The Independent Effect of Type 2 Diabetes Mellitus on Ischemic Heart Disease, Stroke, and Death

A Population-Based Study of 13,000 Men and Women With 20 Years of Follow-up

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Background: Epidemiological studies have reported that patients with type 2 diabetes mellitus (DM) have increased mortality and morbidity from cardiovascular diseases, independent of other risk factors. However, most of these studies have been performed in selected patient groups. The purpose of the present study was prospectively to assess the impact of type 2 DM on cardiovascular morbidity and mortality in an unselected population.

Methods: A total of 13,105 subjects from the Copenhagen City Heart Study were followed up prospectively for 20 years. Adjusted relative risks of first, incident, admission for, or death from ischemic heart disease, acute myocardial infarction, or stroke, as well as total mortality in persons with type 2 DM compared with healthy controls, were estimated.

Results: The relative risk of first, incident, and admission for myocardial infarction was increased 1.5- to 4.5-fold in women and 1.5- to 2-fold in men, with a significant difference between sexes. The relative risk of first, incident, and admission for stroke was increased 2- to 6.5-fold in women and 1.5- to 2-fold in men, with a significant difference between sexes. In both women and men the relative risk of death was increased 1.5 to 2 times.

Conclusions: In persons with type 2 DM, the risk of having an incident myocardial infarction or stroke is increased 2- to 3-fold and the risk of death is increased 2-fold, independent of other known risk factors for cardiovascular diseases.

Arch Intern Med. 2004;164:1422-1426
vously described in detail. The population was derived from a random, age-stratified sample of 19698 individuals 20 years or older, recruited in 1976-1978 among 90 000 people living in a defined area in Copenhagen, Denmark. A total of 14223 subjects (response rate, 72%) attended the first examination in 1976-1978. The present study is based on a subset of 13 105 persons (7198 women and 5907 men) in whom all variables listed in the following paragraph were available. Moreover, subjects who had been admitted to hospital because of ischemic heart disease including AMI or stroke prior to the first investigation in 1976-1978 were excluded.

At the examination in 1976-1978, cardiovascular risk factors were assessed by a self-administered questionnaire and various laboratory tests. Tobacco consumption was categorized as nonsmokers, previous smokers, and present smokers; physical activity as sedentary, moderate activity less than 4 h/wk, and moderate activity 4 h/wk or more; alcohol consumption (with 1 unit corresponding to 10 g of pure alcohol) as less than 1 unit/d, 1 to 2 units/d, 3 to 4 units/d, and more than 4 units/d; and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) as lower than 20, 20 to 24, 25 to 29, and 30 or higher. Arterial blood pressure was measured with the subject in recumbent position after at least 5 minutes of rest and categorized as systolic blood pressure lower than 140 mm Hg without the use of blood pressure–lowering agents, 140 mm Hg or higher and lower than 160 mm Hg without the use of blood pressure–lowering agents, 160 mm Hg or higher without the use of blood pressure–lowering agents, lower than 140 mm Hg with the use of blood pressure–lowering agents, and 140 mm Hg or higher with the use of blood pressure–lowering agents. Patients with systolic blood pressure exceeding 110 mm Hg plus the personage mm Hg (ie, in a person aged 60 years, the systolic blood pressure should exceed 110 + 60 = 170 mm Hg) or having a diastolic blood pressure higher than 100 mm Hg were asked to contact their general practitioner for further evaluation. Triglyceride levels were categorized as lower than 90 mg/dL (<1 mmol/L), 90 to lower than 180 mg/dL (1-2 mmol/L), and 180 mg/dL or higher (≥2 mmol/L). Total cholesterol levels were categorized as lower than 200 mg/dL (<5 mmol/L), 200 to 280 mg/dL (5-7 mmol/L), and 280 mg/dL or higher (≥7 mmol/L). Blood samples were taken from nonfasting participants.

DEFINITION OF DM

All participants were asked about the presence of DM and, if present, whether the treatment consisted of diet alone, oral hypoglycemic agents, or insulin. Moreover, nonfasting plasma glucose measurement was obtained from each participant.

The participants were classified into the nondiabetic (control) group if they reported not having DM and had a nonfasting plasma glucose level of 120 mg/dL (6.5 mmol/L) or lower, the intermediate group if they reported not having DM and had a nonfasting plasma glucose level in the range 120 to 200 mg/dL (6.5-11.1 mmol/L), and the type 2 DM group if they reported having DM and were being treated with either diet or diet and oral hypoglycemic agents or had a nonfasting plasma glucose level above 200 mg/dL (>11.1 mmol/L). Participants who reported receiving treatment with insulin were excluded from the analysis because it was not possible to determine whether they had type 1 or type 2 DM.

