Diabetes Mellitus, Impaired Glucose Tolerance, and Hyperinsulinemia in an Elderly Population

The Rotterdam Study

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To estimate the prevalence of glucose intolerance in the elderly, oral glucose tolerance tests were performed as part of the Rotterdam Study, a population-based study in subjects aged 55 years and over. The study population consisted of 2,668 men and 3,950 women. Diabetes mellitus was defined as the use of antidiabetes medication, or a random or post-load serum glucose level of ≥11.1 mmol/liter. Impaired glucose tolerance was defined as a post-load serum glucose between 7.8 and 11.1 mmol/liter. In men, the frequency of diabetes mellitus ranged from 5.9% in ages <60 years to 19.8% in ages >85 years, and in women from 3.8% in ages <60 years to 18.9% in ages >85 years; more than half of the subjects with diabetes were newly diagnosed. The prevalence of impaired glucose tolerance ranged from 8.8% and 11.0% in men and women aged <60 years to 24.3% and 34.7% in men and women aged >85 years. The prevalence of diabetes mellitus in the total Rotterdam Study population of 7,439 elderly men and women was estimated to be 11.3% (95% confidence interval (CI) 10.5-12.0). Waist/hip ratio, systolic blood pressure, hypertension, and number of cigarettes smoked increased with a worsening of the glucose tolerance from normal, hyperinsulinemia, impaired glucose tolerance to diabetes in both men and women (p < 0.01, adjusted for age). Body mass index was higher in subjects with glucose intolerance, but the frequency of obesity showed a relative decrease with worsening of glucose tolerance. These results show that glucose intolerance, especially impaired glucose tolerance and undetected diabetes mellitus, is common in the elderly. Moreover, not only subjects with diabetes mellitus but also subjects with hyperinsulinemia and impaired glucose tolerance have an increase of cardiovascular risk factors. Am J Epidemiol 1997;145:24-32.

It is a common notion that glucose tolerance decreases with increasing age, as was first reported by Spence (1). Usually the diagnosis of diabetes mellitus in the elderly is made several years after the onset of the disease (2). As a consequence, a large proportion of diabetic subjects are not aware of their disease. In addition, moderate glucose intolerance, i.e., hyperinsulinemia and impaired glucose tolerance, are not associated with specific symptomatology but may increase the risk of diabetes complications (3, 4). This implies that population-based studies, in which serum glucose and insulin levels are measured, are necessary to obtain a complete assessment of the prevalence of glucose intolerance. However, few population-based studies on glucose tolerance in elderly subjects have been reported in the literature and even less data are available on very old subjects, i.e., persons over 80 years of age.

Oral glucose tolerance tests were performed as part of the Rotterdam Study, a large population-based study in the elderly. This paper describes the prevalence of glucose intolerance in this population, including the proportion of older subjects with previously unknown diabetes mellitus. In addition, we investigated the relations between cardiovascular risk factors (obesity, hyperlipidemia, blood pressure, and smoking) and degree of glucose intolerance (normal glucose tolerance, hyperinsulinemia, impaired glucose tolerance, and diabetes mellitus).
MATERIALS AND METHODS

Study population

The Rotterdam Study is a population-based cohort study of determinants of chronic disabling diseases in the elderly. The study focuses on four areas of chronic disease: cardiovascular diseases, neurogeriatric diseases, osteoporosis, and ophthalmologic diseases. An outline of the study and its objectives has been published previously (5). The first part of the study was a structured interview of the participants in their homes by trained research assistants using a computerized questionnaire. This included questions on smoking habits and an assessment of current medication use by means of Anatomical Therapeutical Chemical (ATC) classification index codes (6). Subsequently, the participants came to the research center twice for several clinical examinations, including anthropometry and blood pressure. Blood was drawn by venipuncture. This was followed by an oral glucose tolerance test. Informed consent was obtained from all subjects and the study was approved by the medical ethics committee of the Erasmus University Medical School.

