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Five-year incidence of type 2 diabetes mellitus in patients with familial combined hyperlipidaemia

M.C.G.J. Brouwers*, C.J.H. van der Kallen, N.C. Schaper, M.M.J. van Greevenbroek, C.D.A. Stehouwer

Departments of Medicine and Endocrinology, Laboratory of Vascular Medicine and Metabolism, Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, the Netherlands, *corresponding author: tel.: +31 (0)43-388 21 29, fax: +31 (0)43-367 09 16, e-mail: Martijn.brouwers@intmed.unimaas.nl

ABSTRACT

Background: The current study was conducted to investigate whether patients with familial combined hyperlipidaemia (FCHL) are predisposed to the development of type 2 diabetes mellitus (T2DM).

Methods: A cohort of 56 FCHL patients and 54 spouses was followed over time with a five-year interval. Diagnosis of T2DM was based on fasting glucose levels or use of antidiabetic medication. Baseline body mass index, waist circumference, blood pressure, use of antihypertensive and lipid-lowering medication, plasma cholesterol, triglycerides, apolipoprotein B, glucose, insulin and alanine aminontransferase (ALAT) levels were determined as potential predictors of new onset T2DM.

Results: Baseline prevalence of T2DM was 2% in spouses and 9% in FCHL patients, and 4 and 20%, respectively, after five-year follow-up. The incidence of T2DM was significantly higher in FCHL patients (2 *vs* 14%; OR 9.1; 95% CI 1.0 to 81.4; p=0.04; age and sex adjusted). Of all baseline variables, only plasma insulin levels (not glucose) significantly predicted the development of T2DM (p=0.04).

Conclusion: The present study is the first to present incidence numbers of T2DM in FCHL and demonstrates that FCHL patients, as compared with healthy controls, are predisposed to the development of T2DM. This is – at least in part – accounted for by an increased insulin resistance.

KEYWORDS

Fatty liver, hepatic steatosis, insulin resistance, VLDL

INTRODUCTION

Familial combined hyperlipidaemia (FCHL) is a highly prevalent genetic dyslipidaemia (estimated prevalence 1:100) that is associated with an increased risk to develop premature myocardial disease.[1] It is characterised by different types of hyperlipidaemia within one family, i.e. hypercholesterolaemia, hypertriglyceridaemia or the combination of both, which is the consequence of both hepatic very-low-density lipoprotein (VLDL) overproduction and an impaired clearance of remnant particles.[2]

There is ample evidence that FCHL patients – similar to patients with type 2 diabetes mellitus (T2DM) – display many features of the metabolic syndrome, such as insulin resistance,[3,4] visceral obesity, hepatic steatosis,[5] low HDL cholesterol,[2] low-grade inflammation, endothelial dysfunction and hypertension.[6] Since the metabolic syndrome predisposes to the development of T2DM,[7] it might seem reasonable to assume that FCHL patients may also be predisposed to T2DM.

However, despite this substantial metabolic overlap between FCHL and T2DM, it is also clear that they actually differ in their primary phenotype i.e. increased plasma lipid levels or disturbed glucose metabolism. This might therefore imply that FCHL and T2DM are two distinct entities.[8]

Arguments in favour of this assumption can be derived from the original description of FCHL, in which the presence of T2DM has been an exclusion criterion of FCHL.[1] This could have led to an increase of T2DM-protective genes in the FCHL gene pool. An illustrative example of such a protective gene in the general population is glucokinase regulatory protein, which predisposes to high plasma triglycerides, but simultaneously protects from hyperglycaemia.[9,10]

Prospective studies regarding the incidence of T2DM in FCHL have not been conducted. Although cross-sectional studies have revealed normal hepatic glucose production and undisturbed glucose tolerance when T2DM was used as an exclusion criterion of FCHL,[3,4] they were not able to address the question whether FCHL patients are predisposed to the development of T2DM or not. Therefore, in the present study we investigated the incidence of T2DM in a cohort of FCHL patients and their spouses who were followed over a five-year period.

MATERIALS AND METHODS

Subjects

The incidence of T2DM was determined in our well-defined and documented FCHL cohort which was followed over time with a five-year interval, as described in detail previously. The FCHL cohort consists of index patients (an index patient is the first identified patient in a FCHL family) and their hyperlipidaemic relatives.[11] At follow-up, subjects were re-recruited in the same order as during the baseline measurement, thereby preventing a difference in follow-up period for different subgroups (mean follow-up duration: 4.8 ± 0.5 years). FCHL was diagnosed when at least two different lipid phenotypes (hypercholesterolaemia, hypertriglyceridaemia or combined hyperlipidaemia) and premature myocardial disease, i.e. before the age of 60 years, were present in one family (traditional criteria). Secondary causes of hyperlipidaemia, i.e. obesity (BMI >30 kg/m^2), T2DM, hypothyroidism and kidney or liver disease were exclusion criteria in the index patient.[1,11]

The in-married spouses of the FCHL patients were used as controls. The advantage of spouses as a reference group is that these subjects are exposed to a similar environment as the affected group under investigation.

