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Adipokines and endothelial dysfunction in obesity WHO°III

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ABSTRACT

Obesity is closely associated with the metabolic syndrome (MetS) and subsequent low-grade inflammation links to endothelial dysfunction (ED) and cardiovascular disease. The impact of adipokines on retinal ED is not fully understood, in particular not in severe obesity. The aim of the study was to identify the association of the MetS and prespecified adipokines on retinal ED in obesity WHO°III. 92 obese patients (obesity WHO°III) were assessed for the MetS (IDF), neck circumference, adipokines and inflammatory markers (hsCRP, TNFα, Il-6, MCP-1, sICAM, sVCAM, IGF-BP3, RBP 4 and adiponectin). Retinal ED as determined by the arterio-venous-ratio (AVR) and retinal vessel diameters (CRAE, CRVE) was measured using retinal photographs. Obese subjects with MetS (MetS+ group) differed from the MetS− by neck circumference, fasting plasma glucose, insulin, HOMA-IR, triglycerides and HDL-C. Importantly, IL-6, sICAM and adiponectin were significantly different between groups, while measures of retinal ED showed no differences. Univariate linear regression revealed a significant association between neck circumference and ED for patients with MetS, and a significant association between adiponectin and CRAE for patients without MetS. This study shows that ED in obesity WHO°III is independent of MetS or inflammation and that neck circumference has an impact on ED in obesity WHO°III.

Introduction

Obesity and its metabolic and cardiovascular sequelae have been identified as a large public health problem worldwide (Fernández-Sánchez et al., 2011). The challenges this poses do not only apply to developed countries, but affect all countries having adopted a western diet, and result globally in more obese than underfed people (Lustig et al., 2012). Obesity is strongly associated with the metabolic syndrome (MetS) which is related to a proinflammatory and proatherogenic state with higher risk of cardiovascular disease (Alberti et al., 2009). Adipose tissue is an established endocrine and paracrine organ that is dysregulated in obesity resulting in the development of cardiovascular and metabolic comorbidities (Bays, 2009). Endothelial dysfunction as an early step in the development of atherosclerosis is associated with cardiovascular risk factors (Hadi et al., 2005) and is determined by retinal vessel analysis (Hubbard et al., 1999). The retinal microvasculature offers the opportunity to non-invasively detect vascular processes associated with systemic diseases (Nguyen and Wong, 2006). An association between the metabolic syndrome and retinal endothelial dysfunction has been recently demonstrated (Wong et al., 2004). Several adipocytokines are thought to directly influence vascular processes in the development of ED and atherosclerosis (Tesauro and Cardillo, 2011; Van Gaal et al., 2006). We aimed at identifying the impact of MetS, inflammation and adipokines on retinal ED in obesity WHO°III.

Methods

We assessed 114 obese patients participating the *Mannheim Obesity Study* (MOS, NCT00770276) in anthropometric, metabolic and obesity associated parameters. Because of missing data 16 participants were excluded and 6 patients did not give their written informed consent, resulting in 92 patients (WHO°III, 27 male, 65 female) considered in the present analysis. The study was approved by the local ethics committee.

All participants were clinically assessed in height, weight, waist and neck circumference and blood pressure.

Abbreviations: AVR, Arterio-venous-ratio; CRAE, Central retinal artery equivalent; CRVE, Central retinal vein equivalent; ED, Endothelial dysfunction; hsCRP, High sensitive CRP; IGF-BP 3, Insulin like growth factor binding protein 3; IL-6, Interleukin 6; MCP-1, Monocyte chemotactic protein 1; MetS, Metabolic syndrome; MOS, Mannheim Obesity Study; RBP4, Retinol binding protein 4; sICAM, Soluble intercellular adhesion molecule; sVCAM, Soluble vascular cell adhesion molecule; TNFα, Tumor necrosis factor alpha.

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Blood samples were obtained after an overnight fast. According to the IDF-criteria fasting plasma glucose, HDL-C and triglycerides were measured as well as insulin, LDL-C and total cholesterol.

