ORIGINAL ARTICLE

Similar cardiovascular risk factor profile in screen-detected and known type 2 diabetic subjects

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Abstract

Objective. To compare the cardiovascular disease (CVD) risk factor profile in subjects with screen-detected type 2 diabetes (SDM) and subjects with known type 2 diabetes (KDM). **Design.** Population-based, cross-sectional survey. **Setting and subjects.** In a single, semi-rural general practice 2082 subjects were between 20 and 69 years. Of those, 1970 subjects were invited, and a total of 1374 (69.7%) subjects were examined by blood tests, anthropometric measures, and self-administered questionnaires. **Results.** Before the survey 19 persons were known to have type 2 diabetes. The screening revealed another 31 individuals with type 2 diabetes, diagnosed according to the 1999 World Health Organization criteria. Age, levels of blood pressure, BMI, and dyslipidaemia, and markers of haemostasis and inflammation were comparable in the two groups. Median age in the KDM group was 58 vs. 57 years in the SDM group, $p = 0.82$, 79% were male vs. 61%, $p = 0.23$. In both groups 74% had blood pressure $\geq 130/85$ mmHg, $p = 1.00$. In both groups 90% had BMI ≥ 25 , $p = 1.00$, and about half in both groups had BMI ≥ 30 , $p = 0.56$. In the KDM group 63% had dyslipidaemia (low HDL cholesterol or elevated triglycerides) vs. 80% in the SDM group, $p = 0.32$. Median levels of plasminogen-activator-inhibitor (PAI-1), tissue plasminogen activator (t-PA), as well as fibrinogen and C-reactive protein (CRP) were without statistically significant differences in the two groups, $p > 0.1$. In contrast, in markers of glycaemic regulation statistically significant differences were found between groups. Median HbA1c was 8.0 vs. 6.5, $p < 0.001$. Median fasting whole blood glucose level was 8.8 mmol/L vs. 6.3 mmol/L, $p < 0.001$, and glucose at two hours during OGTT was 16.9 mmol/L vs. 11.2 mmol/L, $p < 0.001$. Median fasting serum insulin level was 52 pmol/L vs. 80 pmol/L, $p = 0.039$ and at two hours 127 pmol/L vs. 479 pmol/L, $p < 0.001$. **Conclusions.** The CVD risk-factor profile of SDM patients was similar to the expected adverse profile of patients with KDM. This indicates an already increased risk of cardiovascular disease in diabetic patients before the diabetes becomes clinically manifest, supporting the need for early diagnosis.

Key Words: Cross-sectional survey, general practice, population-based, screen-detected, type 2 diabetes

Type 2 diabetes (T2DM) is a serious and increasingly prevalent disease, which is often followed by cardiovascular complications and reduced life expectancy. About half of T2DM patients already have cardiovascular complications at diagnosis [1,2]. Given the fact that only half or even less of the subjects with T2DM are diagnosed [3,4], much concern has been expressed to find the undiagnosed diabetic subjects, but so far screening for unknown diabetes is not universally recommended [5–7]. There is, however, increasing evidence of the benefit of screening populations at high risk of cardiovascular disease

(CVD), such as people with hypertension, dyslipidaemia, or obesity [8]. Treatment of hypertension [9,10] and dyslipidaemia [11] in patients with diabetes may reduce CVD complications and CVD-related death. It seems natural to anticipate that KDM subjects are in a more advanced stage of disease than SDM subjects but knowledge is scarce, in particular regarding unselected populations.

The aim of this study was to compare CVD risk factors in SDM subjects with the risk factors in KDM subjects in a Danish general practice population.

Diabetes is a major risk factor for development of cardiovascular complications. Less than half of the prevalent diabetic population is diagnosed. It is not known to what extent screening for diabetes will be a benefit to all.

- The study has shown a similar cardiovascular risk-factor profile in persons with known diabetes compared with persons with screen-detected diabetes.
- When assessing cardiovascular risk it is mandatory to take into account all known metabolic risk factors for cardiovascular disease, i.e. body composition, blood pressure, lipids – and blood glucose.

