Body Weight, Metabolic Dysfunction, and Risk of Type 2 Diabetes in Patients at High Risk for Cardiovascular Events or With Manifest Cardiovascular Disease: A Cohort Study

OBJECTIVE
To quantify the role of BMI and metabolic dysfunction in the risk of development of type 2 diabetes in patients at high risk or with manifest vascular disease.

RESEARCH DESIGN AND METHODS
A total of 6,997 patients participating in the prospective Secondary Manifestations of ARTerial disease (SMART) cohort study were classified according to BMI and metabolic dysfunction, defined as three or more of the modified NCEP metabolic syndrome criteria (waist circumference replaced by hs-CRP ≥2 mg/L). Risk of type 2 diabetes (assessed with biannually questionnaires) was estimated with Cox proportional hazard analysis.

RESULTS
During a median follow-up of 6.0 years (interquartile range 3.1–9.1 years), 519 patients developed type 2 diabetes (incidence rate 12/1,000 person-years). In the absence of metabolic dysfunction (≤2 NCEP criteria) adiposity increased the risk of type 2 diabetes compared with normal weight patients (HR 2.5 [95% CI 1.5–4.2] for overweight and HR 4.3 [95% CI 2.2–8.6] for obese patients). In the presence of metabolic dysfunction (≥3 NCEP criteria) an increased risk of type 2 diabetes was observed in patients with normal weight (HR 4.7 [95% CI 2.8–7.8]), overweight (HR 8.5 [95% CI 5.5–13.4]), and obesity (HR 16.3 [95% CI 10.4–25.6]) compared with normal weight patients without metabolic dysfunction.

CONCLUSIONS
Adiposity, even in the absence of metabolic dysfunction, is a risk factor for type 2 diabetes. Moreover, presence of metabolic dysfunction increases the risk of type 2 diabetes in all BMI categories. This supports assessment of adiposity and metabolic dysfunction in patients with vascular disease or at high risk for cardiovascular events.
Prevalence of obesity and other cardiovascular risk factors increased substantially over the past decades (1). Obesity is one of the most important risk factors that is independently associated with the development of insulin resistance and type 2 diabetes (2). The mechanism by which obesity induces insulin resistance includes adipose tissue inflammation, which disturbs intracellular insulin signaling downstream from the insulin receptor (3). Development of adipose tissue inflammation and metabolic dysfunction depends on several adipose factors such as adipocyte expandability, adipose tissue distribution, adipocytokine secretion pattern, presence of brown adipose tissue, and nonadipose tissue factors such as physical activity, birth weight, and (epi)genetics (3–6).

Systemic inflammation is in part the result of adipose tissue dysfunction and is considered to be the “common soil” underlying cardiovascular risk and development of diabetes (7,8). Adipokines, including interleukin-6 and tumor necrosis factor-α, are produced by dysfunctional adipose tissue and released into the portal circulation, which stimulates hepatic C-reactive protein (CRP) production (9). Various criteria for metabolic dysfunction exist, but in six different definitions of cardiometabolic abnormalities, obese individuals without metabolic dysfunction have lower plasma CRP levels than individuals with metabolic dysfunction independent of abdominal obesity or body fat percentage (10). Systemic low-grade inflammation, as measured by elevated plasma levels of CRP and interleukin-6, is related to the development of type 2 diabetes regardless of adiposity (11).

Prospective cohort studies demonstrate a strong relation between presence of the metabolic syndrome and development of cardiovascular disease and type 2 diabetes (12,13). However, ~20–30% of obese patients do not meet the criteria for metabolic syndrome (14). These obese patients have less systemic inflammation, are more insulin sensitive, have less dyslipidemia and hypertension, and have a normal plasma adipocytokine pattern (15–18). Moreover, severe metabolic abnormalities are equally prevalent among normal or slightly overweight individuals (18). Patients with clinically manifest vascular disease are at high risk for cardiovascular events as well as for development of type 2 diabetes (19,20). Overweight or obese patients without metabolic dysfunction have a low risk for first and recurrent cardiovascular events and mortality compared with their metabolically unhealthy counterparts and equivalent risk compared with normal-weight individuals without metabolic dysfunction (5,21–23). Other, more recent, studies have demonstrated that the follow-up period may have been too short to notice increased risk (24–26). Development of type 2 diabetes, which is strongly related to obesity, may contribute to cardiovascular risk in this high-risk population, as it confers a 2- to 12-fold excess risk for first or recurrent cardiovascular events and mortality (27,28). Therefore, we evaluated the risk of BMI in the presence or absence of metabolic dysfunction on the development of type 2 diabetes in patients with clinically manifest vascular disease or at high risk for cardiovascular events.