All inhabitants of a suburb of Rotterdam aged 55 years and over (including those who lived in institutions) were invited to participate in the Rotterdam Study. Of the 10,275 eligible subjects, 7,983 were examined (response rate = 77.7 percent). The assessment of glucose tolerance was part of the measurements taken of subjects in the Rotterdam Study from July 1990 to the end of the baseline examinations in July 1993. During this period, 7,439 subjects participated, of whom 6,618 (88.9 percent) also visited the research center and underwent a venipuncture. The present analyses were restricted to the 6,618 subjects who underwent a venipuncture. In addition, the prevalence of diabetes mellitus was also analyzed in the group of 7,439 subjects.

Measurements

The participants visited the research center throughout the day, and the time of last food intake was recorded. Blood was drawn by venipuncture, and subjects who did not take antidiabetic medication (tablets or insulin) received a drink containing 75 g of glucose. Two hours later, a second blood sample was obtained. Glucose levels were measured in both samples by the glucose hexokinase method, while insulin was measured by radioimmunoassay (Medgenix diagnostics, Brussels, Belgium) in the first 4,844 participants. Mannheim, Germany) in the first 4,844 participants. The coefficients of variation of glucose, insulin, and fructosamine measurements were less than 2.5 percent, 6.0 percent, and 3.0 percent, respectively.

In the Rotterdam Study, diabetes mellitus was defined as the use of antidiabetes medication, or a random or post-load serum glucose level ≥11.1 mmol/liter according to the World Health Organization (WHO) criteria (7). Subjects with a glucose level in the diabetic range and who did not use antidiabetes medication were classified as newly diagnosed. Impaired glucose tolerance was defined as post-load serum glucose between 7.8 and 11.1 mmol/liter in subjects without diabetes mellitus. Hyperinsulinemia was defined as the upper quintile of the sex-specific post-load insulin distribution in subjects aged less than 65 years without impaired glucose tolerance or diabetes mellitus. In men, the cutpoint of insulin was 62 mU/liter, while in women the cutpoint of 69 mU/liter was used.

Sitting blood pressure was measured at the right upper arm by means of a random-zero sphygmomanometer. The mean of two measurements obtained at one occasion, separated by an assessment of the pulse rate, was used in the analyses. Hypertension was defined as systolic blood pressure of ≥160 mmHg, or diastolic blood pressure of ≥95 mmHg, or current use of medication for hypertension. Weight and height were measured with the participants wearing indoor clothes and no shoes. Waist circumference was measured midway between the lower rib margin and iliac crest; hip circumference was measured at the trochanter major. Body mass index was calculated as weight (kg)/height (m)$^2$, while body fat distribution was assessed by the ratio of hip over waist circumference. Obesity was defined as body mass index ≥27 kg/m$^2$. Subjects were questioned about their alcohol consumption separately for weekdays and the weekend and about which of three categories of alcohol they consumed—beer, wine, or liquor. Based on these answers, the average pure alcohol consumption was calculated in g per day. The amount of cigarettes smoked was converted to pack-years, calculated as the number of packs of cigarettes smoked per day multiplied by the total years of smoking.

Statistical analysis

The prevalence of glucose intolerance (with 95 percent confidence interval) was calculated in subgroups according to age and sex, and separately for those who attended the research center in the fasting state. A subject was considered fasting when at least 3 hours had passed since the last food intake. In this group, the prevalences were also calculated using the WHO cri-
RESULTS

The characteristics of the study population are shown in table 1. Age distributions for the glucose, fructosamine, and insulin levels are given in figures 1–3. In both sexes, all measures increased significantly with age \( (p < 0.01) \). Time since last meal was only marginally related to the random glucose values; the decrease was 0.00010 mmol/liter per hour (95 percent confidence interval CI 0.00008–0.00012).