Material and methods

Study population

During a period of 27 months in 1998–2000 we carried out a survey in a Danish general practice in order to describe the pattern of CVD risk factors with special attention to weight, lipids, blood pressure, and glycaemia, as well as components of coagulation and inflammation, in the diabetic population. A total of 3108 people were listed with this practice, of which 2082 were between 20 and 69 years and thus eligible for the survey. Patients suffering from severe physical or mental illnesses were excluded, as were insulin-treated diabetic patients, including three T2DM patients on insulin treatment (female 41 years, male 56 years, and male 59 years), because administered insulin might interfere with the evaluation of intrinsic insulin secretion. Known T2DM patients treated with diet and/or oral antidiabetics were invited. Of 1970 invited subjects 1374 (69.7%) gave written informed consent and were examined (Figure 1). Self-reported age at onset of disease in KDM subjects was confirmed in the clinical records. The survey was carried out according to the Helsinki Declaration II and was approved by the regional Research Ethics Committee (VN 97/173).

Measurements

After an overnight fasting period of 10 hours blood samples were taken and an OGTT with 75 g of glucose was performed [12]. A physical examination was carried out by the same investigator (PEH) throughout the entire survey. Information on weight, height, and waist circumference was obtained. Body mass index (BMI) was calculated

Figure 1. Flow chart showing inclusion and exclusion of participants.

as weight divided by height squared (kg/m^2). Blood pressure (BP) was measured in the seated position, according to standard procedure, using a Hawksley Random Zero sphygmomanometer. A full description of the survey methods has been published previously [13].

Biochemical methods

The serum concentration of insulin was determined with AutoDELFIA™ (PerkinElmer, Mass, USA), two-sited (double antibody) technique using monoclonal antibodies (insulinpro-insulin crossreactivity $<0.4\%$), total cholesterol (Colorimetric test, VITROS Ektachem 950 IRC, Eastman Kodak, Rochester, NY, USA), HDL cholesterol (Liquid-N-geneous HDL-C, Genzyme, and Technicon RA 1000, Genzyme Diagnostics, West Malling, Kent, UK, and Tarrytown, NY, USA), and triglycerides (TG) (Colorimetric test, VITROS Ektachem 950 IRC,

Eastman Kodak, Rochester, NY, USA). LDL cholesterol was calculated using Friedewald's formula: LDL cholesterol = total cholesterol - $0.45 \times$ triglyceride [14]. Venous whole blood was stabilized with EDTA for analysis of glycated haemoglobin (HbA1c) (HPLC VARIANT™ Bio-Rad Laboratories, Hercules, CA, USA), and for analysis of glucose (Enzymatic amperometric test, EBIO Eppendorf-Netheler-Hinz GmbH, Hamburg, Germany) (CV 3.3%). The result of glucose analysis is reported as the mean of a double analysis. Between-assay coefficient of variation (CV) was 3.28% during the study. Citrate-stabilized plasma was prepared for analysis of plasminogen-activator-inhibitor (PAI)-1 antigen (Imulyse PAI kit, Biopool, Umeå, Sweden) (CV 2.4%), tissue-plasminogen-activator (t-PA) antigen (Imulyse t-PA kit, Biopool) (CV 3.5%), C-reactive protein (CRP) (monoclonal antibodies, BN II analyser, Siemens, Marburg, Germany) (CV 6.3%), fibrinogen (modified Clauss procedure, ACL 7000, Instrumentation Laboratory, Milan, Italy).

Fasting morning urine was analysed for microalbuminuria using albumin-creatinine ratio, albumin (immuno-chemical nephelometric method, Behring Nephelometer II System, Siemens, Marburg, Germany), creatinine (Jaffa method, VITROS analyzer, Ortho Clinical Diagnostics, Rochester, NY, USA).

Statistical analysis

Results on continuously valued variables are reported as medians with inter-quartile range (IQR), and comparisons between the groups of diabetic subjects were made by the Mann-Whitney U-test. Results on categorically valued variables are reported as numbers and percentages, and comparisons were made by Fisher's exact test. A p-value of <0.05 (two-tailed) was considered significant. For comparative purposes the results of the NGT group are shown in the tables without application of specific statistical tests.

To account for multiple testing, significance is assessed by controlling the false discovery rate at 5% [15]. SAS 9.2 for Windows, SAS Institute, Cary, NC, USA was used for the statistical analyses.

Results

Prior to the survey 19 (1.4%) persons of the examined 1374 subjects were known diabetic patients, and a further 31 (2.3%) were diagnosed with T2DM. There was a male preponderance in both groups (Table I). The glycaemic regulation differed statistically significantly between the two groups: HbA1c and blood glucose values during OGTT were higher and insulin values during OGTT were lower in the KDM group than in the SDM group.