RESEARCH DESIGN AND METHODS

Study Population

The Secondary Manifestations of ARTerial disease (SMART) study is an ongoing prospective single center cohort study at the University Medical Center Utrecht designed to establish the prevalence of comitant arterial diseases and risk factors in a high-risk population predominantly of Caucasian ethnicity (≥95%). Patients were newly referred because of manifest atherosclerotic disease or a cardiovascular risk factor (such as diabetes, hypertension, or hypercholesterolemia) and were screened noninvasively for manifestations of atherosclerotic diseases and risk factors other than the qualifying diagnosis. Exclusion criteria were age <18 years, malignancy, dependency in daily activities, and lack of sufficient fluency in the Dutch language. The study protocol complies with the Declaration of Helsinki. The ethics committee of the University Medical Center Utrecht approved the study, and all participants gave their written informed consent. A detailed description of the study has previously been published (29). For the current study, we used SMART data of patients enrolled between 1996 and 2012. Assessment of incident diabetes started in 2006 (see outcome assessment). Therefore, patients who had died (n = 470) or were lost to follow-up (n = 109) before the assessment started were not included. Patients with diabetes (type 1 or 2) at study inclusion, defined as a referral diagnosis of diabetes, self-reported diabetes, use of glucose-lowering agents, or a known history of diabetes, were excluded (n = 1,701). If glucose was ≥7 mmol/L at study entry without a known history of diabetes, patients were only included if they were not on glucose-lowering therapy within 1 year of follow-up. Finally, patients with hs-CRP >20 mg/L (n = 242) were excluded, since these patients were considered to be in an acute inflammatory state. The remaining 6,997 patients were eligible for analysis. Since 2008, patients of the SMART cohort with clinically manifest vascular disease and a follow-up of at least 4 years were invited for reassessment of all baseline measurements (SMART-2 cohort). Every 3 months, 75 patients were consecutively invited by mail resulting in a recruitment efficacy of 58.9%. Baseline characteristics of SMART-2 participants were comparable with those of the nonresponders. Similar exclusion criteria were applied, yielding 1,282 patients eligible for analyses.

Definition of Adiposity Subgroups and Metabolic Dysfunction

Normal weight was defined as a BMI <25 kg/m², overweight as a BMI ≥25 and <30 kg/m², and obesity as a BMI ≥30 kg/m². Within these subgroups, metabolic dysfunction was assessed. To define metabolic dysfunction, we adapted the National Cholesterol Education Program (NCEP) revised criteria for metabolic syndrome by replacing the criterion of an elevated waist circumference, which is highly correlated with BMI, for elevated hs-CRP (≥2 mg/L), as this better reflects the functional and systemic consequences of adipose tissue dysfunction. Metabolic dysfunction was defined as the presence of three or more of the following five risk factors: elevated blood pressure (≥130 mmHg systolic and/or ≥85 mmHg diastolic and/or use of blood pressure–lowering agents), hypertriglyceridemia (≥1.70 mmol/L or treatment for elevated triglycerides), low HDL cholesterol (<1.03 mmol/L for men and <1.30 in women), a high fasting glucose (≥5.6 mmol/L), or an elevated hs-CRP (≥2 mg/L) (21,30).

