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Prevalences of risk factors and angiopathy in diabetic patients in Uppsala

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ABSTRACT

The prevalences of risk factors and angiopathy were studied in 260 diabetic patients, 100 females and 160 males, 35-54 years old, in Uppsala. The prevalence, in females and males separately, of hypertension (WHO-criteria) was 46-34%, of hypercholesterolaemia ($\geq$6.7 mmol·l^{-1}) 32-29%, and of obesity (relative BMI $\geq$120%) 25-20%. Those smoking >15 cigarettes/day were 11-20%. Mean HbA1 was 10.6-10.5%.

The prevalence of angina pectoris was 11-6%, of possible infarction 4-6%, and of major ECG abnormalities 6-4%. Large vessel (cardiovascular) disease was independently related to HbA1 (strongly), hypertension, cholesterol, age and familial NIDDM.

The prevalence of severe retinopathy (blindness, new vessels or large hemorrhage) was 0% with 7-13 years of diabetes duration, and 26% with $\geq$14 years of duration. The prevalence of severe proteinuria was 4% with 7-13 years of diabetes duration, and 15% with $\geq$14 years of duration.

Small vessel (retinopathy and nephropathy) disease was independently related to diabetes duration (strongly), HbA1 and hypertension.

The data were discussed related to data from the London, Berlin and Tokyo centres of the WHO Multinational Study of Vascular Disease in Diabetics, using the same study protocol in the present study.

INTRODUCTION

The WHO Multinational Study of Vascular Disease in Diabetics (WHO Study) from 14 centres has suggested heterogeneity in prevalence of large vessel disease and also possibly of small vessel disease (14). It was the aim of this study to analyse the relationship between risk factors and vascular disease in 260 Uppsala diabetics, using the WHO Study protocol. Some further risk factor variables were also added here. Another aim was to compare prevalences of vascular disease between Uppsala diabetics and some centres of the WHO Study 6 years earlier.

MATERIAL AND METHODS

Two hundred and sixty diabetic patients (100 women and 160 men), diagnosed at least 1 year earlier and undergoing treatment by physicians, were sampled from patient registers at the medical clinic of the University Hospital, and at a primary care centre. As in the WHO Study, the aim was to obtain 9 groups of about similar size, based on 3 age intervals 35-41, 42-48, 49-54 years, and on 3 intervals of diabetes duration 0-6, 7-13, $\geq$14 years. The age range 35- 54 years was chosen, assuming that arterial disease is uncommon below the age of 35, and since selective mortality could distort its representation after the age of 54. Written informed consent was obtained from all subjects, and the study was approved by ethical committee also concerning computer analysis. The questionnaire and the examination protocol were the same as in the WHO Study (14), and performed in the present study by the same observer (except ECG ana- lyses).

Body mass index (BMI) was computed by dividing weight with indoor clothing by the square of height without shoes ($kg \cdot m^{-2}$). Relative BMI (RBMI, %) was used, based on standard BMI values for each sex according to the Society of Actuaries (9), at multiple regressions.

Blood pressure (BP) was measured casually sitting after at least 10 min of rest and >30 min without smoking or eating, with a cuff size 12 x 35 cm, using Korotkoff fifth phase sounds. Hypertension was defined according to WHO-criteria (untreated systolic BP $\geq$160 mm Hg, or diastolic BP mm Hg $\geq$95 mm Hg, or receiving antihypertensive drugs).

Information of cigarette smoking was obtained by standard questions, as also family histories of diabetes and physical activity. Subjects with at least one first-degree relative with NIDDM formed a group with familial NIDDM, and those without any first-degree NIDDM relatives formed a group with no familial NIDDM. Similar grouping was performed concerning family history of insulin-treated diabetes mellitus (ITDM), including both true insulin-dependent relatives and those rightly classified as non-insulin-dependent. Mean daily physical activity was estimated with a 4-point scale previously described, found to be related to maximal oxygen uptake (6). Two groups were formed according to low or high leisure time activity, and similarly 2 groups according to low or high job activity. Social status was grouped as manual worker or not, and marital status as married or not.