The age- and sex-specific prevalences of diabetes mellitus and impaired glucose tolerance are given in table 2. In men, diabetes mellitus was present in 277 subjects (10.4 percent, 95 percent confidence interval CI 9.2–11.5), and 61.4 percent of the cases of diabetes were newly diagnosed in the Rotterdam Study. Impaired glucose tolerance was found in 13.0 percent of the men (95 percent CI 11.6–14.3). In women, diabetes was present in 430 subjects (10.9 percent, 95 percent CI 9.9–11.9), and 56.3 percent of the cases of diabetes were newly diagnosed. Impaired glucose tolerance was found in 18.7 percent of the women (95 percent CI 17.5–20.0). The proportion of subjects with newly diagnosed diabetes mellitus increased with age (table 2). In the oldest age group, about 60 percent had normal glucose tolerance. In the total study population, 264 subjects (3.5 percent) used oral antidiabetes medication, whereas 81 subjects (1.1 percent) were on insulin therapy. These proportions were the same in men and women. In subjects with normal glucose tolerance, impaired glucose tolerance, newly diagnosed diabetes mellitus, and known diabetes mellitus, serum fructosamine was 302.2 \( \mu \)mol/liter (standard deviation SD 36.3), 303.6 \( \mu \)mol/liter (SD 50.1), 347.7 \( \mu \)mol/liter (SD 83.2), and 386.6 \( \mu \)mol/liter (SD 82.8), respectively (test for trend \( p < 0.05 \)).

There were no statistically significant differences between subjects who were fasting for at least 3 hours before the venipuncture and the other participants in mean age, sex, and use of antidiabetes medication. In the 144 fasting men, the prevalences of diabetes mellitus and impaired glucose tolerance were 11.1 percent (95 percent CI 6.0–16.2) and 22.1 percent (95 percent CI 15.1–29.0), respectively. Among the 194 fasting women, these prevalences were 9.8 percent (95 percent CI 5.6–14.0) and 27.1 percent (95 percent CI 20.8–33.5), respectively. Using the WHO criteria in this fasting group, the observed prevalences of diabetes mellitus and impaired glucose tolerance in men were 16.9 percent (95 percent CI 10.6–23.2) and 18.4 percent (95 percent CI 11.9–24.9), respectively, while in women the observed prevalences were 13.8 percent (95 percent CI 8.8–18.7) and 26.1 percent (95 percent CI 20.2–32.7), respectively.

The 823 participants who did not visit the research center, 63 used antidiabetes medication. By means of logistic regression, the prevalence of diabetes mellitus was estimated by age and sex in the remaining 760 subjects. Combined with the complete data on glucose tolerance in the remaining study population, the prevalence of diabetes mellitus in the total population of 7,439 elderly men and women was estimated to be 11.3 percent (95 percent CI 10.5–12.0). Of the total group of 7,439 participants, 491 (6.6 percent, 95 percent CI 6.0–7.2) answered positively to the question “Do you have diabetes mellitus?” This proportion was similar in men and women after adjustment for age. In participants who were also examined at the research center, 6.3 percent answered positively. In 76.0 percent of the latter group, diabetes mellitus was present according to the Rotterdam Study definition. The prevalence of glucose intolerance in the subjects who answered “no” to the question “Do you have diabetes mellitus?” is given in figure 4, which indicates that the reliability of this anamnestic information decreased with age. A prescribed diet for diabetes was eaten by 3.6 percent of the participants. Of this group, 72.0 percent also used antidiabetes medication. According to the Rotterdam Study definitions of glucose intolerance, diabetes mellitus was present in 8.0 percent and impaired glucose tolerance in 1.6 percent of subjects who ate a prescribed diet for diabetes but who did not use antidiabetes medication.

In table 3, several cardiovascular risk factors that have been associated with diabetes mellitus are given by cat-

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**TABLE 1. Characteristics of the study population: the Rotterdam Study, the Netherlands, July 1990–July 1993**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 2,668)</th>
<th>Women (n = 3,850)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD*)</td>
<td>68.2 (8.2)</td>
<td>70.2 (8.7)</td>
</tr>
<tr>
<td>Random glucose (mmol/liter), mean (SD)</td>
<td>7.1 (2.7)</td>
<td>6.8 (2.7)</td>
</tr>
<tr>
<td>Fructosamine (( \mu )mol/liter), mean (SD)</td>
<td>309.7 (53.8)</td>
<td>309.2 (49.8)</td>
</tr>
<tr>
<td>Post-load Insulin (( \mu )mol/liter), mean (SD)</td>
<td>55.6 (48.9)</td>
<td>67.5 (54.9)</td>
</tr>
</tbody>
</table>