MORBIDITY AND MORTALITY

Subjects were followed up until December 1997 with respect to hospital admission for nonfatal or fatal ischemic heart disease (International Classification of Diseases, Eighth Revision [ICD-8] codes 410-414), acute myocardial infarction (ICD-8 code 410), stroke (ICD-8 code 430-438), and death from all causes. The information was obtained from the Denmark National Board of Health, National Hospital Discharge Register, and National Death Certificate Register.

STATISTICAL ANALYSIS

Estimates of relative risks were calculated using the Cox proportional hazards model. Tests for interaction of DM and sex were performed. The relative risks were estimated separately in the various sex and age strata. Analyses were performed using Stata 6 (Stata Corporation, College Station, Tex) statistical software package.

RESULTS

A total of 7198 women were included in the analysis: 4739 (65.8%) were classified into the control group, 2360 (32.7%) into the intermediate group, and 99 (1.4%) into the type 2 DM group. A total of 5907 men were included: 2912 (49.3%) were classified into the control group, 2793 (47.3%) into the intermediate group, and 202 (3.4%) into the type 2 DM group.

In women, the total mortality during the observation period was 1.7 to 2.7 times higher in persons with type 2 DM compared with controls in the under 55 years and 55 to 64 years age groups (Table 1). Compared with controls, the number of women with DM undergoing their first admission for myocardial infarction or stroke was 3.5 to 4.6 times higher in the under 55 years and 55 to 64 years age groups. In the under 55 years age group, approximately 10% of those with type 2 DM were admitted because of acute myocardial infarction and 13% because of stroke, the corresponding figure for the 55 to 64 years age group were 35% and 43%, respectively.

In men, the total mortality during the observation period was 2.5 times higher in persons with type 2 DM compared with controls in the under 55 years age group (Table 2). The number of men undergoing their first admission for myocardial infarction or stroke was 2.7 to 3.2 times higher in the under 55 years age group. In the under 55 years age group, 24% of those with type 2 DM were admitted because of acute myocardial infarction and 20% because of stroke.

The figures pertaining to the subjects in the intermediate group regarding mortality and first admissions for ischemic heart disease, acute myocardial infarction, or stroke were in general not different from those of the control group. The same applies to the adjusted relative risk commented on in the following paragraph.

In women and men with DM, the adjusted relative risk of death was 1.5 to 2 compared with age-matched controls (Figure 1). Besides DM, smoking, hypertension, high triglyceride level, high alcohol intake, and low (<20) and high (≥30) BMI in women and smoking, hypertension, high alcohol intake, and low BMI (<20) in men independently increased the risk of death, whereas high physical activity and high total cholesterol level decreased the risk of death in both sexes.

The adjusted relative risk of first admission to hospital for ischemic heart disease was significantly increased in men aged 55 to 64 years and older than 64 years; in women, the adjusted relative risk was only sig-
significantly increased in the 55 to 64 years age group (Figure 2). The adjusted relative risk of first myocardial infarction was significantly increased in men younger than 55 years and in women aged 55 to 64 years (Figure 3).

The adjusted relative risks of first stroke were significantly increased in men younger than 55 years and older than 64 years. In women, this was also the case in the 55 to 64 years and over 64 years age groups (Figure 4).

**COMMENT**

The present population-based study, with nearly 20 years of follow-up, shows that type 2 DM is associated with increased risk of myocardial infarction and stroke independent of other risk factors and confirms the increased total mortality in patients with type 2 DM.

A possible drawback of the present study is that the classification of the patients was not based on fasting plasma glucose level or oral glucose tolerance test. In participants, nonfasting venous blood samples were drawn, and plasma venous glucose was measured. According to a recent World Health Organization report, a plasma venous glucose level of 200 mg/dL (11.1 mmol/L) or higher 2 hours after a 75-g oral glucose load is diagnostic for DM, and we therefore classified all participants with a nonfasting plasma venous glucose level above this value as having DM, independent of whether they reported to have known DM. The same report concludes that persons with

Table 1. Number (Frequencies) of Deaths and Cases of IHD, AMI, and Stroke During Follow-up Among 7198 Women*