The fundi were examined by direct ophtalmoscopy of each eye, and by photographic registration in most cases with ophtalmologic signs of retinopathy. Venous whole blood was drawn for determination of total cholesterol and creatinine, using routine techniques at the department of clinical chemistry. Hemoglobin A1 (HbA1) was analysed by the microcolumn method (Biorad, normal limit value 7.8%). Fresh urine was collected for determination of proteinuria, graded 1-4, by the Albustix method.

Macrovascular disease components, all classified as in the WHO Study (14), were registered with the standard questionnaire proposed by Rose and Blackburn concerning Angina Pectoris (both 'on the flat' and 'uphill only' responses), Possible Infarction (history of central chest pain >30 min), and Intermittent Claudication (both 'on the flat' and 'uphill only') (12). Stroke was a history of persistent (>24 h) hemiplegia.

Standard 12-lead ECGs were analysed by the same two experienced readers at the physiological department, using the Minnesota Code (1). Classification was as in the WHO Study (1). ECG Coronary Probable consisted of Minnesota items 1.1, 1.2 (large Q-QS waves) and 7.1 (complete LBBB). ECG Coronary Possible included items 1.3 (small Q waves), or any of 4.1, 4.2, 4.3 (S-T-segment abnormalities) and any of 5.1, 5.2, 5.3 (T wave abnormalities). Heart rate was computed from ECG at rest.

The large vessel disease components were grouped, as in the WHO Study (14), into three composites: (i) Heart Vascular Disease (HVD), including Angina Pectoris and/or Possible Infarction and/or ECG Coronary Probable and/or ECG Coronary Possible; (ii) Leg Vascular Disease (LegVD), including Intermittent Claudication and/or Amputation; (iii) Large Vascular Disease (LVD), including any or all of the components of large vessel disease.

Small vessel disease of the eye (SVDE) was grouped, as in the WHO Study (14), in two composites: (i) Mild-medium SVDE included $\geq$1 small or medium red lesions, or $\geq$1 soft or hard exudates, in one or both eyes; (ii) Severe SVDE included $\geq$1 large red lesions, or retinopathic blindness, or new vessels, or vitreous opacity / hemorrhage, in one or both eyes.

Small vessel disease of the kidney (SVDK) was grouped in two composites: (i) Mild SVDK (mild proteinuria: grade 2) and (ii) Severe SVDK (heavy proteinuria: grades 3 or 4), as in the WHO Study (14).

Statistical analysis: The SAS statitical program package was used (SAS Institute Inc, N.C., USA). Mean values were given with SD. Univariate correlations (r) and multiple stepwise regressions (proc stepwise) were used to relate vascular disease endpoints to various characteristics. F-values at the stepwise procedure were given if they corresponded to $p < 0.1$. N-way frequency analysis (proc freq) was used to estimate odds ratio for a vascular endpoint due to the presence of various characteristics, adjusted for the effect of n confounding variables (here adjusted for sex), with Cochran - Mantel - Haenzel statistics.

A p value <0.05 was considered statistically significant.

RESULTS

The proportions of age groups 35-41, 42-48 and 49-54 years were 40%, 22% and 38%. The proportions of diabetes duration groups 0-6, 7-13 and $\geq$14 years were 29%, 22% and 49%. The frequencies of diabetic patients with insulin, oral drugs or diet treatment were 71%, 17% and 12%, respectively. The frequency of those with insulin doses >60 U daily was 10%.

Mean HbA1 was 10.6±2% in females and 10.5±1.9% in males. Mean systolic BP was 143±21 mm Hg in females and 146±18 mm Hg in males. The proportion of those with systolic BP $\geq$160 mm Hg was 29%. Mean diastolic BP was 87±9 mm Hg in females and 87±10 mm Hg in males. The prevalences of hypertension was 46% in females and 34% in males. The proportion of antihypertensive drugs was 28% in females and 19% in males.