* SD, standard deviation.
category of glucose tolerance. Subjects with normal glucose levels were divided into those with normal and increased insulin levels. Obesity was increased in subjects with glucose intolerance compared with those with normal glucose tolerance. However, with increased glucose intolerance (hyperinsulinemia, impaired glucose tolerance, diabetes), the prevalence of obesity decreased, especially in men. Waist/hip ratio, systolic blood pressure, and hypertension increased with an increase of glucose intolerance in both sexes \((p < 0.01, \text{adjusted for age})\). In men, the proportion of subjects who never smoked decreased, and the number of cigarettes smoked increased with increased glucose intolerance. In women, no significant cross-sectional association between smoking and glucose tolerance was found (table 3). There was no association between the amount of alcohol consumed and glucose tolerance in men or women.

Finally, the independence of the associations between cardiovascular risk factors and worsening of glucose tolerance was assessed by multivariate regression analysis, with age, body mass index, waist/hip ratio, total cholesterol, high density lipoprotein (HDL) cholesterol, systolic blood pressure, and smoking as independent variables. In men, waist/hip ratio, total cholesterol, HDL cholesterol, systolic blood pressure, and smoking all remained independently associated with glucose intolerance, whereas in women independent associations were found with body mass index, waist/hip ratio, HDL cholesterol, and systolic blood pressure (for all variables, \(p < 0.01\)).

**DISCUSSION**

The results of this population-based study in subjects aged 55 years and over showed that the prevalence of diabetes mellitus increased with age from 5.9 percent to 19.8 percent in men and from 3.8 percent to 18.9 percent in women, with more than half of the cases of diabetes being newly diagnosed. If subjects who did not undergo a venipuncture were included, the overall prevalence was estimated at 11.3 percent. Impaired glucose tolerance increased from 8.8 percent to 24.3 percent in men and from 11.0 percent to 34.7 percent in women. After adjustment for age, waist/hip ratio, systolic blood pressure,
hypertension, and the number of cigarettes smoked, all increased with a worsening of the glucose tolerance from normal, hyperinsulinemia, impaired glucose tolerance to diabetes. Body mass index was higher in subjects with glucose intolerance, but obesity decreased with increased glucose intolerance. Alcohol consumption was not associated with glucose intolerance.

A limitation of this cross-sectional analysis of the Rotterdam Study is the use of a non-fasting blood sample. We have reported previously that the post-load glucose and insulin levels are similar to the fasting post-load levels (8). The effect of non-fasting on the prevalence of glucose tolerance was limited, as shown by the similar estimates in the subgroup who had not eaten for at least 3 hours (fasting group). Moreover, the change in serum glucose with increasing time since last meal was very small, but this was based on recall of the participants only.

Serum glucose values were only available in those subjects who visited the research center. As expected, the proportion with a history of diabetes mellitus was lower in this group than among those who did not attend the research center, which suggests that the reported prevalences are an underestimation. This was confirmed by a somewhat higher estimated prevalence in the total study population (11.3 percent vs. 10.7 percent). Another limitation of the present study is the use of a single glucose tolerance test, which has a relatively large variation (9). Insulin resistance was assessed by the post-load insulin level. In subjects without diabetes mellitus, this provides a good measure of insulin sensitivity (10). With regard to the diagnosis of insulin resistance/hyperinsulinemia, no uniform criteria exists. It is well known that subjects with impaired glucose tolerance and diabetes mellitus have increased insulin resistance (11). The separate category of hyperinsulinemia among subjects with normal glucose levels is justified by the notion that this group has an increased risk of developing diabetes mellitus (12).

