Insulin Resistance, the Metabolic Syndrome, and Complication Risk in Type 1 Diabetes

"Double diabetes" in the Diabetes Control and Complications Trial

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OBJECTIVE — The presence of insulin resistance and the metabolic syndrome are known risk markers for macrovascular disease in patients with and without type 2 diabetes. This study has examined whether these also were predictors of micro- and macrovascular complications in type 1 diabetic patients participating in the Diabetes Control and Complications Trial (DCCT).

RESEARCH DESIGN AND METHODS — International Diabetes Federation (IDF) criteria were used to identify the metabolic syndrome in 1,337 Caucasian DCCT patients at baseline. Insulin resistance was calculated using their estimated glucose disposal rate (eGDR). Insulin dose (units/kg) was also used as a separate marker of insulin resistance.

RESULTS — The eGDR (but not insulin dose or metabolic syndrome) at baseline strongly predicted the development of retinopathy, nephropathy, and cardiovascular disease (hazard ratios 0.75, 0.88, and 0.70, respectively, per $mg \cdot kg^{-1} \cdot min^{-1}$ change; $P < 0.001$, $P = 0.005$, and $P = 0.002$, respectively). Through mainly weight gain, the prevalence of the metabolic syndrome increased steadily from baseline to year 9 in conventionally treated (from 15.5 to 27.2%) and especially in the intensively treated (from 13.7 to 45.4%) patients.

CONCLUSIONS — Higher insulin resistance at baseline in the DCCT (as estimated by eGDR) was associated with increased subsequent risk of both micro- and macrovascular complications. Insulin dose and the presence of IDF-defined metabolic syndrome were poor predictors by comparison. Although intensive treatment was associated with a higher subsequent prevalence of metabolic syndrome, the benefits of improved glycemia appear to outweigh the risks related to development of the metabolic syndrome.

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The metabolic syndrome is a cluster of metabolically related cardiovascular risk factors, the core components of which comprise of central obesity, insulin resistance, dyslipidemia, and hypertension (1). The presence of the metabolic syndrome predicts the risk of cardiovascular disease in nondiabetic subjects as well as in those with type 2 diabetes (2–6). There are multiple definitions for the metabolic syndrome (7–9), with the most recent being the consensus from the International Diabetes Federation (IDF) (10).

Central to the development of the metabolic syndrome appears to be the presence of increased insulin resistance. Although this is a characteristic usually associated with the development of type 2 diabetes, it can also be a feature of patients with type 1 diabetes (11–13). When present in type 1 diabetes, the phrase "double diabetes" has been coined (14), with the assumption that these patients are likely to be at especially high risk of developing cardiovascular disease.

Beyond the use of labor-intensive and invasive euglycemic-hyperinsulinemic clamp techniques, estimation of insulin resistance in type 1 diabetes is difficult because simpler tools such as the homeostasis model are not applicable for this group of patients (15). Clinically, insulin resistance in type 1 diabetic patients is often recognized by their larger requirements for insulin, but more recently a validated method for estimated glucose disposal rate (eGDR) has been developed (16). This calculates a score based on clinical factors of the patient, which shows a close relationship to insulin resistance when formally measured by the clamp method. Using this technique, data from the Pittsburgh Epidemiology of Diabetes Complications Study has found low eGDR (and therefore high insulin resistance) to be associated with an increased risk of nephropathy (17), peripheral vascular disease (18), and coronary artery disease (19). By comparison, few studies have looked at the metabolic syndrome itself in type 1 diabetes using current criteria. Data to date has shown that in a cross-section of type 1 diabetic patients there was an association between the presence of the metabolic syndrome and that of nephropathy and poor glycemic control (20).