Outcome Assessment of Type 2 Diabetes

The outcome of interest for this study was the development of type 2 diabetes. Dutch national guidelines require physicians to diagnose type 2 diabetes if
patients have two fasting plasma glucose measurements of $\geq 7.0$ mmol/L (corresponding to $\geq 126$ mg/dL) or if patients have a combination of complaints of hyperglycemia with one fasting plasma glucose measurement $\geq 7.0$ mmol/L or one nonfasting measurement $\geq 11.1$ mmol/L. For assessment of the incidence of diabetes, all patients included between start of the study in September 1996 and June 2006 without diabetes at baseline received a questionnaire in the period between June and December 2006 to assess the incidence of type 2 diabetes after study inclusion (response rate 98%). After 2006, all patients were biannually asked to complete this questionnaire. Patients were asked whether they had diabetes, and if “yes,” they received an extensive supplementary questionnaire for confirmation and detailed information of the diagnosis. Questions asked were, for example, about the date of diagnosis, initial and current treatment (diet, oral medication, or insulin), family history of diabetes, pregnancy (diabetes gravidarum), and use of steroid hormones. Patients and/or their general practitioners were contacted by telephone for further information if the answers were incomplete or unclear, and nonresponders were also contacted. All diabetes cases were audited and classified by two independent experienced physicians. Cross-validation with the hospital diagnosis registry revealed that none of the patients who reported not to have diabetes had a physician’s diagnosis of diabetes. Duration of follow-up was defined as the period between study inclusion and development of type 2 diabetes, date of loss to follow-up, or the preselected date of 1 March 2012. Of the 6,997 participants 232 (3.3%) were lost to follow-up owing to migration or discontinuation of the study.

Data Acquisition

All baseline measurements were performed on a single day at the University Medical Center Utrecht. Participants completed a questionnaire on cardiovascular history, risk factors, current medication use, and physical activity. BMI, assessed as weight in kilograms divided by the square of the height in meters, was computed after a standardized anthropometric measurement protocol. Waist and hip circumferences were measured in duplicate, with patients standing relaxed and in light clothing. Waist circumference was measured as the circumference in centimeters halfway between the lower rib and the iliac crest, and hip circumference was measured at the horizontal level around the buttocks posteriorly that yielded the maximum measurement. If duplicate measurements differed by $>2$ cm, a third was taken. Blood pressure was measured twice in a sitting position with a sphygmomanometer, and the average of two measurements was calculated. Visceral and subcutaneous adipose tissue was estimated by ultrasonography (31). Fasting venous blood samples were taken to determine serum lipids, glucose, and hs-CRP. The techniques used for the laboratory tests have previously been described (29). An integrated measure of physical activity was calculated based on type and duration of physical activity derived from the baseline questionnaire. The time spent on a specific activity per week was multiplied by its MET intensity level and subsequently added together if more than one type of activity was reported (32).

Data Analyses

Central estimators and variance measures were calculated for baseline characteristics for each of the subgroups based on the presence or absence of metabolic dysfunction and BMI. Subsequently, diabetes incidence rates per 1,000 person-years were calculated for every subgroup. Cox proportional hazards analysis was used to estimate hazard ratios (HRs) and 95% CIs for the occurrence of type 2 diabetes associated with adiposity and/or metabolic dysfunction with normal-weight individuals without metabolic dysfunction as reference group. Age, sex, smoking status (current, former, or never smoker), physical activity (in MET h/week), and statin usage (yes/no) were considered confounders. Because use of statins was only registered after July 2001, prior to this date no distinction was made regarding lipid-lowering therapy (lipid lowering medication [yes/no]). To evaluate the influence of weight change and event-induced weight loss during follow-up, analyses were performed with additional adjustment for changes in BMI categories and by excluding participants who developed a cardiovascular event or fatal malignancy. For each individual metabolic dysfunction component, age- and sex-adjusted HRs (presence vs. absence) on the risk of type 2 diabetes were calculated. For all Cox analyses, the proportional hazards assumption was verified by log minus log plots where no disproportionality was observed. Finally, the population-attributable fraction was calculated per risk factor (33). This measure is the proportion of disease in the population that is attributable to a specific risk factor and depends on both the prevalence and strength of its association with the disease. Multiple imputation was used to reduce missing covariate data for fasting glucose ($n = 47; 0.7\%$), serum triglycerides ($n = 40; 0.6\%$), HDL cholesterol ($n = 48; 0.7\%$), systolic blood pressure ($n = 45; 0.7\%$), diastolic blood pressure ($n = 49; 0.7\%$), hs-CRP ($n = 758; 10.8\%$), smoking status ($n = 48; 0.7\%$), and physical activity ($n = 88; 1.3\%$), since incomplete case analysis leads to loss of statistical power and possibly bias. Statistical analyses were performed with IBM SPSS, version 20.0, and open source statistical package R, version 3.1.2.