<table>
<thead>
<tr>
<th>Diabetes Status by Age Group</th>
<th>No. at Initial Investigation</th>
<th>No. Dying During Observation Period</th>
<th>First Admission for:</th>
<th>IHD</th>
<th>AMI</th>
<th>Stroke</th>
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<tr>
<td>55-64 y Controls</td>
<td>1382</td>
<td>596 (50)</td>
<td>229 (17)</td>
<td>106 (8)</td>
<td>132 (10)</td>
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<tr>
<td>Intermediates</td>
<td>827</td>
<td>440 (53)</td>
<td>166 (20)</td>
<td>84 (10)</td>
<td>102 (12)</td>
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<tr>
<td>Type 2 DM</td>
<td>40</td>
<td>35 (88)</td>
<td>20 (50)</td>
<td>14 (35)</td>
<td>17 (43)</td>
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<tr>
<td>55-64 y Controls</td>
<td>1099</td>
<td>296 (29)</td>
<td>118 (11)</td>
<td>64 (6)</td>
<td>46 (4)</td>
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</tr>
<tr>
<td>Intermediates</td>
<td>31</td>
<td>16 (52)</td>
<td>4 (13)</td>
<td>3 (10)</td>
<td>4 (13)</td>
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<tr>
<td>Type 2 DM</td>
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<tr>
<td>All age groups Controls</td>
<td>2761</td>
<td>524 (19)</td>
<td>188 (7)</td>
<td>77 (3)</td>
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<tr>
<td>Intermediates</td>
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<td>296 (29)</td>
<td>118 (11)</td>
<td>64 (6)</td>
<td>46 (4)</td>
<td></td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>31</td>
<td>16 (52)</td>
<td>4 (13)</td>
<td>3 (10)</td>
<td>4 (13)</td>
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Abbreviations: AMI, acute myocardial infarction; DM, diabetes mellitus; IHD, ischemic heart disease.

*Data are number (percentage) of patients, unless otherwise indicated, stratified by age and diabetes status at baseline.

Table 2. Number (Frequencies) of Deaths and Cases of IHD, AMI, and Stroke During Follow-up Among 5907 Men*

<table>
<thead>
<tr>
<th>Diabetes Status by Age Group</th>
<th>No. at Initial Investigation</th>
<th>No. Dying During Observation Period</th>
<th>First Admission for:</th>
<th>IHD</th>
<th>AMI</th>
<th>Stroke</th>
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<tr>
<td>55-64 y Controls</td>
<td>1678</td>
<td>514 (31)</td>
<td>250 (15)</td>
<td>146 (9)</td>
<td>103 (6)</td>
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<tr>
<td>Intermediates</td>
<td>1443</td>
<td>499 (35)</td>
<td>260 (18)</td>
<td>165 (11)</td>
<td>128 (9)</td>
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<tr>
<td>Type 2 DM</td>
<td>46</td>
<td>35 (76)</td>
<td>15 (33)</td>
<td>11 (24)</td>
<td>9 (20)</td>
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<tr>
<td>55-64 y Controls</td>
<td>791</td>
<td>551 (70)</td>
<td>241 (31)</td>
<td>143 (18)</td>
<td>118 (15)</td>
<td></td>
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<tr>
<td>Intermediates</td>
<td>844</td>
<td>600 (72)</td>
<td>281 (33)</td>
<td>178 (21)</td>
<td>119 (14)</td>
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<tr>
<td>Type 2 DM</td>
<td>85</td>
<td>77 (91)</td>
<td>37 (44)</td>
<td>22 (26)</td>
<td>19 (22)</td>
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<tr>
<td>55-64 y Controls</td>
<td>443</td>
<td>420 (95)</td>
<td>173 (39)</td>
<td>79 (18)</td>
<td>80 (18)</td>
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<tr>
<td>Intermediates</td>
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<td>478 (95)</td>
<td>210 (42)</td>
<td>101 (20)</td>
<td>107 (21)</td>
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<tr>
<td>Type 2 DM</td>
<td>71</td>
<td>70 (99)</td>
<td>37 (52)</td>
<td>17 (24)</td>
<td>23 (32)</td>
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<tr>
<td>All age groups Controls</td>
<td>2912</td>
<td>1485 (51)</td>
<td>664 (23)</td>
<td>368 (13)</td>
<td>301 (10)</td>
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<tr>
<td>Intermediates</td>
<td>2793</td>
<td>1577 (56)</td>
<td>751 (27)</td>
<td>444 (16)</td>
<td>354 (13)</td>
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</tr>
<tr>
<td>Type 2 DM</td>
<td>202</td>
<td>182 (80)</td>
<td>89 (44)</td>
<td>50 (25)</td>
<td>51 (25)</td>
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</tr>
</tbody>
</table>

Abbreviations: AMI, acute myocardial infarction; DM, diabetes mellitus; IHD, ischemic heart disease.