The Diabetes Control and Complication Trial (DCCT) was performed at a time before patients with diabetes were routinely prescribed lipid-lowering and antihypertensive treatment (21). This means that it is a dataset that can investigate factors that influence the risk of developing diabetes complications while being free from many of the confounding factors found in contemporary studies. This current study has analyzed the DCCT data to establish how the metabolic syndrome, insulin resistance, and insulin

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Abbreviations: DCCT, Diabetes Control and Complications Trial; eGDR, estimated glucose disposal rate; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Demographic and other baseline features*

Variable	IDF metabolic syndrome	
	Yes	No
n	291	1,046
Age (years)	26.5 ± 7.5	27.0 ± 6.9
Waist circumference (cm)	96.1 ± 13.4	87.8 ± 10.2
BMI (kg/m^2)	24.7 ± 2.9	23.1 ± 2.7
HDL cholesterol (mmol/l)	1.08 ± 0.19	1.37 ± 0.32
Triglycerides (mmol/l)	1.13 ± 0.69	0.87 ± 0.48
Systolic blood pressure (mmHg)	115.3 ± 12.2	114.1 ± 11.4
Diastolic blood pressure (mmHg)	73.7 ± 9.4	72.5 ± 8.6
eGDR (mg · kg^{-1} · min^{-1})	7.4 ± 1.7	8.3 ± 1.3
A1C (%)	9.2 ± 1.6	8.8 ± 1.5
Blood glucose (mmol/l)	12.7 ± 5.3	12.0 ± 4.9

Data are means ± SD. A total of 54 subjects did not have waist circumference measured. A further 50 non-Caucasians were excluded.

dosage at trial baseline related to the subsequent risk of developing micro- and macrovascular complications in this group of patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The datasets

We used the publicly accessible datasets collected by the DCCT, which was stored in SAS format (available at www.gcrc.umn.edu). The DCCT was a 9-year follow-up study of 1,441 participants with type 1 diabetes comparing the effect of intensive versus conventional blood glucose management on the development of the microvascular complications of diabetes. The study participants were randomized into intensive (n = 711) and conventional (n = 730) treatment groups. The study did not include individuals at especially high cardiovascular risk, as both hypertension and severe dyslipidemia were exclusion criteria.

Definition of events

Severity of retinopathy was determined by the 25-point Early Diabetic Retinopathy Treatment Study interim score (21). The development and progression of sustained retinopathy was defined as a change from baseline of three or more units on the Early Diabetic Retinopathy Treatment Study score on any two successive annual evaluations. During the 9 years of follow-up, 242 people developed sustained retinopathy, 67 of whom were in the intensive treatment group. Nephropathy was defined as an increase in albumin excretion rate ≥40 mg/24 h (28 μg/min) on any annual evaluation providing that the baseline albumin excretion rate was <40 mg/dl (28 μg/min) (22).

Cardiovascular events during the trial were those as defined as by the DCCT group and included angina, fatal and nonfatal myocardial infarction, coronary revascularization, and major electrocardiogram events (23). Analysis was performed on a time-to-first-event basis. In addition to these 31 initial events, there were another 73 macrovascular events including those affecting cerebrovascular and peripheral arteries.

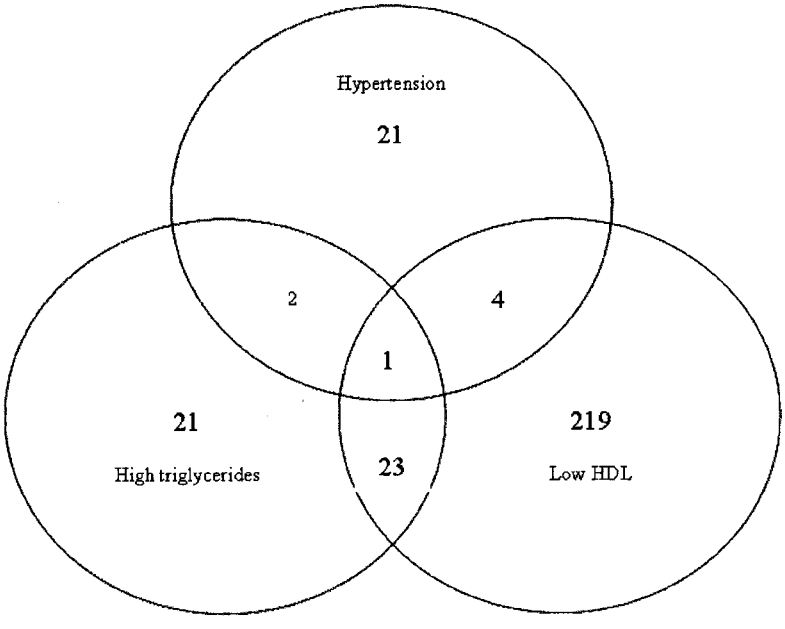

Figure 1—*Criteria in addition to raised waist circumference defining study patients at baseline as having the metabolic syndrome.*