Mean total cholesterol was 5.9±1.2 $mmol \cdot l^{-1}$ in females and 5.8±1.3 $mmol \cdot l^{-1}$ in males. Hypercholesterolaemia ($\geq$6.7 $mmol \cdot l^{-1}$) was found in 32% of females and 29% of males. Mean BMI was 25.5±5 $kg \cdot m^{-2}$ in females and 24.7±4 $kg \cdot m^{-2}$ in males. The proportion of obesity (BMI $\geq$27 $kg \cdot m^{-2}$) was 25% in females and 20% in males. The frequencies of groups smoking >24, 15-24 or 1-14 cig/day were 1, 10, 22% in females and 6, 14, 18% in males, respectively.

Prevalences (females-males) of large vessel components were: Angina Pectoris 11-6%, Possible Infarction 4-6%, ECG Coronary Probable 6-4%, ECG Coronary Possible 4-6%, and Stroke 5-6%. Prevalences (females-males) of the composites were: Heart Vascular Disease 17-13%, Leg Vascular Disease 7-4%, and Large Vascular Disease 24-19%, respectively.

Table 1. F-values at multiple stepwise regressions with LVD, HVD, ECG Coronary Probable and ECG Coronary All (Probable + Possible) as dependent variables, n=260.

	LVD	HVD	ECG Cor. Prob.	ECG Cor. All
Predictors:				
HbA1	11 ***	16 ***	-	4.5 *
Hypertension	-	3.4	-	7.2 *
Cholesterol	5.1 *	-	7.1 *	-
Age	6.0 *	-	-	-
Familial NIDDM	4.0 *	3.1	-	4.5 *
R^2	0.12	0.13	0.07	0.07

R^2=coefficient of determination. F-values given only when corresponding to p <0.10. Significance levels: *** p <0.001, * p <0.05.

Odds ratios (adjusted for sex) for HVD and LVD were: 2.2 and 3.6 with hypertension, 2.2 and 2.1 with hypercholesterolaemia ($\geq$6.7 mmol.l^{-1}), 2.3 and 4.4 with obesity (BMI $\geq$27 kg.m^{-2}), 2.6 and 3.2 with high HbA1 ($\geq$11%), respectively. With both hypertension, hypercholesterolaemia and obesity simultaneously present, odds ratios for LVD and HVD increased to 6.1 and 20. With these 3 and also high HbA1 simultaneously present, odds ratios were further increased to 11 and 30.

Multiple stepwise regressions (Table 1) show that large vessel disease endpoints were related to HbA1 (strongly), hypertension, cholesterol, age and familial NIDDM. Exclusion of the predictor HbA1 yielded hypertension and familial NIDDM significantly related also to HVD. The following predictors were not significantly related to the large vessel disease endpoints: diabetes duration, smoking, familial ITDM, heart rate, physical activity, social or marital status, sex. By univariate correlation (r), LVD was significantly correlated to all predictors in Table 1, including hypertension ($p < 0.001$-0.01).

Concerning small vessel diseases, no differences were seen between sexes. With diabetes duration of 7-13 years, the frequencies were: Severe SVDE 0%, Mild-medium SVDE 23%, Severe SVDK 4%, and Mild SVDK 9%, respectively. With diabetes duration of $\geq$14 years, corresponding frequencies above were 26%, 36%, 15% and 20%.

Table 2. F-values at multiple stepwise regressions with small vessel disease of the eye and of the kidney as dependent variables, n = 260.

	SVDE	SVDK
Predictors:		
Diabetes duration	68 ***	22 ***
Hypertension	6.3 *	10 **
HbA1	7.3 *	-
Familial NIDDM	4.1 *	-
R^2	0.31	0.12

Significance levels: *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$. R^2=coeff. determ.