The Rotterdam Study definitions of glucose intolerance differ slightly from the WHO criteria (7). Because the first blood sample of the glucose tolerance test shows a larger variation in the non-fasting state compared with the fasting state, the diagnostic limit for diabetes mellitus is set at 11.1 mmol/liter instead of...
Fructosamine (umol/l)

FIGURE 3. Serum fructosamine level by 5-year age categories: the Rotterdam Study, the Netherlands, July 1990-July 1993. Box-and-whisker plots indicate 5, 25, 50, 75, 95 percentiles. The width of the boxes are proportional to the number of subjects in that age category.

TABLE 2. Prevalence (in percent) of diabetes mellitus and impaired glucose tolerance, by age and sex: the Rotterdam Study, the Netherlands, July 1990-July 1993

<table>
<thead>
<tr>
<th>Sex</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-74</th>
<th>75-79</th>
<th>80-84</th>
<th>≥85</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>5.9</td>
<td>7.5</td>
<td>12.1</td>
<td>10.9</td>
<td>13.3</td>
<td>15.9</td>
<td>19.8</td>
<td>10.4</td>
</tr>
<tr>
<td>Newly diagnosed diabetes†</td>
<td>4.7</td>
<td>5.2</td>
<td>6.7</td>
<td>5.0</td>
<td>8.6</td>
<td>9.8</td>
<td>14.1</td>
<td>6.4</td>
</tr>
<tr>
<td>Impaired glucose tolerance‡</td>
<td>8.8</td>
<td>10.9</td>
<td>17.4</td>
<td>11.7</td>
<td>12.3</td>
<td>15.7</td>
<td>24.3</td>
<td>13.0</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>3.8</td>
<td>6.2</td>
<td>10.4</td>
<td>11.2</td>
<td>14.8</td>
<td>21.0</td>
<td>18.9</td>
<td>10.9</td>
</tr>
<tr>
<td>Newly diagnosed diabetes†</td>
<td>2.1</td>
<td>4.2</td>
<td>6.1</td>
<td>5.1</td>
<td>7.4</td>
<td>12.1</td>
<td>12.1</td>
<td>6.1</td>
</tr>
<tr>
<td>Impaired glucose tolerance‡</td>
<td>11.0</td>
<td>14.5</td>
<td>17.9</td>
<td>22.4</td>
<td>21.1</td>
<td>20.6</td>
<td>34.7</td>
<td>18.7</td>
</tr>
</tbody>
</table>

* Use of antidiabetes medication or random or post-load glucose value ≥11.1 mmol/liter.
† Random or post-load glucose level ≥11.1 mmol/liter and not using antidiabetes medication.
‡ Post-load glucose 7.8-11.1 mmol/liter and not having diabetes mellitus.

7.8 mmol/liter. As a consequence, a number of subjects with diabetes according to the WHO criteria are not included. This leads to an underestimation of the prevalence of diabetes, which was confirmed in the fasting subgroup where both classifications could be applied. However, the number of false-positive diagnoses of diabetes mellitus is reduced by this approach. Information on the use of a prescribed diet for diabetes is not part of the Rotterdam Study protocol, which seems justified by the small proportion of increased glucose levels in subjects who ate such a diet but did not use antidiabetes medication. As shown by our data,
the use of a simple question in a questionnaire would lead to a considerable proportion of misclassification in this elderly population (figure 4).

The prevalence of diabetes mellitus differs markedly between ethnic groups, from almost 50 percent in the Pima Indians to less than 1 percent in Chile, although differences in the prevalence of impaired glucose tolerance are somewhat smaller, ranging from 1 to 25 percent (13). Only a few European population-based studies in the elderly have been reported. Among the 2,468 Caucasian men and women aged 50–75 years in the Hoorn Study in the Netherlands (14), diabetes mellitus was present in 8.3 percent and impaired glucose tolerance in 10.3 percent. Among men aged 70–89 years in the Zutphen Study (15), the Dutch cohort of the Seven Countries Study, diabetes was present in 7.2 percent and impaired glucose tolerance in 9.7 percent. In contrast, in the Finnish cohort of the Seven Countries Study (16), the prevalence of diabetes among subjects aged 65–84 years was 30 percent, whereas impaired glucose tolerance was diagnosed in 32 percent of the men. In another population-based study in Finland (17), among men and women aged 65–74 years, diabetes was present in 15.7 percent of men and 18.8 percent of women, whereas impaired glucose tolerance was present in 17.8 percent of the men and 19.1 percent of the women. In a population-based study in northern Italy in subjects aged 45 years and over (18), the age-adjusted prevalence of diabetes mellitus was 11.0 percent in men and 11.3 percent in women, whereas impaired glucose tolerance was found in 7.7 percent and 8.9 percent, respectively. Similar prevalences have been reported from studies in the United States, such as the second National Health and Nutrition Examination Survey (NHANES II) (19), the Rancho Bernardo Study (20), the San Luis Valley Diabetes Study (21), and the Wadena City Health Study (22).