Metabolic syndrome

Metabolic syndrome was defined according to the recent IDF consensus criteria (10). These criteria make central obesity essential for the diagnosis. Central obesity was defined as a waist circumference ≥94 cm (in male subjects), ≥80 cm (in female subjects), and/or a BMI ≥30 kg/m^2. Since we used the Europid definition for waist circumference, races other than Caucasians were excluded (n = 50). In addition to central obesity, the metabolic syndrome required the presence of any two additional criteria, namely raised triglycerides (>1.7 mmol/l), reduced HDL cholesterol (<1.03 mmol/l in male subjects and <1.29 mmol/l in female subjects), raised blood pressure (systolic ≥130 mmHg, diastolic ≥85 mmHg), or raised fasting plasma glucose (>5.6 mmol/l). All DCCT patients were assumed to fulfill the latter criterion. Although many of these risk factors are known to track with age (and many of the individuals in the DCCT were adolescents), none of the currently recommended definitions of metabolic syndrome (10) vary their thresholds according to subject age.

Waist circumference was only recorded at baseline, whereas BMI data were collected annually. To determine the prevalence of metabolic syndrome throughout the DCCT study period, we used a BMI threshold of ≥25 kg/m^2 instead (10). Indeed, the waist circumference cutoffs described above were originally chosen because they were felt,

Table 2—*IDF-defined metabolic syndrome by randomization group*

Assessment	Intervention group	Total	Metabolic syndrome (*n*)	Relative risk (95% CI)
Baseline	Conventional	722	112	1.0
	Intensive	705	97	0.9 (0.7–1.1)
1 year	Conventional	715	122	1.0
	Intensive	694	141	1.2 (1.0–1.5)
2 years	Conventional	715	124	1.0
	Intensive	673	166	1.4 (1.2–1.8)
3 years	Conventional	708	128	1.0
	Intensive	654	176	1.5 (1.2–1.8)
4 years	Conventional	701	146	1.0
	Intensive	643	184	1.4 (1.1–1.7)
5 years	Conventional	616	124	1.0
	Intensive	549	196	1.8 (1.5–2.2)
6 years	Conventional	422	80	1.0
	Intensive	397	135	1.8 (1.4–2.3)
7 years	Conventional	265	70	1.0
	Intensive	246	98	1.5 (1.2–1.9)
8 years	Conventional	159	41	1.0
	Intensive	147	55	1.5 (1.0–2.0)
9 years	Conventional	125	34	1.0
	Intensive	119	54	1.7 (1.2–2.4)

Metabolic syndrome by IDF criteria, but using BMI ≥25 kg/m^2 to replace waist circumference, which was not measured annually.

based on Europid data, to be the best values for identifying a BMI ≥25 kg/m^2 (10,24). The other IDF criteria remained unchanged.

While concentrating analysis on the IDF definition of metabolic syndrome, we also established which patients met the previous National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria (8). Obesity is not an absolute requirement using the NCEP definition, but at least three risk factors are required from a possible five. Four of these five factors comprise raised triglycerides, reduced HDL cholesterol, raised blood pressure, and raised fasting plasma glucose using the same criteria as the IDF definition, but the fifth—waist circumference—uses thresholds that are greater (102 cm for male subjects and 88 cm for female subjects).