RESULTS

Baseline Characteristics

The mean age of all patients was $56 \pm 12$ years and was comparable across normal-weight, overweight, and obese patients with and without metabolic dysfunction (Table 1). The majority had experienced manifest cardiovascular disease within 2 years before inclusion: 2,912 had coronary artery disease, 1,407 cerebrovascular disease, 831 peripheral artery disease, and 353 an abdominal aortic aneurysm. Within overweight and obese patients, 44% ($n = 1,426$) and 26% ($n = 293$), respectively, did not satisfy the criteria for metabolic dysfunction, whereas metabolic dysfunction was present in 33% ($n = 870$) of the normal-weight patients. Patients without metabolic dysfunction had lower levels of insulin resistance (HOMA of insulin resistance) and were more physically active than patients with metabolic dysfunction. In contrast, patients with metabolic dysfunction had more visceral adipose tissue and higher waist circumference and smoked more frequently. The study population that underwent reassessment of measurements (SMART-2 cohort, $n = 1,282$)
showed comparable baseline characteristics (Supplementary Table 1).

**Effect of Adiposity and Metabolic Dysfunction on Risk of Incident Type 2 Diabetes**

Of the 6,997 patients in this study, a total of 519 patients developed type 2 diabetes during a median follow-up of 6.0 years (interquartile range 3.1–9.1; 44,216 person-years) with an average incidence rate of 12 diabetes cases per 1,000 person-years. In patients without metabolic dysfunction (≥2 NCEP criteria), overweight (HR 2.5 [95% CI 1.5–4.2]) and obese (HR 4.3 [95% CI 2.2–8.6]) patients had an increased risk for developing type 2 diabetes compared with normal-weight patients (Table 2). In the presence of metabolic dysfunction (≥3 NCEP criteria), the risk of developing type 2 diabetes was even higher. Compared with patients with normal weight and absence of metabolic dysfunction, patients with normal weight with presence of metabolic dysfunction had a higher risk for developing type 2 diabetes (HR 4.7 [95% CI 2.8–7.8]) with even higher risk in patients who were overweight (HR 8.5 [95% CI 5.5–13.4]) or obese (HR 16.3 [95% CI 10.4–25.6]). Additional adjustment for changes in BMI categories (increase, stable, decrease) during follow-up (SMART-2, n = 1,282) yielded comparable HRs for overweight and obesity. A sensitivity analysis on complete data (n = 6,658) and exclusion of patients that developed a cardiovascular event or fatal malignancy during follow-up (n = 686) yielded comparable results.

**Change in Prevalence of Adiposity and Metabolic Dysfunction During Follow-up**

In the 1,282 patients for whom BMI and metabolic dysfunction criteria were reassessed (SMART-2 cohort) after a median follow-up of 6.1 years (interquartile range 4.0–10.7), prevalence of the overweight and obese phenotype without metabolic dysfunction increased from 22 to 27% and from 4 to 7%. Of the individuals who at follow-up remained within the same BMI category, overweight and obese individuals had developed more metabolic dysfunction compared with normal-weight individuals. The development of metabolic dysfunction was 10% in normal-weight patients, 15% in overweight patients, and 23% in obese patients as displayed in Fig. 1.

**Relation Between Metabolic Syndrome Components and Risk of Incident Type 2 Diabetes**

Metabolic dysfunction components in decreasing order of prevalence included presence of high blood pressure (89%), high fasting glucose (52%), elevated hs-CRP (46%), low HDL cholesterol (35%), and elevated triglycerides (34%) (as displayed in Supplementary Fig. 1). Hypertension was highly prevalent in patients with and without metabolic dysfunction. When metabolic dysfunction components
were assessed separately, presence of high blood pressure (HR 2.4 [95% CI 1.5–3.5]), high fasting glucose (HR 8.5 [95% CI 6.4–11.1]), high hs-CRP (HR 1.7 [95% CI 1.4–2.1]), low HDL cholesterol (HR 1.9 [95% CI 1.6–2.3]), and elevated triglycerides (HR 2.9 [95% CI 2.5–3.5]) were related to an increased risk for type 2 diabetes. The population-attributable fraction, combining both prevalence and strength of the risk factor with incident diabetes, was highest for elevated fasting glucose with 77% and elevated blood pressure with 58% (Fig. 2). Despite low prevalence, elevated triglycerides had an attributable fraction of 43% because of its high risk for diabetes. Risk factors with comparable attributable fractions were low HDL cholesterol (24%) and elevated hs-CRP (19%).