Table I. Demographic, anthropometric, and biochemical measurements in subjects with known vs. screen-detected Type 2 diabetes, and in subjects with normal glucose tolerance.

	KDM (n = 19)	SDM (n = 31)	p	Sign.	NGT (n = 1183)
Male	15 (79%)	19 (61%)	0.228		588 (50%)
Age (years)	58 (53–65)	57 (51–65)	0.818		42 (34–52)
T2DM diagnosis age (years)	51 (45–59)	57 (51–65)	0.029		NA
Waist circumference (male) (cm)	102 (96–108)	108 (99–115)	0.096		92 (86–99)
Waist circumference (female) (cm)	101 (98–104)	102 (91–108)	0.952		82 (76–90)
BMI (kg/m ²)	29.1 (26.9–31.5)	30.4 (27.3–34.7)	0.197		24.6 (22.3–27.3)
Blood pressure, systolic (mm Hg)	144 (124–156)	144 (126–152)	0.568		118 (108–128)
Blood pressure, diastolic (mm Hg)	78 (70–94)	86 (74–92)	0.435		74 (66–82)
HbA1c (%)	8.0 (6.9–9.2)	6.5 (6.1–7.2)	<0.001	*	5.5 (5.3–5.8)
Fasting blood glucose (mmol/L)	8.8 (7.2–10.4)	6.3 (6.0–7.6)	<0.001	*	4.7 (4.4–4.9)
2 h blood glucose (mmol/L)	16.9 (15.8–20.0)	11.2 (9.2–15.2)	<0.001	*	4.1 (3.5–4.9)
Fasting insulin (pmol/L)	52 (32–83)	80 (53–101)	0.039		35 (26–51)
2 h insulin (pmol/L)	127 (99–241)	479 (322–868)	<0.001	*	165 (106–274)
Cholesterol (mmol/L)	5.6 (4.5–6.3)	6.0 (5.4–6.5)	0.116		5.1 (4.5–5.9)
HDL cholesterol (male) (mmol/L)	1.2 (0.9–1.3)	1.3 (1.0–1.7)	0.169		1.4 (1.2–1.6)
HDL cholesterol (female) (mmol/L)	1.2 (1.2–1.3)	1.5 (1.2–1.7)	0.275		1.7 (1.4–1.9)
LDL cholesterol (mmol/L)	3.4 (2.5–3.9)	3.8 (3.1–4.1)	0.152		3.0 (2.4–3.6)
Triglycerides (mmol/L)	1.8 (1.4–3.4)	2.2 (1.7–3.5)	0.165		1.2 (0.9–1.7)
Albumin/creatinine ratio (mg/mmol)	1.4 (0.6–3.3)	0.6 (0.4–1.6)	0.180		0.5 (0.4–0.6)
PAI-1 antigen (ng/mL)	28.0 (14.0–39.1)	23.8 (5.9–38.4)	0.549		5.4 (2.5–12.0)
t-PA antigen (ng/mL)	12.1 (10.1–17.4)	17.1 (10.3–18.8)	0.368		7.2 (4.7–10.3)
CRP (mg/L)	3.1 (1.8–7.6)	3.3 (1.7–6.1)	0.992		0.9 (0.4–2.1)
Fibrinogen (mg/dL)	381 (313–434)	320 (288–381)	0.145		302 (263–346)

Data are medians (interquartile range) or numbers (%). NA = not applicable. P-value according to a Mann-Whitney U-test for continuous valued variables or Fisher's exact test for categorical valued variables. Significance (denoted by*) in the presence of multiple testing is assessed by controlling the false discovery rate at 5% [15].

The prevalence of hypertension, i.e. blood pressure $\geq 130/85$ mmHg, was not different in the two groups. A total of nine persons (47%) in the KDM group vs. 12 persons (39%) in the SDM group were being treated with antihypertensive or diuretic drugs (Table II). Dyslipidaemia as defined by the presence of either low HDL cholesterol or elevated triglycerides was relatively more frequent in the SDM group (for definitions, see Figure 2). Two persons were being treated with lipid-lowering medication.