Odds ratios (adjusted for sex) for SVDE and SVDK were 2.0 and 2.4 with hypertension, 1.5 and 1.6 with hypercholesterolaemia ($\geq$6.7 mmol.l^{-1}), 3.0 and 1.7 with high HbA1 ($\geq$11%), respectively. With both hypertension and high HbA1 simultaneously, the ratios for SVDE and SVDK increased to 6.3 and 3.8, respectively.

Multiple stepwise regressions (Table 2) showed that both SVDE and SVDK were

independently related to diabetes duration (strongly) and hypertension. Adding all the same variables as in the regression with large vessel disease above, we also found SVDE independently related to HbA1 and familial NIDDM.

DISCUSSION

Relationships in the present study. This study analysed risk factors for and prevalences of angiopathy in 260 diabetic patients, using the protocol of the WHO Study (14). We found large vessel disease independently related to hypertension and cholesterol, as in the WHO Study. This seems reasonable, as these are risk factors also in the general population. Also similar to the WHO Study, we found no relationship between LVD and smoking. A reason for this might be the cessation of smoking with manifestation of complications. A strong association was found between SVD and diabetes duration, as in the WHO Study (14). Interestingly here, no clear relationship was seen between LVD and duration. The same tendency was underlined in the WHO Study, with the similar mean duration in groups with or without cardiovascular disease. Other investigators also have reported minor importance of duration regarding CVD in diabetes (14).

We also found LVD independently related to HbA1 (not analysed in the WHO Study). Furthermore, the actual HbA1 value agreed fairly well with mean HbA1 during the previous year in almost all of the participants (not given in Results). As far as we know, very few previous reports have demonstrated an association between the HbA1 variable and cardiovascular disease (5,11). This finding should imply an influence by blood glucose per se (glycation, for instance) or that HbA1 here was a marker for not measured background variables, like triglycerides or coagulation factors. Fasting blood glucose in the WHO Study was not related to large vessel disease, probably due to a higher daily variability of glucose, compared to HbA1 (6).

In the present study, LVD was also weakly related to familial NIDDM (not givenin the WHO Study). Parental NIDDM has recently been related to insulin resistance (7), which in turn is related to hypertension (3,10). This might imply a reason for the link between familial NIDDM and CVD.

Concerning SVDE and SVDK, we found independent associations not only to diabetes duration (strongly) but also to hypertension. These were also the main predictors of small vessel disease in the WHO Study (1). Furthermore, we could demonstrate a relationship SVDE - HbA1 (not in the WHO study), underlined by previous studies relating HbA1 with retinopathy (4,8,15).

Comparison of prevalences with the WHO Study. As no Scandinavian centre was included in the 14 international centres of the WHO Study, this implied us to compare various prevalences in our study with the two closely situated European centres, London and Berlin, and also with the Tokyo centre (14). It was not possible, due to local circumstances, to include as many patients in Uppsala as in the WHO centres. Our study contained similar proportions in the young and old age groups, while the proportion with diabetes duration $\geq$14 years was relatively large. The WHO Study, especially Tokyo, had a relative weighing towards older age and shorter duration. Tokyo also differed somewhat by relatively few insulin-treated and many diet-treated (14). As in the WHO Study, the aim of the sampling method here was to avoid the bias of more complicated cases or frequent visitors, and non-screening avoided the bias of new uncertain cases.

Comparing risk factors, given separately for females and males, the mean systolic blood pressure was higher in Uppsala (143-146 mm Hg) and Berlin (143-145 mm Hg), than in London (139-135 mm Hg) and Tokyo (133-130 mm Hg). The prevalence of hypertension (WHO-criteria) was also higher in Uppsala (46-34%) and Berlin (36-39%), than in London (30-22%) and Tokyo (27-29%). Then, hypertension was as prevalent here as in Berlin. Obesity is a possible confounding variable, but was more frequent in Berlin than in Uppsala and London (see below). Those with antihypertensive drugs were similar in Berlin and Uppsala, and lower in London. There is agreement that hypertension is at least as damaging in diabetics as in non-diabetics.

