ORIGINAL CONTRIBUTIONS

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Contribution of Type 2 Diabetes Mellitus to Subclinical Atherosclerosis in Subjects with Morbid Obesity

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Abstract

Introduction Type 2 diabetes mellitus (T2DM) and obesity are both related to increased risk of cardiovascular disease and mortality. Early atherosclerotic vascular changes can be detected by non-invasive tests like carotid artery intima-media thickness (cIMT) and pulse wave velocity (PWV). Both cIMT and PWV are significantly impaired in T2DM patients and in obese patients, but the additional effect of T2DM on these vascular measurements in obese subjects has not been evaluated.

Methods Two hundred morbidly obese patients with or without T2DM were enrolled in a prospective cohort study and underwent extensive laboratory testing, including cIMT and PWV measurements. The cohort was divided into a group with and a group without T2DM.

Results Within this cohort, 43 patients (21.5%) were diagnosed with T2DM. These patients were older and had more often (a history of) hypertension as compared to patients without T2DM. HbA1c levels were significantly increased, while LDL cholesterol was significantly lower and the use of statins higher than in non-diabetic participants. cIMT and PWV were significantly increased in subjects suffering from T2DM. The variability in cIMT and PWV was related to differences in age and systolic blood pressure, but not to the presence of T2DM.

Conclusion While T2DM negatively affects the vasculature in morbid obesity, hypertension and age seem to be the major risk factors, independent from the presence of T2DM.

Clinical Trial Registration Dutch Trial Register NTR5172.

Keywords Morbid obesity · Atherosclerosis · Type 2 diabetes mellitus · Cardiovascular risk factors

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Introduction

Type 2 diabetes mellitus (T2DM) is a growing chronic health problem worldwide and its microvascular and macrovascular complications cause significant morbidity and mortality [1]. T2DM is associated with atherosclerosis [2] and a major risk factor for cardiovascular disease (CVD) [3, 4]. Atherogenic dyslipidemia is a key factor linking T2DM to CVD and includes reduced levels of high-density lipoprotein cholesterol (HDL-C) and increased levels of triglycerides (TG) and small dense low-density lipoprotein cholesterol (LDL-C) [3]. LDL-C-lowering therapy can modify the cardiovascular risk in adults suffering from T2DM, although the risk of CVD remains higher than in non-diabetic adults [3]. Both the onset and the progression of atherosclerosis are more rapid in T2DM patients [1]. In addition, the disease may cause premature aging of the cardiovascular system [5].

Vascular health can be easily monitored by measuring carotid artery intima-media thickness (cIMT) using carotid ultrasound. cIMT is an easy and non-invasive method for the detection of structural signs of carotid atherosclerosis, which is a significant indicator of subclinical atherosclerosis and of future cardiovascular disease [1, 3, 6–8]. Close associations have been seen between cIMT and conventional cardiovascular risk factors, such as smoking status, hypertension, and dyslipidemia [8, 9]. Patients suffering from T2DM are also known to have an increased cIMT in comparison to non-diabetic controls [8] and the presence of T2DM increases the likelihood of early carotid atherosclerosis [9]. Both hyperglycemia and hyperinsulinemia are associated with an increased risk of atherosclerotic cardiovascular disease, and changes in cIMT are correlated with changes in fasting plasma glucose, HbA1c, and insulin levels [1, 9].

Another measure for vascular health is arterial stiffness, which is an independent risk factor for cardiovascular disease and mortality [3, 4, 10, 11]. The "gold standard" measurement for arterial stiffness is the measurement of the pulse wave velocity (PWV) [4, 5]. Subjects suffering from T2DM are known to have a higher PWV than non-diabetic subjects [4].

Both, IMT and PWV are also known to be increased in patients suffering from obesity [4, 9, 12] and obesity is also strongly associated with cardiovascular risk and the occurrence of coronary heart disease [4]. Furthermore, obese subjects are more likely to develop T2DM. It is unknown whether suffering from T2DM worsens vascular conditions in morbidly obese subjects. As IMT and PWV may be used as prospective markers for vascular disease, we selected these markers to establish the effect of T2DM on the vascular status in morbidly obese subjects.