At baseline and in follow-up, diagnosis of T2DM was established in all subjects by fasting venous whole blood glucose levels ≥6.1 mmol/l,[12] or by the use of glucose-lowering medication.

The study protocol was approved by the Human Investigations Review Committee at Maastricht University/ Academic Hospital Maastricht. All subjects gave written informed consent.

Measurements

At both visits, subjects filled in questionnaires concerning current use of medication and history of coronary artery disease (CAD) and cardiovascular disease (CVD). Use of β-blockers is specifically provided in the results section, given their recently observed association with incident T2DM.[13]

CAD was defined as a self-reported history of angina pectoris, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery. CVD was defined as a self-reported history of CAD, ischaemic cerebrovascular attack, transient ischaemic attack or interventions with regard to peripheral artery disease.

Height, weight and waist circumference measurements, and plasma cholesterol, triglycerides, insulin, glucose, alanine aminotransferase (ALAT) and apolipoprotein B determinations were all done as described previously.[11] HOMA-IR (homeostasis model assessment insulin resistance) was calculated as (glucose * insulin)/22.5.[14]

Blood pressure was measured twice in sitting position after ten minutes of rest (Omron 705CP, OMRON Health Care, GmbH, Hamburg, Germany). Hypertension was defined as systolic blood pressure ≥140 mmHg, and/or diastolic blood pressure ≥90 mmHg and/or current use of antihypertensive medication.

Statistical analyses

Differences between FCHL patients and their spouses were analysed with a Student's T-test, after log transformation in case of non-normal distribution, or with a χ^2 test in case of dichotomous variables. Differences between continuous traits during five-year follow-up were compared with a paired samples T-test, and with a McNemar test for paired samples in case of dichotomous traits.

Logistic regression models were constructed to compare the age- and sex-adjusted incidence and prevalence of T2DM between FCHL patients and spouses. For this purpose, baseline age, sex (male = 0 , female = 1) and FCHL status (spouse = 0, FCHL = 1) were simultaneously entered in the logistic model as independent variables. Subsequently, we determined which baseline variable of interest, i.e. BMI, waist circumference, blood pressure, use of lipid-lowering medication, use of antihypertensive medication (and more specifically use of β-blockers), plasma cholesterol, triglycerides, apolipoprotein B, glucose, insulin, HOMA-IR and ALAT levels, predicted incident T2DM, independent of FCHL status. Given the small sample size, only one variable of interest was entered in each logistic regression model together with age, sex and FCHL status. Therefore, for each variable of interest a new model was constructed.

SPSS 13.0 statistical package was used for all analyses (SPSS Inc, Chicago, Ill, USA).

RESULTS

Prevalence of T2DM in FCHL patients and their spouses

Baseline and five-year follow-up characteristics of FCHL patients and their spouses are presented in *table 1*. At baseline, all variables under investigation,

Table 1. *Baseline and five-year follow-up characteristics of familial combined hyperlipidaemia (FCHL) patients and their spouses*

	Baseline		Five-year follow-up	
	Spouses	**FCHL**	**Spouses**	**FCHL**
Male / Female	27/27	27/29	27/27	27/29
Age, years	47±10	50±13	52±10	55±13
BMI, kg/m²	25.5±3.7	28.1±3.9*	25.9±4.0	28.3±3.8*
Waist circumference, cm	90.2±10.5	96.5±10.5*	91.9±11.7‡	98.9±10.1*‡
Lipid-lowering medication, %	2	36†	9	50†§
Cholesterol, mmol/l	5.2±0.8	6.7±1.2*	5.4±0.9	6.7±2.0*
Triglycerides, mmol/l	1.1 (0.7-1.6)	2.0 (1.4-2.6)*	1.2 (0.8-1.8)‡	2.0 (1.4-2.9)*
Apolipoprotein B, g/l	1.0±0.2	1.4±0.3*	1.0±0.2	1.3±0.3*‡
Glucose, mmol/l	5.0±0.6	5.1±0.7	5.0±0.5	5.5±1.8*‡
Insulin, mU/l	4.9 (2.0-9.1)	8.2 (5.2-13.5)*	5.6 (2.0-9.3)	9.6 (6.1-14.2)*
HOMA-IR	1.2 (0.5-1.9)	1.7 (1.0-3.0)*	1.3 (1.0-2.1)	2.2 (1.3-4.0)*
ALAT, U/l	14.8 (11.9-19.4)	24.4 (18.3-31.1)*	15.9 (12.9-18.3)	20.0 (16.2-27.9)*‡
Antihypertensive medication, %	11	25	15	46†§
Beta-blockers, %	6	14	9	27†§
Systolic BP, mmHg	132±20	145±19*	132±20	145±19*
Diastolic BP, mmHg	85±12	91±11*	84±11	90±9*
Hypertension, %	52	93†	52	90†
CAD, %	7	14	9	21
CVD, %	9	20	11	27†