The prevalence of overweight was not statistically significantly different in the two groups, whether comparing BMI or abdominal obesity as assessed by waist circumference. Abdominal obesity was found in 84% and 90% in the two groups respectively, $p = 0.66$. Some 90% of both groups had BMI ≥ 25 kg/m² and around half in both groups were obese, i.e. had BMI ≥ 30 kg/m², $p = 0.56$. Levels of PAI-1, t-PA, fibrinogen, and CRP were not statistically significantly different in the two groups.

Discussion

Despite our anticipation that SDM patients were in a less advanced state of disease than the KDM patients, we found a comparable adverse CVD risk-factor profile in the two groups. Only glycaemic regulation reflected our anticipation.

Comparison with existing literature

It has previously been reported that onset of diabetes happens as much as seven years or even more before clinical symptoms occur [16]. The age in the KDM group and the SDM group was similar, although the mean diabetes duration in the KDM group was 7.2 years. We are not able to tell when, or even if, the SDM diabetic subjects would eventually have been diagnosed if they had not participated in this study, so one might speculate that the two groups could be

as much as 10 years apart when it comes to age of diabetes onset.

Despite the difference in diabetes duration, we were unable to demonstrate any major differences in the pattern of risk factors for CVD between the groups of KDM and SDM, except the already mentioned differences in glycaemic regulation. The findings in the SDM group in our survey, e.g. concerning hypertension and degree of treatment, as well as body composition, glycaemic control, and dyslipidaemia, compares well with the baseline characteristics reported from the ADDITION study of 3057 screen-detected diabetic subjects [17].

Our findings are also in accordance with results from the Hoorn Study. In this study diabetic subjects found by targeted screening were compared with diabetic subjects simultaneously diagnosed in general practice [18,19]. In NHANES III a similar pattern was found, when comparing the group of known diabetic subjects and the newly diagnosed [20].

Weight is of great importance in relation to diabetes, although a fraction of overweight persons are otherwise metabolically normal. In the NHANES III survey 917 of 3280 (28%) individuals aged 40–74 years had BMI > 30 kg/m², and of those, 14% had normal fasting glucose, normal blood pressure, and normal lipids [21]. Others have found that even the metabolically normal overweight subjects seem to have an increased mortality risk [22]. There was a non-significant tendency towards higher weight in the SDM group. Diagnosis of diabetes has been demonstrated to result in loss of weight. It is possible that awareness of disease and treatment in KDM influences weight in this group [23]. It has also been demonstrated that weight gain in the 10 years up to diagnosis of diabetes is less than in the preceding years [24].

The prevalence of dyslipidaemia was equally distributed in the two groups. Treatment might have influenced the possible difference between the groups. Omitting the two subjects in the KDM group

Table II. Cardiovascular risk factors and complications, and treatment, in subjects with known vs. screen-detected Type 2 diabetes and in subjects with normal glucose tolerance.

	KDM (n = 19)	SDM (n = 31)	p	Sign.	NGT (n = 1183)
Abdominal obesity	16 (84%)	28 (90%)	0.661		569 (48%)
Overweight (BMI ≥ 25 kg/m ²)	17 (90%)	28 (90%)	1.000		534 (45%)
Obesity (BMI ≥ 30 kg/m ²)	8 (42%)	17 (55%)	0.561		143 (12%)
Hypercholesterolaemia	12 (63%)	25 (81%)	0.199		703 (59%)
Dyslipidaemia	12 (63%)	24 (80%)	0.319		373 (32%)
Lipid-lowering medication	2 (11%)	0 (0%)	0.140		9 (1%)
Hypertension	14 (74%)	23 (74%)	1.000		337 (29%)
Antihypertensive medication	9 (47%)	12 (39%)	0.570		94 (8%)
Microalbuminuria	6 (33%)	4 (13%)	0.140		17 (2%)

Data are numbers (%). P-value according to Fisher's exact test. Significance in the presence of multiple testing is assessed by controlling the false discovery rate at 5%.

Item	Definition
Abdominal obesity	Waist circumference ≥ 94 cm (male) or ≥ 80 cm (female)
Hypercholesterolaemia	Total cholesterol ≥ 5.0 mmol/L
Dyslipidaemia	HDL cholesterol < 1.0 mmol/L (male), < 1.3 (female) or triglycerides ≥ 1.7 mmol/L
Lipid-lowering medication	ATC code C 10
Hypertension	Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg
Antihypertensive medication	ATC codes C 02, C 03, C 04, C 07, C 08, C 09
Microalbuminuria	Albumin/creatinine ratio, male 2.5–25 mg/mmol, female 3.5–25 mg/mmol

Figure 2. Definitions and cut-off points.

on lipid-lowering medication did not alter the results (data not shown). At the time of the study there was no consensus on treating modestly elevated lipid values, and no consensus on using lipid-lowering medication as primary prevention of CVD [25–27].