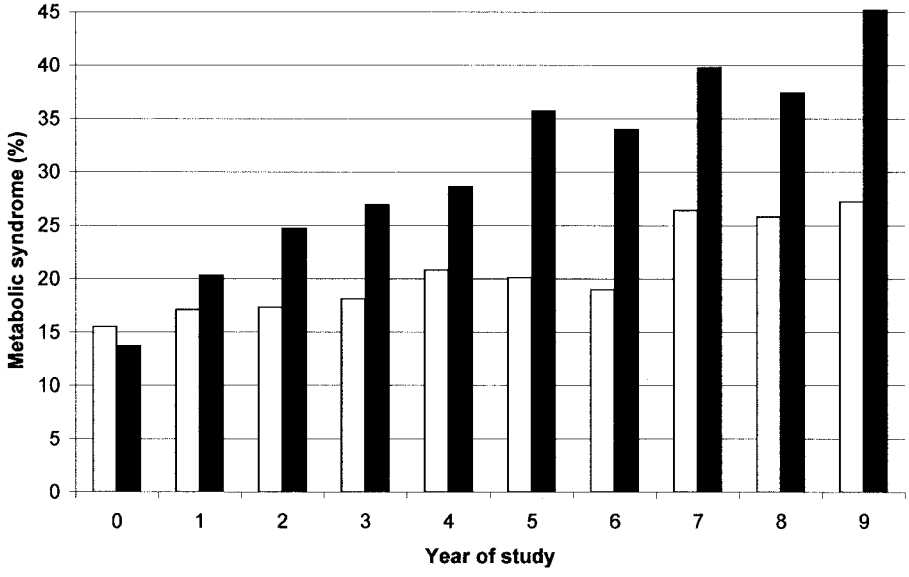

Figure 2—*Prevalence of IDF-defined metabolic syndrome by randomization group throughout the study period. ■, intensively treated group; □, conventionally treated group.*

Insulin resistance and insulin dose

Insulin resistance was calculated using the eGDR according to the following equation: $24.31 - (12.22 \times \text{WH}) - (3.29 \times \text{HT}) - (0.57 \times \text{A1C})$, where the units are mg · kg^{-1} · min^{-1}, the WH = waist-to-hip ratio, and HT = hypertension (16). This formula has been adapted for the use of A1C rather than HbA_1 (20). Insulin dose was measured in units per kilogram body weight at baseline.

Statistical methods

The relationship between the baseline covariates and the time-to-event data (e.g., retinopathy development) was carried out by Cox proportional hazards modeling. Statistical modeling of time-to-event data are known in general terms as "survival analysis." A distinguishing feature of survival data is that the end of the follow-up period will not have occurred in all patients. In such patients, the survival time is said to be "censored." This censoring makes survival models difficult to analyze statistically (25) but was made possible by the theoretical development of the Cox proportional hazards model (26).

In the DCCT data the Cox model allows for the prediction of retinopathy from a given set of baseline covariates, such as eGDR and metabolic syndrome. The covariates may be continuous, binary, or categorical. The relationship between the covariates and retinopathy is expressed by the hazard ratio (HR) (essentially the risk of, say, retinopathy for a given covariate). A key statistical assumption is that the HR is constant over time (known as proportionality of hazards). This "proportionality" assumption can be tested by residual plotting (27). The precision of the HR is determined from the 95% CI; the narrower the CI the more precise the HR and vice versa. The *P* value, which represents the probability of a false-positive result, was calculated by the likelihood ratio test statistic, the calculation of which determines whether an association between a baseline covariate and retinopathy is random or not (albeit at an arbitrary level of 5%). The GLIM4 and SPSS statistical computer packages were used to analyze the data (28).

Table 3—*Cox regression models relating metabolic syndrome and measures of insulin resistance to microvascular risk*

Variable	Retinopathy	*P* value	Nephropathy	*P* value
Metabolic syndrome	0.85 (061–1.18)	0.33	0.98 (0.71–1.35)	0.91
eGDR	0.75 (0.69–0.81)	<0.001	0.88 (0.80–0.96)	0.005
Insulin dose	0.77 (0.41–1.45)	0.42	1.61 (0.93–2.82)	0.09

Data are HR (95% CI). Units for eGDR are $mg \cdot kg^{-1} \cdot min^{-1}$ and for insulin dose are units per kilogram body weight. Models adjusted for the following baseline covariates: age, sex, disease duration, randomization treatment (conventional/intensive), and prevention cohort (primary/secondary).