Methods

Study Population

Data of this study are derived from the ASSISI study, a prospective cohort study established between April 2015 and April 2016 and including 200 patients scheduled for bariatric surgery within our bariatric clinic. All met the international IFSO criteria for bariatric surgery [13], i.e., patients with a BMI of ≥ 40 kg/m^2 or patients with a BMI of ≥ 35 kg/m^2 and obesity-related comorbidity, aged 18 to 65 years. Patients with a previous cholecystectomy, with a previous bariatric procedure, with an acute inflammatory disease within 6 weeks prior to inclusion, or using immune-modulating medication were excluded from this study. All data presented here were collected at study entry, before bariatric surgery.

The study was approved by the independent Regional Medical Research Ethics Committee Rotterdam (Maasstad Hospital, Rotterdam, The Netherlands, ABR No. NL47891.101.14) and all patients gave written informed consent. The ASSISI study is registered in the Dutch Trial Register (NTR5172).

Definitions

T2DM was defined as a HbA1c ≥ 48 mmol/mol (6.5%) [14] and/or previously diagnosed T2DM using glucose lowering medication. Hypertension was defined by a systolic blood pressure > 140 mmHg and/or the use of antihypertensive medication [15]. Hypercholesterolemia was defined as LDL-C > 2.5 mmol/l and/or the use of lipid-lowering drugs [15].

Baseline Characteristics

Baseline characteristics were obtained during standard preoperative screening by the internist prior to bariatric surgery and included the medical history and current medication [16]. Anthropometric characteristics included height, weight, waist circumference, and blood pressure.

Laboratory Measurements

Preoperative laboratory testing was carried out in all participants using non-fasting samples. C-reactive protein (CRP), glucose, total cholesterol, HDL-C, and triglycerides (TG) were determined using the DxC analyzer (Beckman Coulter, Crea, CA, USA). LDL-C values were calculated using the Friedewald formula. HbA1c was measured using an HPLC G8 analyzer (Tosoh Bioscience, King of Prussia, PA, USA). Apo B was determined by rate nephelometry using IMAGE analyzer (Beckman Coulter).

Carotid Intima-Media Thickness

Carotid intima-media thickness (cIMT) measurements were performed according to the consensus guidelines for carotid ultrasound for CVD risk assessment as described previously [17]. The measurement was carried out using the ART-LAB (Esaote, Italy) by a trained and experienced sonographer, who was unaware of the patient's medical history. Ultrasound scans were performed with the patients lying in a supine position with the head resting comfortably and the neck slightly hyperextended and rotated in the opposite direction of the probe. The ultrasound images were obtained from the distal 1 cm of the far wall of each common carotid artery (CCA) using B-mode ultrasound producing two echogenic lines. These lines represent the combined thickness of the intimal and medial layers of the arterial wall. Each CCA was imaged in three different projections: CCA right side 90-120-150 and CCA left side 210-240-270 degrees. The segments were measured semi-automated in triplicate.

Pulse Wave Velocity

Pulse wave velocity (PWV) measurements were carried out using the Mobil-O-Graph (I.E.M, Germany) as previously described [18]. The Mobil-O-Graph uses an inflatable cuff to measure the PWV. The cuff was placed on the patient's bare left upper arm. Triplicate manual measurements were performed. PWV was calculated by the provided software and was expressed in meter per second.

Statistical Analysis

All analyses were performed using SPSS (PASW) 18.0 software (SPSS Inc., Chicago, IL, USA).

Data are given as mean ± standard deviations. Skewed variables are given in median and interquartile range (IQR). Categorical data were described in absolute numbers and percentages. Differences between subjects with and without T2DM were analyzed using independent t tests, chi-square tests, Fisher's exact tests, and independent sample Mann-Whitney U tests. For statistical analysis, cIMT was defined as the mean of the six individual measurements, as described above, and PWV was defined as the mean of three individual measurements. Systolic and diastolic blood pressures were integrated in the mean arterial pressure (MAP), which is the sum of one-third systolic blood pressure and two-third diastolic blood pressure.

The association between IMT and PWV, both intermediate measures of subclinical atherosclerosis, with T2DM was evaluated with univariate linear regression analysis. To evaluate the effects of both the occurrence of T2DM and the severity of dysregulation of glucose homeostasis, linear regression analyses were performed using both the previously described definition of T2DM and the HbA1c level. In further analyses, covariables included gender, age, smoking status, BMI, waist circumference, TG, HDL-C, LDL-C, CRP, and MAP. Correlations between covariables (multicollinearity) were checked for confounding and interaction effects using stratified analysis. Within the regression models of T2DM and HbA1c on both IMT and PWV, a significant interaction effect was observed between HDL-C and TG, while gender was a significant confounder. Other confounding factors were ignored in the analyses for having a low correlation (< 0.30) or small impact on the outcome measures. After stratification for gender, the associations of both T2DM and HbA1c level on cIMT and PWV were evaluated with multivariable linear regression analysis (model: backward stepwise). The following variables were entered into the models: gender, age, smoking status, waist circumference, TG, HDL-C, LDL-C, CRP, HDL-C × TG, and MAP. Results of these models were reported as B coefficients with 95% confidence intervals. Goodness of fit was evaluated with the adjusted R^2. A p value < 0.05 (two-sided) was considered a statistically significant difference.