Microalbuminuria is a strong predictor of CVD mortality, and has been demonstrated to be independently associated with diabetes duration [28]. We found a tendency towards more participants having microalbuminuria in KDM, but again the difference was not statistically significant. It is uncertain when in the natural history of diabetes indicators of haemostasis and inflammation start to increase. We found levels of these factors to be equally elevated in the two groups. It has been reported that the concentration of PAI-1 is elevated in subjects with T2DM but not in subjects with impaired glucose tolerance (IGT) [29]. Our group has, as previously reported, found elevated but not statistically significant differences in PAI-1, t-PA, fibrinogen, and CRP between groups of persons with pre-diabetes, i.e. impaired glucose tolerance (IGT), and impaired fasting glycaemia (IFG) [13]. This finding indicates a disturbance in coagulability and inflammatory mechanisms well before the diabetes becomes clinically manifest.

Insulin resistance is a condition in the body where the passage of glucose into the cells is restrained, demanding more insulin to maintain normal glucose levels in the blood, and resulting in increased beta cell function up to the point where the beta cells can no longer satisfy the demands, and pre-diabetes and later diabetes become manifest. Fasting insulin levels and insulin secretion during the OGTT were significantly

higher in the SDM group as compared with the KDM group reflecting a lesser degree of deteriorated beta-cell function, possibly due to shorter duration of diabetes in the SDM group, which was expected (data on insulin resistance otherwise not shown).

Weaknesses and strengths

The weaknesses of this survey are small numbers of participants and the use of only one OGTT for diagnosis. Although this is justifiable in epidemiological research, it is not so in everyday clinical practice [30]. We are aware of the problems concerning test and retest. One strength of the study is the unselected population. All persons were listed with one general practice and the non-attenders chose to refuse participation of their own free will and were in no way influenced in their decision. The distribution of age and gender roughly reflects that of the Danish population. The small differences found are largely restricted to the age groups 20–29 and 30–39 years, in which only a few persons were found to have abnormal test results. The mean ages in the age group 40–69 years are very similar between participants and non-attenders (53.0 [SD 8.4] and 53.3 [SD 9.1], $t = 0.573$, $p = 0.567$) (data not otherwise shown). The examinations were done by only one investigator, who was also the GP of the participants, and one medical laboratory technologist, which on one hand implies minimal imprecision but on the other hand may carry a risk of systematic bias. This was taken care of by previous intensive training. All participants received a letter with the results of the examination. For the participants with all results in normal ranges, the study was completed by this letter. For those with values outside the reference intervals, the letter suggested that the participants return for a discussion and evaluation of the results. No results were entered into the clinical records before this visit and then only if the patient gave permission [31].

The cardiovascular risk-factor profile of SDM patients was not different from the adverse CVD risk-factor profile of the KDM patients. Thus, the CVD risk-factor profile of patients with undiagnosed T2DM may worsen well before the diabetes itself becomes symptomatic or diagnosed by screening. Although there is no universal consensus on screening the whole population, all items in the WHO statement on screening are fulfilled [32], and it seems important to intensify efforts to find the non-diagnosed T2DM subjects. Obviously the screening procedure will result in a higher prevalence of the disease in areas of high screening activity [33]. Finding the undiagnosed T2DM patients is, however, not enough. It is mandatory that both doctors and patients adhere to the existing guidelines for good

treatment. There is a discrepancy in knowledge of and adherence to guidelines concerning treatment of different risk factors [34], and it has been shown that a great proportion of persons with, e.g., high blood pressure are left without treatment [17].

Conclusions

We have in general practice an obligation to enhance our awareness of cardiovascular risk factors in patients seeking our advice and to bear in mind that when screening for diabetes one should include assessment of the entire adverse CVD risk-factor profile, i.e. blood pressure, weight, and lipids, and not focus only on glycaemia, which seems to be only slightly affected in SDM. Future research is needed to answer the question of whether we do well to all or harm to some SDM subjects by diagnosing and thereby labelling them before they actually develop symptoms of their diabetes.

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Conflicts of interest

None.

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