
</tr>
<tr>
<td>Alcohol consumption$^e$</td>
<td>22.6</td>
<td>24.6</td>
</tr>
</tbody>
</table>

$^a$ Data are expressed as mean (standard deviation) or % (proportion of the group). Continuous variables for the 2 groups were compared by using Student's $t$ test. The $\chi^2$ test was used for categorical variables. No statistical difference was noted between the 2 groups.

$^b$ Defined as systolic blood pressure $>140$ mm Hg or diastolic blood pressure $>90$ mm Hg or history of hypertension or current use of antihypertensive medications.

$^c$ Defined as fasting plasma glucose level $>7.0$ mmol/L (126 mg/dL) or a known history of diabetes mellitus and current use of antidiabetic agents.

$^d$ Defined as a yes response to the questions, Have you ever smoked cigarettes? and Do you smoke now?

$^e$ Defined as a yes response to the question, Have you consumed alcohol within the past 3 months?
calculated by using the “modification of diet in renal disease” equation and was estimated from plasma creatinine obtained in a blood sample provided by participants at the health examination (14). Chronic kidney disease was defined in a number of ways. Firstly, the population was divided into 2 groups: 1) those without albuminuria and an eGFR of greater than 60 mL/minute per 1.73 m² (the reference group); and 2) those with either albuminuria or an eGFR of less than 60 mL/minute per 1.73 m². The latter group was further divided into 1) those with albuminuria only (eGFR >60 mL/minute per 1.73 m²), 2) those with an eGFR of less than 60 mL/minute per 1.73 m² only (no albuminuria), and 3) those with both albuminuria and an eGFR of less than 60 mL/minute per 1.73 m².

Statistical analysis

This cross-sectional analysis was based on individuals who both completed the questionnaire and had health examination data available. The exposure variable (FPG) and outcomes (peripheral neuropathy and chronic kidney disease) were all measured during the same visit as the health examination. Of 7,742 participants, 5,157 also attended the health examination. Of this group, participants whose FPG and plasma creatinine were not measured (n = 63) were excluded; thus, data on 5,094 participants were left for analysis. Of this latter group, 3,957 participants were assessed for peripheral neuropathy and 4,512 for chronic kidney disease (Figure 1). The population of participants whose FPG was less than 7.0 mmol/L (126 mg/dL) and who were not taking antidiabetic agents was divided into 4 FPG groups based on approximate quartile cutpoints: less than 4.5 mmol/L (<81 mg/dL) (quartile 1), 4.5–4.7 mmol/L (81 mg/dL–85 mg/dL) (quartile 2), 4.8–5.1 mmol/L (86 mg/dL–92 mg/dL) (quartile 3), and 5.2–6.9 mmol/L (93 mg/dL–125 mg/dL) (quartile 4). In addition, we considered a fifth group comprising individuals who had diabetes mellitus, as defined above. The chi-square test was used to compare proportions of categorical variables between the groups. Odds ratios and 95% confidence intervals were obtained by using the logistic regression model to determine the association between different quartiles of FPG and diabetes mellitus with microvascular outcomes. The reference group was FPG quartile 1 (<4.5 mmol/L (<81 mg/dL)). The population was also categorized into 3 groups: 1) normal fasting glucose—less than 5.6 mmol/L (<100 mg/dL), 2) impaired fasting glucose—5.6 mmol/L–6.9 mmol/L (100 mg/dL–125 mg/dL), and 3) diabetes mellitus (as previously defined). Odds ratios and 95% confidence intervals were also obtained with the normal fasting glucose group as the reference.

Stata 10 for Windows software (Stata Corporation, College Station, Texas) was used. All statistical tests were 2-sided, with a level of significance defined as P < 0.05. In this paper, all values are given as mean (standard deviation) unless stated otherwise.

RESULTS

The characteristics of participants who completed only the questionnaire (n = 2,585) compared with those who completed both the questionnaire and the health examination are shown in Table 1. Note that, for this table, history of hypertension was derived from participants who answered yes to the question, Has a physician, a nurse, or other healthcare professional told you that you have high blood pressure? or Are you currently taking antihypertension medications?; history of diabetes was derived from participants who answered yes to the question, Has a physician ever told you that you have diabetes? or Are you currently taking antidiabetic agents? Groups of participants who completed only the questionnaire and both the questionnaire and the health examination were similar regarding age and...
Table 3. Association Between Microvascular Complications and Categories of Fasting Plasma Glucose and Diabetes Mellitus, the Singapore Prospective Study Program, 2004–2007