Results

The total cohort included 200 patients, 52 men and 148 women, with a mean age of 41 (± 11.8) years and a mean BMI of 42.7 (± 5.2) kg/m^2. Within this cohort, 43 patients (21.5%) were diagnosed with T2DM. T2DM patients were older and suffered more frequently from hypertension. In addition, these patients had more frequently a history of myocardial infarction. While mean HbA1c values were significantly increased in diabetes patients, their LDL-C levels were significantly lower than those in non-diabetics. Diabetic patients were more frequently treated with lipid-lowering drugs and antihypertensive drugs. Of all diabetic patients, 35 patients (81.4%) were treated with glucose-lowering drugs; 13 patients received monotherapy with metformin, 8 received a combination of insulin and metformin, 10 received a combination of metformin with another oral glucose lowering drug, and 4 received another treatment. Additional characteristics are displayed in Table 1.

The median cIMT was significantly increased in patients suffering from T2DM, when compared to non-diabetics (0.576 mm (IQR 0.531–0.726) and 0.540 mm (IQR 0.481–0.634), respectively, $p = 0.016$). The median PWV was also significantly higher in diabetic patients compared to non-diabetics (7.6 m/s (IQR 6.9–8.4) and 6.8 m/s (IQR 5.9–8.0), respectively, $p = 0.005$) (Fig. 1).

Univariate linear regression showed that the presence of T2DM was associated with an increased IMT (crude beta 0.048, adjusted R^2 0.021, $p = 0.033$). Additionally, higher HbA1c levels were associated with an increased cIMT

Table 1 Baseline characteristics

Number	Non-T2DM 157	T2DM 43	p value
Age (years)	39.8 (±12.1)	47.4 (±8.3)	$p < 0.001^a$
Female gender	123 (78.3%)	25 (58.1%)	$p = 0.007^b$
Medical history (n, %)			
Hypertension	77 (49.0%)	31 (72.1%)	$p = 0.007^b$
Hypercholesterolemia	124 (79.0%)	34 (79.1%)	$p = 0.990^b$
Stroke	3 (1.9%)	2 (4.7%)	$p = 0.293^c$
Myocardial infarction	2 (1.3%)	4 (9.3%)	$p = 0.020^c$
Medication use (n, %)			
Lipid-lowering agents	10 (6.4%)	21 (48.8%)	$p < 0.001^b$
Antihypertensive agents	38 (24.2%)	27 (62.8%)	$p < 0.001^b$
Smoking habit (n, %)			$p = 0.861^b$
No	68 (43.3%)	19 (44.2%)	
Former smoker	50 (31.8%)	12 (27.9%)	
Yes	39 (24.8%)	12 (27.9%)	
BMI (kg/m^2)	42.7 (±5.2)	42.7 (±5.2)	$p = 0.990^a$
Waist circumference (cm)	129 (±12.9)	132 (±13.5)	$p = 0.102^a$
Systolic blood pressure (mmHg)	138 (±19)	143 (±19)	$p = 0.143^a$
Diastolic blood pressure (mmHg)	81 (±10)	82 (±11)	$p = 0.671^a$
HbA1c (mmol/mol)	38 (±4)	61 (±17)	$p < 0.001^a$
Triglycerides (mmol/l)	1.70 (1.13–2.44)	1.96 (1.26–2.93)	$p = 0.073^d$
LDL cholesterol (mmol/l)	3.3 (±0.9)	2.5 (±0.9)	$p < 0.001^a$
HDL cholesterol (mmol/l)	1.2 (±0.3)	1.2 (±0.3)	$p = 0.699^a$
Apo B (g/l)	1.16 (±0.30)	1.00 (±0.25)	$p = 0.002^a$
Lipoprotein(a) (mg/l)	196 (80–568)	126 (43–361)	$p = 0.201^d$
CRP (mg/l)	5 (3–10)	6 (3–12)	$p = 0.577^d$
Leukocytes (10^9/l)	8.5 (±2.3)	9.3 (±3.0)	$p = 0.082^a$