Compared with other population-based studies, the prevalence of diabetes mellitus and impaired glucose tolerance is somewhat higher in the Rotterdam Study. As shown in table 2, this is mainly due to the inclusion of a considerable number of very old subjects in the present study, among whom a high prevalence of glucose intolerance is present. The results of our study confirm that serum insulin level also increases with age (23). Figure 2 suggests that this increase continues in old age. The increase with age of all degrees of glucose intolerance (hyperinsulinemia, impaired glucose tolerance, and diabetes mellitus) leads to a very high prevalence of glucose intolerance based on the current criteria.

Based on the age of the participants and the infrequent use of insulin therapy, the number of subjects with insulin-dependent diabetes mellitus in this population is negligible. It is, however, important to realize that the diagnosis non-insulin-dependent diabetes mellitus (NIDDM) is a diagnosis by exclusion, and therefore likely reflects a mixture of diseases with different

![FIGURE 4. Glucose tolerance in subjects who answered "no" on the question "Do you have diabetes mellitus?" in 10-year age categories: the Rotterdam Study, the Netherlands, July 1990-July 1993. *Based on anti-diabetes drug use.](image-url)
etiolologies (24). This heterogeneity probably applies even more for the subjects with newly diagnosed diabetes. Part of these subjects will have glucose values in the normal range on retesting (9). Similar to the situation in the present study, several authors (14, 16-18, 20, 25) have reported that about half of the subjects with diabetes mellitus in their population surveys were newly diagnosed. These results indicate that a considerable proportion of the elderly population is unaware of their glucose intolerance, either impaired glucose tolerance or non-diagnosed diabetes. It has been shown (25) that cardiovascular risk factors, mortality, and the prevalence of microvascular and macrovascular complications are similar among subjects with newly diagnosed and known diabetes mellitus. Subjects with impaired glucose tolerance also have an increased risk of cardiovascular disease and diabetic complications (4). These associations, mainly based on studies in middle-aged subjects, are confirmed in the present study (table 3).

The results in table 3 show that subjects with glucose intolerance have increased levels of cardiovascular risk factors, notably body mass index, waist/hip ratio, cholesterol, and blood pressure. This clustering of risk factors has been referred to as insulin resistance syndrome (26). All components of this cluster have been reported as risk factors for the development of NIDDM (27). The results of our study suggest that obesity is less frequent in subjects with known diabetes (table 3), a finding that was also observed in a Finnish study (17). This suggests that established diabetic patients lose weight, either because of the prescribed changes in diet or because of the disease itself. A similar trend was observed for total cholesterol, which is also influenced by changes in diet (28). Several population-based studies have reported that
smoking is a risk factor for the development of NIDDM in men (29, 30). The results of the present cross-sectional study support this hypothesis (table 3). Pack-years of smoking also increased in women with diabetes, but this difference did not reach statistical significance. However, among women the proportion of smokers was about half that among men, which may explain the weaker association in women. An association between alcohol consumption and glucose intolerance, as suggested by some authors (29, 31), was not found in this population.

In conclusion, the results of this study show that glucose intolerance is common in the elderly and that glucose intolerance increases with age. The prevalence of asymptomatic conditions, impaired glucose tolerance and unknown diabetes mellitus, is especially high. Cardiovascular risk factors are increased in subjects with glucose intolerance, including hyperinsulinemia and impaired glucose tolerance, which suggests that these factors are also associated with the development of diabetes mellitus.

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