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose, mmol/L</th>
<th>&lt;4.5 (Quartile 1)</th>
<th>4.5–4.7 (Quartile 2)</th>
<th>4.8–5.1 (Quartile 3)</th>
<th>5.2–6.9 (Quartile 4)</th>
<th>≥7 or Known Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>1.00</td>
<td>1.00</td>
<td>1.35</td>
<td>0.90</td>
<td>1.67**</td>
</tr>
<tr>
<td>Multivariate^a</td>
<td>1.19</td>
<td>0.83</td>
<td>1.54</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>Multivariate^b</td>
<td>1.16</td>
<td>0.80</td>
<td>1.24</td>
<td>0.77</td>
<td>0.77</td>
</tr>
<tr>
<td>Albuminuria alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>1.00</td>
<td>1.29</td>
<td>1.24</td>
<td>2.05</td>
<td>2.84***</td>
</tr>
<tr>
<td>Multivariate^a</td>
<td>1.16</td>
<td>1.04</td>
<td>1.55</td>
<td>2.18</td>
<td>2.18</td>
</tr>
<tr>
<td>Multivariate^b</td>
<td>1.07</td>
<td>0.90</td>
<td>1.28</td>
<td>1.81</td>
<td>1.81</td>
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<tr>
<td>Low eGFR alone</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>1.00</td>
<td>1.31</td>
<td>1.65</td>
<td>3.74***</td>
<td>2.30</td>
</tr>
<tr>
<td>Multivariate^a</td>
<td>1.06</td>
<td>1.14</td>
<td>1.25</td>
<td>2.07**</td>
<td>1.25</td>
</tr>
<tr>
<td>Multivariate^b</td>
<td>1.02</td>
<td>1.05</td>
<td>1.13</td>
<td>1.89**</td>
<td>1.13</td>
</tr>
<tr>
<td>Albuminuria and low eGFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>1.00</td>
<td>0.84</td>
<td>0.87</td>
<td>4.64***</td>
<td>2.07</td>
</tr>
<tr>
<td>Multivariate^a</td>
<td>0.57</td>
<td>0.48</td>
<td>0.82</td>
<td>1.90</td>
<td>0.82</td>
</tr>
<tr>
<td>Multivariate^b</td>
<td>0.54</td>
<td>0.42</td>
<td>0.68</td>
<td>1.59</td>
<td>0.68</td>
</tr>
<tr>
<td>Albuminuria or low eGFR</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>1.00</td>
<td>1.25</td>
<td>1.54</td>
<td>3.22***</td>
<td>2.47</td>
</tr>
<tr>
<td>Multivariate^a</td>
<td>1.06</td>
<td>1.15</td>
<td>1.57</td>
<td>2.08***</td>
<td>1.57</td>
</tr>
<tr>
<td>Multivariate^b</td>
<td>0.99</td>
<td>0.99</td>
<td>1.32</td>
<td>1.76***</td>
<td>1.32</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.
^a P < 0.05; **P < 0.01; ***P < 0.0001.
^b Adjusted for age, gender, ethnicity, and hypertension.

Gender. Slightly more Chinese and fewer Malays attended the health examination. Notably, fewer participants with known hypertension or diabetes mellitus completed the health examination.

The characteristics of participants assessed for peripheral neuropathy and chronic kidney disease are shown in Table 2. With the exception of a smaller proportion of Chinese among those assessed for peripheral neuropathy, no significant differences were noted between the groups available for analysis in relation to each of the complications.

The prevalence of peripheral neuropathy in the overall population was 7.5%. For chronic kidney disease, the prevalence of albuminuria only was 10.5%, of eGFR less than 60 mL/minute per 1.73 m² was only 4.1%, and of both albuminuria and eGFR less than 60 mL/minute per 1.73 m² was 2.1% (Figure 2). Participants with diabetes had a higher prevalence of microvascular complications when compared with those without diabetes: 16.6% versus 6.4% (P < 0.001) for peripheral neuropathy, 37.6% versus 8.6% (P < 0.001) for albuminuria only, 8.9% versus 4.5% (P = 0.001) for eGFR less than 60 mL/minute per 1.73 m² only, and 15.1% versus 1.5% (P < 0.001) for both albuminuria and eGFR less than 60 mL/minute per 1.73 m². For both peripheral neuropathy and chronic kidney disease, prevalence increased with increasing quartiles of FPG, beginning with a FPG level of less than 4.5 mmol/L.

