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Metabolic consequences of adipose tissue dysfunction and not adiposity per se increase the risk of cardiovascular events and mortality in patients with type 2 diabetes

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ABSTRACT

Objectives: To quantify the risk of obesity and its associated metabolic dysfunction on the development of cardiovascular events and mortality in patients with type 2 diabetes.
Methods: In 1827 patients with type 2 diabetes enrolled in the Secondary Manifestations of ARTerial disease (SMART) cohort study, the risk of higher BMI, waist circumference and intra-abdominal fat on the development of cardiovascular events (composite of myocardial infarction, stroke, and vascular mortality) was quantified using Cox regression. Second, risk of cardiovascular events related to obesity associated metabolic dysfunction (≥3 adapted NCEP metabolic syndrome criteria) was quantified for tertiles of intra-abdominal fat.
Results: 217 patients died from cardiovascular causes and 338 patients developed the composite endpoint of cardiovascular events during a median follow-up of 7.0 years (interquartile range 3.9 to 10.5 years). No increased risk for cardiovascular events and mortality was observed per SD higher BMI, waist circumference and intra-abdominal fat (HR varying from 1.00, 95% CI 0.88–1.14 to 1.13, 95% CI 0.96–1.33). Compared to the first tertile of intra-abdominal fat without metabolic dysfunction, the presence of metabolic dysfunction increased the risk of cardiovascular events in all tertiles of intra-abdominal fat with the highest risk observed for metabolic dysfunction in the first tertile of intra-abdominal fat (HR 2.47, 95% CI 1.32–4.62).
Conclusions: Body-mass index, waist circumference and intra-abdominal fat are not related to the risk of cardiovascular events and mortality in patients with type 2 diabetes. Instead, in these patients the metabolic consequences of adipose tissue dysfunction are more important than strict measures of adiposity when estimating cardiovascular risk.

1. Introduction

Worldwide prevalence of type 2 diabetes is estimated to increase from 2.8% in 2000 to 4.4% in 2030, at least in part due to the increasing prevalence of obesity, physical inactivity and increased life expectancy [1]. The presence of type 2 diabetes confers a 2- to 12-fold excess risk for first or recurrent cardiovascular events and mortality [2,3]. Type 2 diabetes often coincides with atherosclerotic vascular disease, although both diseases can manifest independently. This indicates that type 2 diabetes and atherosclerotic vascular disease share a 'common soil' of metabolic, genetic and environmental risk factors [4,5].

Obesity, and in particular abdominal obesity, is related to metabolic changes including dyslipidemia, elevated blood pressure, hyperglycemia, low-grade inflammation and hypercoagulability and is a well-known and independent risk factor for both type 2 diabetes and atherosclerotic vascular disease [6–8]. During chronic positive energy balance adipose tissue is challenged to store large amounts of triglycerides and glucose-derived free fatty acids. However, once adipocytes are no longer able to expand and to safely store nutrients, adipose tissue becomes dysfunctional, instigates spillover of free fatty acids and releases pro-inflammatory cytokines such as IL-6 and TNF-alpha. These adipokines activate hepatic CRP production and contribute to a chronic low-grade inflammatory state that stimulates development of atherosclerosis and insulin resistance [9]. Development of insulin resistance not only

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increases the risk for type 2 diabetes but also contributes to the metabolic changes such as hypertension and dyslipidemia and adds thereby to the development of atherosclerosis [10].

Given the central role of obesity and insulin resistance in the pathogenesis of both type 2 diabetes and atherosclerosis, it is likely to assume an increased cardiovascular risk in obese patients with established type 2 diabetes. However, in patients with coronary heart disease, heart failure or hypertension, no increased vascular or mortality risk of overweight or obesity has been observed compared to normal-weight patients. In contrary, in these high risk patients a lower risk was seen, a phenomena often referred to as the 'obesity paradox' [11]. Several explanations for the obesity paradox have been considered. Obesity may function as a metabolic reserve that protects patients from complications during periods of illness. On the other hand the obesity paradox has been challenged as an untrue phenomena and to be the result of reverse causality and a consequence of muscle wasting or sarcopenic obesity due to aging or (occult) comorbidity [12,13].