RESULTS

Metabolic syndrome

Using the IDF criteria, 291 patients (22% of those with complete data and after excluding non-Caucasians) had metabolic syndrome at baseline; 1,046 did not have metabolic syndrome; 61 did not have their waist circumference recorded, 7 of whom had a BMI≥30 kg/m^2. Thirty-two percent (n = 93) of patients with metabolic syndrome were male compared with 59% (n = 620) without metabolic syndrome. Other demographic features are presented in Table 1. Those without waist circumference recorded were younger (mean age 24.9 years) and had lower BMI on average (22.6 kg/m^2) than the rest, and 24 (44%) were male.

The Venn diagram (Fig. 1) shows which factors (raised blood pressure, high triglycerides, and low HDL cholesterol) classified patients as having the metabolic syndrome. Most patients had low HDL cholesterol (n = 247); a further 47 had high triglycerides, while 28 had raised blood pressure. Only one patient had all three of these criteria together.

The changing prevalence of the metabolic syndrome, using BMI rather than waist circumference criteria, are presented in Table 2 and Fig. 2. The prevalence of metabolic syndrome increases in both conventionally and intensively treated groups but at a statistically higher rate in the latter group from year 1 onwards. The baseline prevalence of BMI ≥25 kg/m^2 was 25.6% in the intensively treated group and 27.9% in the conventionally treated patients. This rose to 61.0 and 45.0%, respectively, by year 9 of the study. Mainly as a consequence of the higher waist circumference thresholds, fewer patients (n = 114) had metabolic syndrome at baseline when defined by NCEP criteria.

Insulin resistance and insulin dose

All subjects with a waist measurement also had a waist-to-hip ratio (20). The mean (median) eGDR was 8.11 $mg \cdot kg^{-1} \cdot min^{-1}$ (8.21) (SD 1.49). One quarter (n = 344) had an eGDR >9.03. The mean (median) dose of insulin at baseline was 0.67 units/kg (0.63) (range 0.08–2.06).

Cox regression

Multivariable Cox regression models for both microvascular and macrovascular risks are presented in Tables 3 and 4, respectively. After adjusting for insulin dose and the presence of metabolic syndrome, there was still a significant inverse association between lower eGDR at baseline and a subsequent increased risk of retinopathy and nephropathy progression (Table 2), cardiovascular events, and macrovascular disease (Table 3). By comparison, there were no significant relationships between baseline metabolic syndrome or insulin dose on microvascular or macrovascular disease risk. In addition, models that did not adjust eGDR, metabolic syndrome, and insulin dose for one another yielded similar results, as did further adjustment for smoking. Substituting the NCEP in place of the IDF definition of metabolic syndrome did not alter the findings either. The waist-to-hip ratio was measured at the iliac crest. Replacing this by the "natural" waist-to-hip ratio made little difference to the HRs. The eGDR did not seem to be superior to baseline A1C (itself a component of eGDR) for predicting any of the complications studied.

Subgroup analyses

We carried out Cox modeling stratifying by randomization group (excepting cardiovascular diseases for which there were too few events). The relationship between eGDR and complication outcome was stronger in the conventionally treated group. The HR for any macrovascular disease in the conventionally treated group was 0.81 (0.70–1.00; P = 0.05) per unit change, with the HR in the intensive group 0.85 (0.70–1.04; P = 0.11). The HR for retinopathy in the conventionally treated group was 0.69 (0.62–0.76; P < 0.001), while in the intensive group was 0.83 (0.72–0.96; P = 0.013). The HR for nephropathy in the conventionally treated group was 0.84 (0.74–0.95; P = 0.005), while in the intensive group was 0.92 (0.80–1.06; P = 0.24). There were fewer micro- and macrovascular events in both groups separately (especially in the intensively treated patients), so any differences in statistical significance could be a function of reduced power.

CONCLUSIONS

— This study has shown that DCCT patients with the highest insulin resistance at their baseline visit (as assessed by a low eGDR) were at the highest subsequent risk of developing the microvascular and macrovascular complications of type 1 diabetes, independently of their assigned treatment group. In comparison, the presence of the metabolic syndrome at the start of the study, defined using IDF criteria, showed little predictive value. Furthermore, a clinical estimate of insulin resistance—the insulin dose required by a patient in units per kilogram body weight—was also a poor predictor of future complications.