The odds ratios for each complication associated with each quartile, using the lowest quartile as the reference, are shown in Table 3. In univariate analysis, higher FPG was associated with increased risk of complications. This increased risk reached statistical significance at an FPG level of 5.2–6.9 mmol/L for peripheral neuropathy and as low as 4.8–5.1 mmol/L for chronic kidney disease. After adjustment for age, gender, and ethnicity, FPG below the level used to diagnose diabetes was no longer associated with peripheral neuropathy. However, for chronic kidney disease, the associations with FPG were attenuated but remained statistically significant even after adjustment for age, gender, ethnicity, and hypertension. On visual inspection, there was no clear threshold above which prevalence increased substantially (Figure 2). Exclusion of individuals with diabetes mellitus receiving treatment, and those with hypertension, did not change the observed patterns of association (data not shown). The association between FPG and the presence of microvascular complications was also consistent in all ethnic groups (data not shown).
Participants were also further grouped as having normal fasting glucose, impaired fasting glucose, and diabetes mellitus for each of the outcomes (Table 4). Our findings illustrate an increasing risk of microvascular complications, with impaired fasting glucose associated with an intermediate risk between normal fasting glucose and diabetes mellitus.

**DISCUSSION**

In this population-based study, we showed that the prevalence of chronic kidney disease and peripheral neuropathy is substantial (approximately 5%), even at the lowest FPG levels. Furthermore, prevalence of these disorders increased gradually with FPG, beginning well below the currently accepted threshold of 7.0 mmol/L (126 mg/dL) for diagnosing diabetes mellitus. This finding was especially true for chronic kidney disease, where the association with blood glucose remained statistically significant despite adjustment for age, gender, ethnic group, and the presence of hypertension. Our findings thus confirm, and extend, those from previous studies that have reported that impaired glucose tolerance and impaired fasting glucose are associated with increased prevalence of albuminuria (15–17) and peripheral neuropathy (18, 19), although these results were not found in all studies (20, 21).

Strengths of our study include the following. A large number of participants with normal glucose levels offered the opportunity to examine the association between FPG and microvascular complications at levels below the currently defined FPG threshold of 7.0 mmol/L (126 mg/dL). Ethnic groups representative of the major populations in Asia, a region in which the prevalence of diabetes mellitus is expected to increase over the next several decades (22), were included. In addition, both reduced eGFR and albuminuria were considered in the definition of chronic kidney disease, whereas other studies have often used only one parameter to define chronic kidney disease.

**Table 4.** Association Between Microvascular Complications and Categories of Normal Fasting Glucose, Impaired Fasting Glucose, and Diabetes Mellitus, the Singapore Prospective Study Program, 2004–2007

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted ORa</th>
<th>95% CI</th>
<th>Adjusted ORb</th>
<th>95% CI</th>
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<tr>
<td><strong>Peripheral neuropathy</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Normal fasting glucose</td>
<td>3,166</td>
<td>65.6</td>
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<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Impaired fasting glucose</td>
<td>358</td>
<td>10.1</td>
<td>1.4</td>
<td>0.9, 2.1</td>
<td>0.75</td>
<td>0.49, 1.15</td>
<td>0.73</td>
<td>0.48, 1.12</td>
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<td>433</td>
<td>24.3</td>
<td>3.06***</td>
<td>2.3, 4.1</td>
<td>1.36</td>
<td>0.99, 1.89</td>
<td>1.31</td>
<td>0.95, 1.18</td>
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<td><strong>Albuminuria and eGFR</strong></td>
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<tr>
<td>&gt;60 mL/minute per 1.73 m²</td>
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<td>Normal fasting glucose</td>
<td>3,691</td>
<td>57.9</td>
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<td>1.00</td>
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<td>375</td>
<td>12.0</td>
<td>2.37***</td>
<td>1.74, 3.23</td>
<td>1.79***</td>
<td>1.30, 2.47</td>
<td>1.55**</td>
<td>1.12, 2.15</td>
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<tr>
<td>Diabetes mellitus</td>
<td>446</td>
<td>30.1</td>
<td>7.07***</td>
<td>5.55, 9.00</td>
<td>5.06***</td>
<td>3.90, 6.57</td>
<td>4.31***</td>
<td>3.31, 5.63</td>
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<tr>
<td>No albuminuria and eGFR</td>
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<td>Normal fasting glucose</td>
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<td>57.9</td>
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<td>1.00</td>
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<tr>
<td>Impaired fasting glucose</td>
<td>375</td>
<td>11.8</td>
<td>1.77*</td>
<td>1.11, 2.82</td>
<td>0.99</td>
<td>0.61, 1.62</td>
<td>0.94</td>
<td>0.57, 1.53</td>
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<td>30.1</td>
<td>2.20**</td>
<td>1.39, 3.49</td>
<td>1.01</td>
<td>0.62, 2.65</td>
<td>0.90</td>
<td>0.55, 1.47</td>
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<td>&gt;60 mL/minute per 1.73 m²</td>
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<tr>
<td>Impaired fasting glucose</td>
<td>375</td>
<td>13.8</td>
<td>3.81***</td>
<td>2.01, 7.22</td>
<td>1.62</td>
<td>0.82, 3.19</td>
<td>1.36</td>
<td>0.68, 2.70</td>
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<td>Diabetes mellitus</td>
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<td>44.7</td>
<td>14.64***</td>
<td>9.28, 23.08</td>
<td>5.39***</td>
<td>3.23, 8.98</td>
<td>4.14***</td>
<td>2.47, 6.95</td>
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<tr>
<td>No albuminuria or eGFR</td>
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</tr>
<tr>
<td>Normal fasting glucose</td>
<td>3,691</td>
<td>60.3</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
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<tr>
<td>Impaired fasting glucose</td>
<td>375</td>
<td>12.2</td>
<td>2.31***</td>
<td>1.79, 2.98</td>
<td>1.50**</td>
<td>1.14, 1.96</td>
<td>1.33*</td>
<td>1.01, 1.75</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>446</td>
<td>27.5</td>
<td>6.20***</td>
<td>5.02, 7.65</td>
<td>3.68***</td>
<td>2.93, 4.63</td>
<td>3.17***</td>
<td>2.51, 4.00</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio of microvascular complications, with the normal fasting glucose group as the reference.