*Data are number (percentage) of patients, unless otherwise indicated, stratified by age and diabetes status at baseline.
nonfasting plasma glucose values lower than 100 mg/dL (<5.5 mmol/L) are unlikely to have or develop DM. The Danish recommendation regarding diagnosis and treatment of type 2 DM, issued in 2000, suggests that if a person has a nonfasting blood glucose level lower than 100 mg/dL (<5.5 mmol/L), DM is unlikely. In that recommendation, plasma glucose level was suggested to be 10% to 15% higher, and we therefore decided to use a nonfasting plasma glucose value of 120 mg/dL (6.5 mmol/L) as the cutoff between normal and intermediate. We tried to apply a cutoff between the normal (control) and intermediate group of 100 mg/dL (5.5 mmol/L); however, it turned out that only 20% to 30% of the total population could be classified as normal. As can be seen from the “Results” section, there were no significant differences between the control group and the intermediate group.

The prevalence of type 2 DM in the present study was 1.4% in women and 3.4% in men. These figures seem low. However, in a study performed in another area of greater Copenhagen in 1976 based on fasting blood glucose values and oral glucose tolerance test results, the prevalence of type 2 DM was reported only to be 20% to 40% higher than those reported in the present study. In the present study, we excluded all participants taking insulin, which may explain some of the difference. It is therefore unlikely that the number of persons with type 2 DM is underreported in the present study.

This study reports that DM independently increases the risk of death by a factor of 1.5 to 2. In the Reykjavik Study, which is also population based, the relative risk was approximately 2 in both sexes for total mortality and coronary heart disease mortality. Thus, the results of the 2 studies are comparable. Other studies of selected groups (ie, physicians4 and nurses5), in which adjustment for other risk factors were done, have reported relative risks of 2 to 3 for total mortality.

The present study also reports the relative risk of being admitted for the first time for either acute myocardial infarction or stroke, since this is an estimate of the relative risk of having either an incident acute myocardial infarction or stroke. Studies on cardiovascular death rely on the precision of the death certificate. With regard to the diagnosis of acute myocardial infarction, the precision of this diagnosis in the National Hospital Discharge Register is more than 90%. Moreover, in Denmark nearly 100% of patients with these diagnoses are admitted to a hospital. Thus, it is likely that diagnoses on which the present study is based are accurate and precise.
The independent effect of DM for admission for incident acute myocardial infarction or stroke was an increased risk of 1.5- to 2-fold in men and 1.5- to 6.5-fold in women. In a cohort study from Scotland, it was reported that during a 7-year observation period, approximately 4% of patients with type 2 DM were admitted for acute myocardial infarction. In the present study, about 20% to 25% of the participants experienced myocardial infarction during the observation period of approximately 20 years. The reason for the discrepancy is not clear.

An analysis of the UK Prospective Diabetes Study (UKPDS) data reports that the adjusted rate myocardial infarction in persons with hemoglobin A1c values of 9% to 10% is approximately 2 times higher than that of persons with a normal hemoglobin A1c value.

The independent effect of type 2 DM for stroke has previously been analyzed in a few studies. Two studies from Scotland report an increased relative risk of developing a stroke of 2-fold in men and approximately 3-fold in women. In a recent Finish study of persons aged 30 to 60 years at entry, type 2 DM was reported to increase the risk of stroke by a factor of 3 in men and 4 to 4.5 in women. In the present study, the risk of developing stroke in men with type 2 DM in comparable age groups was approximately 2, whereas the corresponding figure in women was 2.5 to 6.5 and thus significantly higher than that in men.

The issue of whether there is a difference between sexes in regard to DM-related increased risk of cardiovascular diseases has been debated for a number of years. A recent meta-analysis examined whether there is a difference between sexes in the risk of death from coronary heart diseases in persons with type 2 DM and reports a risk of 2.2 in men and 2.9 in women without significant differences. In the present study, when comparing men and women in all aged groups, test results for interaction showed that the effect of DM was significantly more pronounced for women in regard to acute myocardial infarction and stroke but not in regard to death or admission for ischemic heart disease. When studying the various age groups, a difference between sexes was only found in women aged 55 to 64 years, who had a significantly higher risk of stroke. Generally, there was a tendency toward a higher risk also for the other end points in this age group. This observation suggests that special attention should be given to women with DM in the first postmenopausal decade.

In conclusion, the present study shows an independent 2- to 3-fold increased risk of having an incident myocardial infarction or stroke in patients with type 2 DM. Moreover, this study confirms that patients with type 2 DM have a 2-fold increased risk of death, independent of other known risk factors for cardiovascular diseases. These results emphasize the importance of controlling all known risk factors in patients with type 2 DM, as well as encouraging persons with type 2 DM to increase their physical activity.

Accepted for publication October 3, 2003.

This study was supported by the Danish Heart Foundation and the Danish Medical Research Council, Copenhagen, Denmark.

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REFERENCES