Our findings in relation to the value of the eGDR in predicting those patients at highest risk of small- and large-vessel disease are consistent with those from the Pittsburgh Epidemiology of Diabetes Complications Study. This prospective cohort study found low eGDR to be associated with the risk of nephropathy (17), peripheral vascular disease (18), and coronary artery disease (19). An analysis of the cross-sectional FinnDiane study also showed that type 1 diabetic patients with

Table 4—*Cox regression models relating metabolic syndrome and measures of insulin resistance to macrovascular risk*

Variable	Cardiovascular	*P* value	Any macrovascular	*P* value
Metabolic syndrome	1.15 (0.41–3.20)	0.79	1.15 (0.69–1.92)	0.60
eGDR	0.70 (0.56–0.88)	0.002	0.83 (0.73–0.96)	0.009
Insulin dose	3.35 (0.58–19.5)	0.18	1.45 (0.55–3.87)	0.45

Data are HR (95% CI). Notes: Models adjusted as in Table 3.

microalbuminuria had lower eGDR than those without but, in contrast to our findings, found the metabolic syndrome (defined using NCEP criteria [8]) to be more common in microalbuminuric patients as well (20).

The same study showed that the metabolic syndrome is a frequent finding in type 1 diabetes. We have confirmed this to be the case in the DCCT but have also found that as the study progressed the prevalence of the metabolic syndrome, using BMI rather than waist circumference criteria, increased markedly in both treatment groups. This was especially so in those treated intensively, which meant that by year 9 of the study three times as many intensively treated patients remaining had the metabolic syndrome than at baseline, resulting in nearly half the patients meeting the IDF criteria.

The bulk of this rise was due to the weight gain experienced during the study. Since it is known that patients with type 1 diabetes are at particularly high risk of cardiovascular disease already (29–31), there has been concern that this increase in body weight may only add to this likelihood, with intensively treated patients being placed at especial risk. Indeed, in the DCCT itself the excess weight gain with intensive therapy was associated with increases in visceral adiposity (32), which had consequent deleterious effects on lipids, blood pressure (33), and inflammatory markers (34). However, despite these concerns, the long-term follow-up study of the DCCT cohort (the Epidemiology of Diabetes Interventions and Complications) has found that intensive treatment during just the period of the DCCT greatly reduced, rather than increased, the long-term risk of cardiovascular disease by 42% (35). Differences in A1C during the DCCT (rather than simply changes in known cardiovascular risk factors) seemed to account for much of the benefit. Thus, together with the findings from other studies (36,37), it indicates that there is likely to be a net benefit to improving glycemic control in type 1 diabetes, even if there is resultant weight gain associated with it.

As a consequence, this study has identified a second reason why labeling a patient with type 1 diabetes as having the metabolic syndrome may be of limited use: not only was the presence of metabolic syndrome at baseline in the DCCT unrelated to micro- and macrovascular complications during the original study period but the group of patients most likely to develop the metabolic syndrome during the course of the study were those least likely to have subsequent long-term microvascular and cardiovascular sequelae (35,38).

In its defense, the metabolic syndrome definition was never primarily intended for patients with type 1 diabetes, although there continues to be debate surrounding its value in other clinical situations for which it is proposed (39,40). Consideration also has to be given to the fact that the IDF definition of the metabolic syndrome may not be as specific as other criteria in identifying patients at high cardiovascular risk because of the lower waist circumference thresholds used (41). In respect of this current analysis, the NCEP definition of the metabolic syndrome at study baseline did not predict complication risk either, although this may be partly related to the fact that far fewer patients were identified when using these criteria.

In summary, this study has shown that the IDF definition of the metabolic syndrome appears to have little clinical utility in distinguishing type 1 diabetic patients most likely to develop micro- and macrovascular disease. Indeed, some patients who acquire this label might have done so through the pursuit of glycemic goals that may ultimately reduce their risk of complications. Assessing insulin resistance through the dosage of insulin taken by an individual was equally poor at predicting outcome. By contrast, assessing insulin resistance by calculating the eGDR identified type 1 diabetic patients who were at highest risk of subsequent small and large vessel disease.

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