Data are given as mean ± SD, percentage, or median (IQR)

[a] Independent Student's *t* test

[b] Chi-square test

[c] Fisher's exact

[d] Independent samples Mann-Whitney *U* test

(crude beta 0.001, adjusted R^2 0.019, $p = 0.041$). In a multiple regression analysis, both T2DM and HbA1c did not contribute to the cIMT after stratification for gender and adjusted for age, LDL-C, HDL-C, and MAP. The other parameters included in the analysis did not have any significant effect on the cIMT.
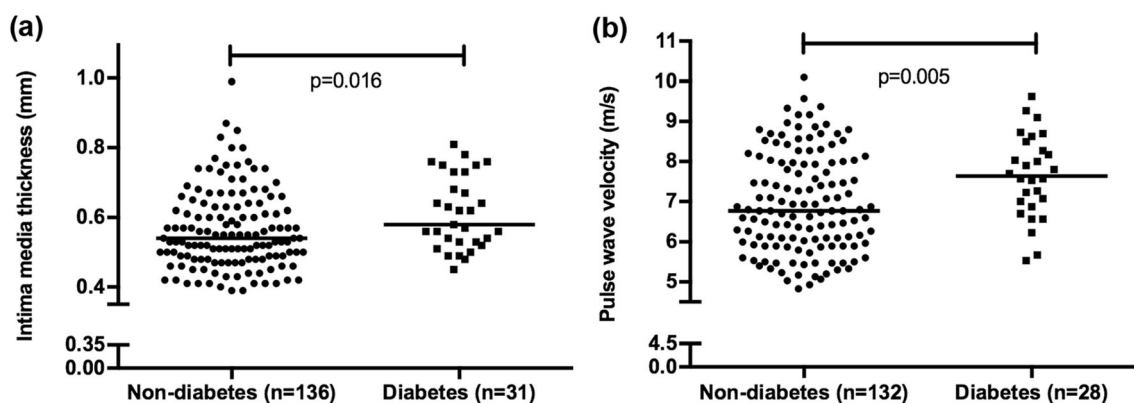

Fig. 1 Median intima-media thickness (**a**) and pulse wave velocity (**b**) in morbidly obese patients with and without type 2 diabetes mellitus

Using univariate analysis, T2DM was associated with increased PWV (crude beta 0.685, adjusted R^2 0.039, $p = 0.007$). Furthermore, HbA1c levels were also associated with an increased PWV (crude beta 0.023, adjusted R^2 0.043, $p = 0.005$). In the multivariable analysis, stratified for gender and after adjustment for age, waist circumference, and MAP, T2DM was not associated with increased PWV. HbA1c tended to show a small contribution to PWV in men only (Table 2).

Discussion

Vascular disease as measured by cIMT and PWV is significantly worse in morbidly obese subjects suffering from T2DM, in comparison to their non-diabetic counterparts. This is in line with previously described differences in non-obese subjects [4, 8]. Our data suggest that the presence of T2DM is not a significant contributor to the levels of IMT and PWV within the morbidly obese subjects after adjustment for age, blood pressure, and lipid profile. PWV was mainly determined by differences in gender, age, waist circumference, and blood pressure.

cIMT and PWV values are increased in both T2DM [8] and obesity [4, 9, 12]. However, the impact of having T2DM in a morbidly obese population on subclinical atherosclerosis has not been described before. Our study suggests that patients with T2DM and morbid obesity have a significantly impaired vascular function, compared to their non-diabetic obese counterparts. However, it should be noted that other cardiovascular risk factors, linked to T2DM, may have a greater impact on vascular function, than T2DM itself. The consequence of our study is that in subjects with morbid obesity and T2DM, one should consider more strict targets of conventional cardiovascular risk factors.

In general, it is well known that cIMT is mainly influenced by age and gender in which men and elderly people have an increased cIMT when compared to women and young subjects [19–23]. In terms of classic cardiovascular risk factors, blood pressure is the main contributor to increased cIMT. Blood pressure influences cIMT, for example in young healthy subjects [20, 23, 24], in lean subjects suffering from T2DM [25], and in elderly patients with cardiovascular risk factors [21]. Additionally, a decrease in blood pressure, for example by administering antihypertensive drugs, can provide a decrease in measured cIMT [26]. The second important cardiovascular risk factor to influence cIMT is dyslipidemia [20–22] and intensive lipid-lowering therapy can also positively influence IMT [26–28], although this effect was not observed in diabetic subjects [29]. The results in these non-obese study populations are in agreement with the results in our study. Smoking habit is also thought to influence cIMT in different populations [20–23], but this association was not observed in our morbidly obese subjects.