Mean body mass index, separately for females and males, was similar in the present study (25.5-24.7 $kg \cdot m^{-2}$) to mean BMI in 800 non-diabetic subjects in Uppsala (24.8-25.3 $kg \cdot m^{-2}$) (2). The frequency of obesity (BMI $\geq$28 $kg \cdot m^{-2}$) was highest in Berlin (40-25%), somewhat lower in Uppsala (25-20%) and London (30-16%), and considerably lower in Tokyo (7-4%). Comparison of BMI should be drawn with some caution, as ethnic differences may influence, like different patterns of body fat distribution in Oriental and Western subjects.

Mean cholesterol was higher in Berlin (6.3-6.3 $mmol \cdot l^{-1}$) than in Uppsala (5.9-5.8 $mmol \cdot l^{-1}$) and London (5.9-5.9 $mmol \cdot l^{-1}$), and lowest in Tokyo (5.3-5.1 $mmol \cdot l^{-1}$). Similarly, hypercholesterolaemia ($\geq$6.7 mmol l) was more frequent in Berlin (33-31%) and Uppsala (32-29%) than in London (21-19%), and lowest in Tokyo (12-10%) (14). This should be of importance for regional variations of CVD prevalence, as hypercholesterolaemia is established as CVD risk factor in diabetics as well as in non-diabetics.

Smoking mainly differed in that male heavy smokers were less frequent in Uppsala (6%), London (12%) and Berlin (6%), and obviously more frequent in Tokyo (26%) (14). Generally in the WHO Study, men smoked more than women. Differences of smoking rates were difficult to interprete here, however, as smoking surprisingly was not a predictor of diabetic complications. Probably, diabetics

ceased smoking when they got complications.

Comparing large vessel disease, separately for females and males, there was a tendency to find the highest prevalences in Berlin, lower levels in Uppsala and London, and the lowest levels in Tokyo. This was manifested by subjective evidence, as the prevalence of Angina Pectoris was 15-11% in Berlin, 11-6% in Uppsala, 10-8% in London, and 4-4% in Tokyo. Similarly, the prevalence of Possible Infarction was 17-15% in Berlin, 4-6% in London, 8-7% in London, and 2-3% in Tokyo. We also found objective evidence of this fact,as the prevalence of ECG Coronary Probable (major abnormalities) was 11-5% in Berlin, 6-4% in Uppsala, 6-3% in London, and 2-2% in Tokyo (14). This finding should support the hypothesis, that major variations in LVD prevalence occur. One of the major aims of this and the WHO study was to examine this assertion. Furthermore, as we have chosen to compare our Northern European centre with one Central European, one Western European and one Oriental Centre, we could also demonstrate a tendency to variability pattern between these four centres, regarding prevalences of both LVD risk factors and LVD per se. Thus, higher levels of blood pressure, cholesterol and BMI, and a higher prevalence of LVD, seemed to coexist in Berlin. In Tokyo on the contrary, frequencies were lower concerning both these risk factors and LVD. Uppsala and London seemed to be in the middle regarding these aspects.

Comparing small vessel disease, we have chosen to compare between groups with 7-13 years of diabetes duration, since the 7-13 years interval was the best defined duration interval. No clear differences were noted here between sexes.

Regarding this 7-13 years interval, the prevalence of severe SVDE was 0% in Uppsala, 2% in London, 3% in Berlin, and 12% in Tokyo. In the same 7-13 years interval, the prevalence of severe SVDK was 4% in Uppsala, 4% in London, 9% in Berlin, and 18% in Tokyo (14). Thus, a tendency to regional variability was found also concerning SVD in this defined interval. Mainly similar prevalence figures were found in Uppsala, London and Berlin. The prevalence figures in Tokyo were higher than elsewhere.