In the present study we quantified the risk of body-mass index (BMI), waist circumference and intra-abdominal fat on the development of cardiovascular events and cardiovascular mortality in patients with type 2 diabetes. Second, taking into consideration the chronic low-grade inflammatory state and metabolic changes that emerge once adipose tissue becomes dysfunctional, we quantified how metabolic status influences the cardiovascular risk of obesity in patients with type 2 diabetes.

2. Methods

2.1. Study population

For this study we used data from 1827 participants with type 2 diabetes enrolled in the Secondary Manifestations of ARTerial disease (SMART) cohort study before March 2014. Diabetes was defined as a referral diagnosis of type 2 diabetes, self-reported type 2 diabetes, a fasting serum glucose concentration of ≥7.0 mmol/L at study inclusion combined with initiation of glucose-lowering treatment within 1 year, or the use of oral anti-hyperglycemic agents or insulin at baseline. Underweight participants with a BMI <18.5 kg/m^2 (n = 2) were excluded. Patients with high-sensitivity C-Reactive Protein (hsCRP) above 20 mg/L (n = 76) were excluded only for analysis concerning metabolic dysfunction since these patients were considered to be in an acute inflammatory state. The SMART study was started in 1996 and is an ongoing prospective, single-center, cohort study at the University Medical Center Utrecht (the Netherlands) designed to establish the prevalence of cardiovascular risk factors and concomitant arterial diseases 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 mellitus, hypertension or hypercholesterolemia. Therefore, in the current study population of patients with type 2 diabetes, patients without manifest cardiovascular disease concerned patients with either only type 2 diabetes or a combination of type 2 diabetes and hypertension or dyslipidemia. All patients were screened non-invasively for manifestations of atherosclerotic diseases and risk factors other than the qualifying diagnosis. For the SMART study, exclusion criteria were age <18 years, known malignancy, dependency in daily activities or insufficient fluency in the Dutch language. The study protocol conforms to the ethical guidelines of the 1975 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 been published previously [14].

2.2. Assessment of body-mass index, waist circumference, intra-abdominal fat and covariates

All measurements were performed at the UMC Utrecht on a single day and according to a standardized protocol in an accredited vascular laboratory. BMI, the weight in kilograms divided by the square of the height in meters, was computed after a standardized anthropometric measurement protocol. Waist circumference was measured in centimeters halfway between the lower rib and the iliac crest with patients standing relaxed and in light clothing. If duplicate measurements differed by >2 cm, a third was taken. Intra-abdominal fat was estimated by ultrasonography using a strict protocol and was measured as the distance between the peritoneum and the lumbar spine or psoas muscles using electronic calipers at the end of a quiet inspiration [15]. Each distance was measured three times at three different positions. Finally, participants completed a questionnaire on cardiovascular history, risk factors and current medication use. An integrated measure of physical activity was calculated by multiplying the time spent on a specific activity per week by its metabolic equivalent intensity level (MET) and subsequently added together if more than one type of activity was reported [16].

2.3. Assessment of metabolic dysfunction within tertiles of intra-abdominal fat

To quantify the cardiometabolic consequences of adipose tissue dysfunction, we categorized tertiles of intra-abdominal fat for the presence of metabolic dysfunction which we defined according to an adapted version of the National Cholesterol Education Program (NCEP) revised criteria for metabolic syndrome [6]. The criterion of elevated waist circumference, which strongly correlates with adipose tissue quantity, was replaced for elevated hsCRP (≥2 mg/L) as this better reflects the functional and systemic consequences of adipose tissue dysfunction [9,17]. Additionally, the criterion of fasting glucose (≥5.6 mmol/L) was replaced for HbA1c >7.0% (>53 mmol/mol) as this better reflects the actual glycemic state of the past 2–3 months. The presence of metabolic dysfunction was defined as three or more of the following five risk factors: elevated blood pressure (≥130 mm Hg systolic and/or ≥85 mm Hg diastolic and/or use of blood pressure lowering agents), hypertriglyceridemia (≥1.70 mmol/L or treatment for elevated triglycerides), low high-density lipoprotein (HDL)-cholesterol (<1.03 mmol/L for men and <1.30 in women), HbA1c (>7.0% or >53 mmol/mol) or an elevated hsCRP (hsCRP ≥2 mg/L).