* P < 0.05; **P < 0.01; ***P < 0.0001.

a Adjusted for age, gender, and ethnicity.
b Adjusted for age, gender, ethnicity, and hypertension.

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Our study also has several limitations. FPG level as well as albuminuria were measured on only one occasion, which may have resulted in a degree of misclassification, particularly for albuminuria. However, this misclassification is likely non-differential and therefore would have only reduced the magnitude of the associations observed. Our overall response rate was low (50%), and persons with known diabetes mellitus and hypertension were less likely to attend the health examination during which the presence of microvascular complications was assessed. This limitation may have led to underestimation of the prevalence of these microvascular complications, particularly in the diabetic range. However, since this study dealt primarily with the association between FPG below the range generally associated with diabetes mellitus, we believe that our findings, and interpretation of these findings, are valid. Finally, because this study is cross-sectional, we can determine only that an association exists between FPG and microvascular complications; we cannot infer causality.

The finding of a considerable number of non-diabetics with peripheral neuropathy and chronic kidney disease deserves public health attention. After all, blood pressure control and blockade of the renin-angiotensin system has been shown to reduce the risk of progression to renal failure (23), and lifestyle changes with diet and exercise have been shown to improve peripheral neuropathy in patients with impaired glucose tolerance (24). One way to identify the sizable number of individuals with FPG in the lower glycemic range who nevertheless have peripheral neuropathy and chronic kidney disease would be to lower the threshold by which we diagnose diabetes mellitus. In our study, lowering the cutpoint for the diagnosis of diabetes from 7.0 (126 mg/dL) to 6.0 mmol/L (110 mg/dL) increased the sensitivity for the cutpoint for the diagnosis of diabetes mellitus. In our study, lowering the cutpoint for the diagnosis of diabetes from 7.0 (126 mg/dL) to 6.0 mmol/L (110 mg/dL) increased the sensitivity for the cutpoint for the diagnosis of diabetes mellitus. However, since this study dealt primarily with the association between FPG below the range generally associated with diabetes mellitus, we believe that our findings, and interpretation of these findings, are valid. Finally, because this study is cross-sectional, we can determine only that an association exists between FPG and microvascular complications; we cannot infer causality.

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One possible explanation for our findings may relate to the fact that hyperglycemia, although a major contributor to the pathogenesis of microvascular disease, is not the only cause. A few examples include trauma, vitamin deficiencies (especially vitamin B), alcoholism, lupus, rheumatoid arthritis, and certain cancer medications, which can all cause neuropathy. As fasting glucose level rises and the prevalence of a specific microvascular complication increases, it becomes more likely that the condition in that individual is the result of hyperglycemia. At lower levels of glycemia, other causes may predominate. If the goal of glucose testing is to identify these individuals at an early stage of disease, when intervention may prevent progression of disease, then it is possible that incorporating other variables into a multivariate predictive function that includes FPG as a continuous measure may improve our ability to identify these individuals.

Having said that, we may not want to do away with established categories; although the cutpoints for diagnosis have inherent limitations, they do provide clinicians with the convenience of being able to simply categorize patients. To our knowledge, data are also limited showing that intervention in individuals with microvascular complications not related to diabetes mellitus would be beneficial to the same extent as in individuals with diabetes mellitus. Studies that specifically address these issues would be an important follow-up to this study.

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