It was not possible to point to regional variability of risk factors as explanatory background variables to SVD, however. Hypertension was an established risk factor of SVD both here and in the WHO Study, but hypertension was not more prevalent in Tokyo than elsewhere. Concerning the risk factor diabetes duration, this could neither explain a regional difference of SVD prevalence. When we compared the diabetic groups with $\geq$14 years duration, we noticed that the Uppsala diabetics in this interval group included more patients with >20 years duration than the diabetics in Tokyo. In spite of this, Severe SVDE in the $\geq$14 years interval was almost similar in Tokyo (21%) as in Uppsala (26%) (14). Another finding in the WHO Study concerning this aspect was, that

the two participating centres in the WHO Study had somewhat differing prevalences of Severe SVD, being lower in Hong Kong than in Tokyo (14).

In conclusion, the heterogeneity of risk factor patterns and vascular disease prevalences found in the WHO Study was underlined when comparing with the Uppsala diabetics, especially concerning cardiovascular disease. We also found HbA1 to be an independent risk factor of vessel disease, not clearly demonstrated previously regarding cardiovascular disease.

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REFERENCES

1. Blackburn, H. & Keys, A. The electrocardiogram in population studies. A classification system. Circulation 21: 1160-1175, 1960.
2. Cederholm, J. & Wibell, L. Findings in a health survey of middle-aged subjects in Uppsala 1981-82. Ups J Med Sci 90: 201-227, 1985.
3. Cederholm, J., & Wibell, L. Insulin resistance in the oral glucose tolerance test - a link with hypertension. Scand J Prim Healh Care 9: 53-57, 1991.
4. Doft, B.H., Kingsley, L.A., Orchard, T.J. & Becker, D. The association between long-term diabetic control and early retinopathy. Ophtalmology 91: 763-769, 1984.
5. Ekoe, J-M. Diabetes mellitus. Aspects of the world-wide epidemiology of diabetes mellitus and its long-term complications. Elsevier, Oxford, pp 211-220, 1988.
6. Grimby, G., Wilhelmsen, L., Björntorp, P., Saltin, B. & Tibblin, G. Habitual physical activity, aerobic power and blood lipids. In: Muscle metabolism during exercise (ed. B. Pernow & B. Saltin), pp 469-481, Plenum Press, New York, 1971.
7. Ho, L.T., Chang, Z.Y., Wang, J.T. & Reaven, G.M. Insulin insensitivity in offspring of parents with type 2 diabetes. Diabetic Med 7: 31-34, 1990.
8. The KROC Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria. N Engl J Med 311: 365-372, 1984.
9. National Diabetes Data Group, NIH. Classification and diagnosis of diabetes and other categories of glucose intolerance. Diabetes 28: 1039-1057, 1979.
10. Pollare, T., Lithell, H. & Berne, C. Insulin resistance a characteristic feature of primary hypertension, independent of obesity. Metab 39: 167-174, 1990.
11. Reichard, P. Intensified insulin treatment and late complications in insulin-dependent diabetes mellitus. In: Treatment of insulin-dependent diabetes mellitus (ed. Drug Information Comittee), NBHW, Stockholm, 2: 45-50, 1990.
12. Rose, G.A. & Blackburn, H. Cardiovascular survey methods. WHO Monograph Series No56. WHO, Geneva, 1968.
13. West, K.M., Ahuja, M.M.S., Bennett, P.H., De Acosta, O.M., Fuller, J.H., Grabauskas, V. & Jarrett, J. Relationship of macroangiopathy to blood glucose, triglycerides, and other risk factors in diabetics of nine populations. Diabetologia 22: 412-420, 1982.
14. WHO Multinational Study of Vascular Disease in Diabetics. Prevalence of small vessel and large vessel disease in diabetic patients from 14 centres. Diabetologia 6 (Suppl): 615-640, 1985.
15. Wikblad, I., Montin, K.R. & Wibell, L. Metabolic control, residual insulin secretion and self-care behaviours in a defined group of patients with Type 1 diabetes. Ups J Med Sci 96:

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