2.4. Follow-up and outcome assessment

Patients were biannually asked to complete a follow-up questionnaire. Events of interest for the current study were the occurrence of cardiovascular death defined as death from stroke, myocardial infarction, congestive heart failure, rupture of abdominal aortic aneurysm and vascular death of other causes (i.e. death from sepsis following a diabetic ulcer), and the occurrence of cardiovascular events defined as a composite of nonfatal and fatal myocardial infarction, nonfatal and fatal stroke and cardiovascular mortality. Definitions are included in Supplementary Table 1. When a possible event was reported by the participant, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. With this information, all events were independently audited by three members of the SMART study End Point Committee, comprising physicians from different departments [14].

2.5. Data analyses

Baseline measurements were stratified in classes of normal weight (BMI ≥18.5 and ≤25 kg/m^2), overweight (BMI >25 and ≤30 kg/m^2) and obesity (BMI >30 kg/m^2) and presented as mean with standard deviation (SD) for normally distributed variables and as median with interquartile range (IQR) for non-normally distributed variables. Cox proportional hazards analysis was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the relation between higher BMI, waist circumference, intra-abdominal fat and the occurrence of cardiovascular events and mortality. All three measures of adiposity were analyzed per 1SD increase. Additionally, BMI was evaluated in classes of overweight and obesity with normal-weight functioning as reference group and waist circumference and intra-abdominal fat were evaluated in tertiles with the first tertile functioning as reference group. If a patient had multiple events, the first recorded event was used for analysis. In model I relations were adjusted for age and sex and in model II relations were adjusted for age, sex, time since diabetes diagnosis, smoking status (ever versus never smoking), physical activity and use of cardiovascular risk lowering medication (use of oral glucose lowering agents, insulin, lipid lowering agents, blood pressure lowering agents and anti-platelet agents). Second, to quantify the risk associated with the cardiometabolic consequences of adipose tissue dysfunction, tertiles of intra-abdominal fat were stratified for the presence of metabolic dysfunction with the first tertile without metabolic dysfunction functioning as reference group. This relation was adjusted for similar covariates except use of cardiovascular lowering medication which is already included in the definition of metabolic dysfunction. The proportional hazards assumption was verified by log minus log plots and no disproportionality was observed. All relations were tested for effect modification by sex and for effect modification by the presence of clinical manifest cardiovascular disease. For both outcomes incidence rates per 1000 person years were calculated. Multiple imputation was used to reduce missing covariate data for intra-abdominal fat (n = 333, 18%), hsCRP (n = 296, 16%), waist circumference (n = 194, 11%), HbA1c (n = 132, 7%), LDL-cholesterol (n = 153, 8%) and physical activity (n = 23, 1%) since incomplete case analysis leads to loss of statistical power and possibly bias. Statistical analyses were performed with IBM SPSS version 21.0.

2.6. Sensitivity analyses

Additional analyses were performed by consecutively excluding 1) patients with missing data, 2) patients with a low estimated glomerular filtration rate (<60 mL/min/1.73 m^2) to determine whether muscle wasting and subsequent weight loss due to chronic kidney disease may have influenced results, 3) patients diagnosed with type 2 diabetes less than six months ago to determine whether weight change shortly after newly diagnosed type 2 diabetes may have influenced results, 4) patients with a cardiovascular event or death within one year of follow-up to determine whether occult comorbidity at the time of weight measurements may have influenced results and 5) patients with manifest vascular disease, because patients who developed vascular disease in the absence of obesity may have a more adverse predisposition of (unknown) risk factors compared to patients that developed vascular disease as a result of obesity. Therefore, obesity may appear protective in patients with manifest vascular disease on recurrence of events whereas a relation may be found in patient with only risk factors for cardiovascular disease.