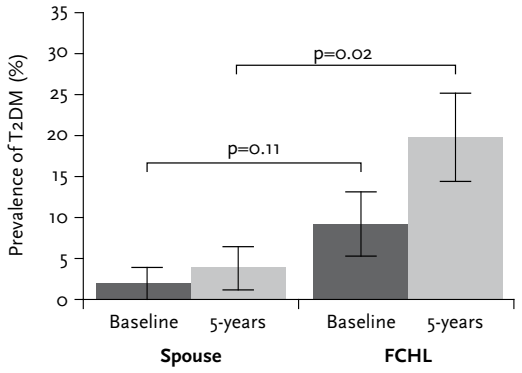
Data are expressed as mean ± SD or as medians with interquartile range between parentheses. * p <0.05, FCHL patients *vs* spouses, Student's T-test; † p <0.05, FCHL patients *vs* spouses, χ^2 test; ‡ p <0.05, 2004 *vs* 1999, paired samples T-test; § p <0.05, 2004 *vs* 1999, McNemar test for paired samples. BMI = body mass index; HOMA-IR = homeostasis model of insulin resistance; ALAT = alanine aminotransferase; CAD = coronary artery disease; CVD = cardiovascular disease.

except for age, fasting whole blood glucose levels and prevalence of antihypertensive drugs, CAD and CVD were significantly different between both groups. At follow-up, a significant increase in waist circumference was observed in both FCHL patients and their spouses. Of interest, as a significant rise in plasma triglycerides was demonstrated for spouses, an increment in plasma glucose levels was only observed in FCHL patients. Furthermore, use of antihypertensive medication, and more specifically the use of β-blockers, almost doubled in FCHL patients after five-year follow-up (*table 1*). Of note, exclusion of FCHL patients with T2DM at baseline hardly affected plasma insulin levels at baseline and in follow-up.

At baseline, the prevalence of T2DM was not statistically significant between FCHL patients and their spouses (9 *vs* 2%, respectively; p = 0.11, *figure 1*). After five-year follow-up, the prevalence of T2DM increased nonsignificantly in both spouses and FCHL patients, but the absolute increase was more pronounced in FCHL patients (from 2% to 4% in spouses *vs* 9 to 20% in FCHL patients, *figure 1*). Correspondingly, the prevalence of T2DM after five-year follow-up was significantly higher in FCHL patients than their spouses (p = 0.02, *figure 1*).

Of note, of the 11 FCHL patients who were diagnosed with T2DM after five-year follow-up, only two subjects were related. Therefore, familial relationships do not account for the significantly higher prevalence of T2DM after follow-up.

Figure 1. *Prevalence of type 2 diabetes mellitus in FCHL patients and spouses at baseline and after five-year follow-up*



Error bars represent 95% confidence intervals. Analysed with logistic regression, with correction for age and sex.

Incidence of T2DM in FCHL patients and their spouses

The number of new cases of T2DM after five-year follow-up, i.e. the incidence, was significantly higher in

FCHL compared with spouses (14 *vs* 2%, odds ratio [OR] 9.1; 95% CI 1.0 to 81.4; p = 0.04; adjusted for sex and age at baseline). Similar results were obtained when the index patients were omitted from analyses (data not shown).

Although there was a substantial difference in BMI between FCHL patients and their spouses, it did not appear to affect the difference in incidence between the groups of interest. The highest incidence numbers were consistently observed in FCHL patients when standardised for BMI, as shown in *table 2*. Similar results were obtained when (sex specific) quartiles for waist circumference were used (data not shown).

Indeed, of all variables presented in *table 1*, including BMI and waist circumference, only baseline plasma insulin levels were independently associated with the onset of T2DM after correction for sex, age and FCHL status (p = 0.04). FCHL status was no longer significant after adjustment for insulin (OR 6.2; 95% CI 0.6 to 64.7; p = 0.11).

When the change in BMI during five-year follow-up entered the model together with age, sex and FCHL status, the odds ratio for FCHL status was hardly affected, although it was not significant anymore (OR 8.6; 95% CI 1.0 to 74.3; p = 0.05).