The determinants of arterial stiffness, measured as the pulse wave velocity, have been less well studied compared to cIMT. In healthy middle-aged and elderly subjects, not suffering from T2DM or CVD, PWV is mainly determined by age, blood pressure, and waist circumference [30], which is in accordance with the results in our morbidly obese population. Fasting glucose levels are thought to have a modest impact on PWV and only when diabetic and cardiovascular patients are included in the study group [30]. Additionally, both HbA1c [25] and TG [24] levels are thought to play a role in the development of arterial stiffness, although that effect is only seen in selected subjects and cannot be

Table 2 Impact of HbA1c levels on pulse wave velocity (PWV). The impact of HbA1c level on PWV was evaluated with multiple linear regression analysis (backward stepwise analysis)

Parameter	PWV			
	Male		Female	
	Adj. B coefficient (95% CI)	p value	Adj. B coefficient (95% CI)	p value
Constant	0.714 (−0.567; 1.996)	$p = 0.265$	−1.086 (−2.628; 0.457)	$p = 0.166$
HbA1c	0.007 (0.000; 0.014)	$p = 0.060$	–	–
Age	0.082 (0.070; 0.095)	$p < 0.001$	0.085 (0.075; 0.096)	$p < 0.001$
Waist circumference	–	–	0.016 (0.007; 0.025)	$p = 0.001$
Mean arterial pressure	0.026 (0.014; 0.038)	$p < 0.001$	0.027 (0.016; 0.037)	$p < 0.001$

confirmed in all studies or patient groups. Both parameters were no major determinant of PWV within our morbidly obese study population.

Obesity is both a major and modifiable risk factor for the development of metabolic and cardiovascular disease [12]. Weight loss can be an important pillar in the prevention strategy for cardiovascular events. For example, bariatric surgery can significantly reduce cardiovascular morbidity and mortality. One study showed that cIMT values were significantly decreased 1 year after bariatric surgery [31]. An interesting finding in the current study is the fact that the degree of obesity, in terms of both BMI and waist circumference, did not influence the value of cIMT or PWV. It can be suggested that being morbidly obese indeed increases the values of PWV and cIMT, but that the level of obesity does not really matter once a certain BMI threshold is surpassed (ceiling effect). A certain ceiling effect was previously described for markers of dyslipidemia [32, 33] and may be true for other cardiovascular risk factors or vascular outcome measures, such as cIMT and PWV. Consequently, once morbid obesity is a fact, further increment of body weight may not cause further deterioration of subclinical atherosclerosis.

When analyzing the impact of diabetes on cIMT or vascular function, differences in cardiovascular risk management between diabetics and non-diabetics can affect the results. For example, one important pillar of the treatment for type 2 diabetes is the reduction of diabetic dyslipidemia with prescription of statins. Within our morbidly obese population, diabetic patients were more likely to use statins and therefore their mean LDL cholesterol level was significantly lower than that in the non-diabetic group. The differences in cIMT and PWV between diabetics and non-diabetics may be limited due to the extensive use of statins in diabetics. However, a previous study showed that statin use does not influence cIMT in diabetic patients without previous cardiovascular disease [29] and only aggressive treatment goals, such as LDL-cholesterol ≤ 70 mg/dl, can influence the progression of cIMT [34]. Another important target in the treatment of diabetic patients is the prevention of micro- and macrovascular complications by administration of antihypertensive drugs. Within our cohort, the diabetic patients were more likely to be diagnosed with hypertension and to be treated with antihypertensive drugs. Diabetic patients with hypertension are known to have increased cIMT values and increased cIMT progression over time [35, 36]. Even though the actual value of systolic and diastolic blood pressures was not significantly different between the diabetic and non-diabetic subjects in our cohort, it was previously shown that treatment with antihypertensive drugs had a positive influence on cIMT and progression of cIMT, independent of the level of blood pressure [35]. Therefore, the effect of type 2 diabetes on cIMT in this study may be limited due to the excessive use of antihypertensive agents within this group.

In conclusion, although T2DM negatively affects the vasculature in morbid obesity, age and hypertension seem to be the main risk factors independent from the presence of T2DM.

Compliance with Ethical Standards

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