**CONCLUSIONS**

Overweight and obese patients without metabolic dysfunction and manifest vascular disease or high risk for cardiovascular events are at increased risk for developing type 2 diabetes compared with normal-weight patients without metabolic dysfunction. Additionally, overweight and obese patients developed more metabolic dysfunction compared with normal-weight patients at follow-up. Moreover, when metabolic dysfunction is present, the risk of developing type 2 diabetes is strongly increased in all BMI categories and is highest in obese patients. Patients with normal weight and metabolic dysfunction are at even higher risk for type 2 diabetes than overweight or obese patients without metabolic dysfunction.

Different criteria for metabolic dysfunction have been used in various studies. Most studies include a combination of obesity, hypertension, dyslipidemia, and abnormal glucose tolerance; however, no standard criteria have been set (10). In the current study, we adapted the most commonly used definition for metabolic syndrome (NCEP criteria) by replacing waist circumference, which is highly correlated with BMI, for hs-CRP ≥2 mg/L. This better reflects the functional and systemic consequences of adipose tissue dysfunction (7). Additionally, we assessed changes in adiposity and metabolic status over time. One other study incorporated hs-CRP into the definition of metabolic syndrome (using hs-CRP ≥3 mg/L and Hba1c ≥6%) and also found obese without metabolic dysfunction to be at risk (HR 8.6 [95% CI 2.4–30.4]) for type 2 diabetes in a British cohort of 3,066 participants born before 1952 (34). However, even with more stringent criteria for metabolic health as applied in the current study, overweight and obese patients are at increased risk for type 2 diabetes. The results of the current study are in accordance with a meta-analysis of seven studies investigating the effect of obesity without metabolic dysfunction in 1,770 adults with a pooled adjusted relative risk for incident type 2 diabetes of 4.03 (95% CI 2.66–6.09) in populations without overt vascular disease. Most studies included were performed in middle-aged adults (34). However, adiposity without metabolic dysfunction is an adverse condition at any age, as young men (mean age 30.9 ± 5.2 years) with overweight (HR 1.89 [95% CI 1.25–2.86]) or obesity (HR 3.88 [95% CI 1.94–7.77]) are also at increased risk for type 2 diabetes (35).

Components of the metabolic syndrome besides fasting glucose with the highest population-attributable fractions for incident diabetes were high blood pressure and elevated triglycerides. These components are considered...
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...that it is insufficient to only assess an individual’s BMI, as their metabolic status largely influences the risk of developing diabetes. These findings support lifestyle modifications on diet and physical activity to prevent obesity and its associated metabolic disruptions and to study the effect of weight loss in obese patients on the risk of type 2 diabetes development. Furthermore, metabolic dysfunction is not solely a consequence of adipose tissue quantity, which supports the need for optimal treatment of modifiable metabolic risk factors and the need for more research on adipose tissue functionality and factors inducing or ameliorating metabolic dysfunction such as adipocyte expandability, adipose tissue distribution, and brown adipose tissue.

Strengths of the current study are the large cohort of patients with a low percentage lost to follow-up, a substantial median follow-up of 6 years, a large number of end points, and reassessment of baseline characteristics over time to evaluate changes in adiposity and metabolic status. Study limitations need to be considered and include that metabolic dysfunction was dichotomized as being present or absent, while metabolic derangement is likely to be a more graded continuum. Therefore, to compare the strength of the metabolic dysfunction components, we additionally analyzed them separately. Finally, whereas the population-attributable fraction is an informative measure to provide insight into the combination of prevalence and strength of risk factors for this specific population of high-risk patients, it may be overestimated when interpreted as the potential preventive fraction. In reality, a single risk factor may be neither necessary nor sufficient, as multiple combinations of risk factors can cause type 2 diabetes. Therefore, the population-attributable fractions can sum up to >100%.

In conclusion, overweight and obese patients without metabolic dysfunction and with manifest vascular disease or at high risk for cardiovascular events are at increased risk for developing type 2 diabetes compared with normal-weight patients without metabolic dysfunction. This risk becomes increasingly higher with the presence of metabolic dysfunction and increases with BMI. These findings support adequate assessment and treatment of both adiposity and metabolic dysfunction.

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