Table 2. *Five-year incidence of type 2 diabetes mellitus (T2DM) standardised by baseline body mass index (BMI) in spouses and FCHL patients*

BMI quartile	Spouse	FCHL
BMI <23.5 kg/m²	0/20 (0)	0/5 (0)
BMI 23.5 to 26.4 kg/m²	0/12 (0)	1/14 (7.1)
BMI 26.4 to 29.4 kg/m²	1/11 (9.1)	2/14 (14.2)
BMI >29.4 kg/m²	0/7 (0)	4/17 (23.5)

Data are expressed as new cases of total; percentages are presented between parentheses.

DISCUSSION

From the original description of FCHL almost four decades ago, T2DM has been used as an exclusion criterion.[1,11] Nevertheless, many metabolic syndrome-related features that have been observed in T2DM, such as insulin resistance, abdominal obesity, fatty liver and hypertension, are also present in FCHL.[3-6] In the present study we have demonstrated that FCHL patients have a greater risk to develop T2DM when compared with their spouses. The advantage of spouses as a reference group is that these subjects are exposed to a similar environment as the affected group under investigation. Although there was a substantial difference in the degree of obesity between the two groups, this factor did not confound the observed difference in T2DM incidence, since stratification and statistical correction for BMI did not materially alter the results.

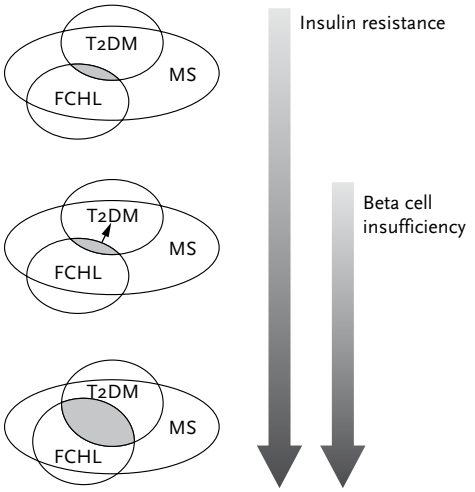
Of all baseline variables that were determined, only plasma insulin levels significantly predicted incident T2DM. Since FCHL status was no longer significant in these analyses, these data imply that the increased susceptibility for FCHL patients to develop T2DM is, at least in part, accounted for by an increased insulin resistant state. Of interest, stable isotope studies and large longitudinal cohort studies have demonstrated that (hepatic) insulin resistance has also been associated with the overproduction of VLDL particles and the hypertriglyceridaemic phenotype, respectively.[15,16] Furthermore, Bredie and others have demonstrated that insulin resistance is commonly observed in FCHL patients, independent of the degree of obesity.[4,17] Finally, Pihlajamäki *et al.* have reported that an increased insulin resistant state is a heritable trait of FCHL.[18] These findings, together with our observations, demonstrate that insulin resistance is an integral feature of FCHL that drives not only the development of hypertriglyceridaemia but also the progression of T2DM. This underlines the importance to unravel its metabolic and genetic background of this complex disease.

The small sample size probably explains that only baseline insulin levels were a significant predictor of incident T2DM. Further studies in larger FCHL cohorts are required to study the contribution of other candidates, which have already been confirmed in the general population, such as the degree of obesity and plasma ALAT levels.[19,20]

The present study was not originally designed to address the incidence of T2DM in FCHL. For this reason, oral glucose tolerance tests (OGTT) were not performed, which should be regarded as a limitation. Of note, previous studies have shown that the prevalence of T2DM diagnosed by fasting glucose levels does not substantially differ from an OGTT.[21] Furthermore, the incidence number of T2DM in the spouses is in concordance with a previous large-scaled Dutch cohort.[21]

The present data demonstrate that FCHL and T2DM are not distinct entities, as was suggested previously.[8] Instead, FCHL appears to be a dynamic entity that may progress into T2DM as insulin resistance progresses and – most likely – also beta cell insufficiency develops (*figure 2*). Therefore, our observations may have marked implications on how this genetic dyslipidaemia should be viewed in relation to T2DM. It emphasises that clinicians should be alert on the development of T2DM in this highly prevalent entity and underlines the necessity to unravel the genetic and metabolic background of insulin resistance.

Figure 2. *Familial combined hyperlipidaemia (FCHL) and type 2 diabetes mellitus (T2DM) are the two major entities within the metabolic syndrome (MS).[8] The present study suggests that at least some of the FCHL patients migrate towards T2DM, as insulin resistance progresses and, most likely, beta cell insufficiency develops*



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