Using common available ELISA, selected adipokines reflecting systemic inflammation and proatherogenic influences by adipose tissue were measured [including high sensitive c-reactive protein (hsCRP [mg/l]/Dimension RxL, Siemens, Eschborn, Germany), tumor necrosis factor α (TNFα [pg/ml]/ImmunoTools GmbH, Friesoythe, Germany), interleukin 6 (IL-6 [pg/ml]/R&D Systems, Wiesbaden, Germany), monocyte chemotactic protein 1 (MCP 1 [pg/ml]/DIACLONE, Cologne, Germany), soluble intercellular adhesion molecule (sICAM [ng/ml]/DIACLONE, Cologne, Germany), soluble vascular cell adhesion molecule (sVCAM [ng/ml]/DIACLONE, Cologne, Germany), retinol binding protein 4 (RBP4 [ng/ml]/R&D Systems, Wiesbaden, Germany), insulin like growth factor binding protein 3 (IGF-BP 3 [ng/ml]/Ray Biotech, Norcross, Georgia, USA) and adiponectin ([ng/ml]/Mediagnost, Reutlingen, Germany)].

Clinical ED was determined in retinal photographs using retinal vessel analysis (IMEDOS™, Jena, Germany). Central retinal artery/vein equivalent (CRAE, CRVE) and arterio-venous-ratio (AVR) were calculated using the equation of Parr and Hubbard (Hubbard et al., 1999).

Insulin resistance was determined via HOMA-IR using the formula of Matthews et al. (1985).

The group was divided in a cohort of 65 patients with the diagnosis MetS (MetS+) according to the IDF-criteria for MetS and a cohort of 27 patients who did not meet the requested 3 or more of the 5 criteria for the diagnosis MetS (MetS−).

We first compared the two groups (MetS+/MetS−) in all assessed parameters. To identify a possible impact of MetS or adipokines on ED, we then divided the whole group in quartiles of adipokines and compared the 1st quartile with the 4th quartile in parameters of ED. Additionally, we performed univariate and multivariate regression models, using CRAE, CRVE and AVR as dependent and MetS, neck circumference and adipokines as independent variables.

All statistics were done with SAS for Windows, version 9.2 (Statistical Analysis System, SAS corporation, North Carolina, USA). We tested for differences between the MetS+ and the MetS− group and between the upper and the lower quartiles using a Mann–Whitney U test. For differences in categorical data the Chi-squared test was performed. Possible outliers were detected via Cook's distance measures before doing regression analysis.

Results

The whole group was divided in subgroups containing 65 patients with MetS (MetS+) and 27 without MetS (MetS−). Characteristics of the two groups regarding MetS are shown in Fig. 1. Within the MetS+ group 100% fulfilled the IDF-criterion for waist circumference, 97% the criterion for blood pressure, 65% that for triglycerides, 62% that for HDL-C and 49% that for fasting plasma glucose. 53% fulfilled 3, 25% fulfilled 4 and 22% fulfilled 5 out of the 5 IDF-criteria. Within the MetS− group 100% fulfilled the criterion for waist circumference, 70% that for blood pressure, 7% that for triglycerides, 4% that for HDL-C and 4% that for fasting plasma glucose. 15% fulfilled just one and 85% fulfilled two of the five IDF-criteria.

55% of the MetS group and 30% of the MetS− group were on antihypertensive treatment ($p < 0.05$). None of the MetS− patients was on antidiabetic treatment, whereas 8% of the MetS+ group were treated with insulin (difference compared to MetS− not significant), 15% were treated with metformin ($p = 0.03$) and 5% were treated with other oral antidiabetic medication (p = n.s.).

We analyzed the groups by all assessed parameters and compared MetS+ with MetS−. Patients with MetS (MetS+) showed higher neck circumference compared to those without MetS (MetS−). Higher levels of glucose, insulin and subsequently HOMA-IR were observed in MetS+ and the group showed more dyslipidemia as reflected by higher levels of triglycerides and lower levels of HDL-C. Higher levels of IL-6 and sICAM and lower levels of adiponectin were also found ($p < 0.05$ for all). No differences were observed in age, weight, BMI, waist circumference, blood pressure, LDL-C, total cholesterol, parameters of ED, hsCRP, TNFα, sVCAM, MCP-1, IGF-BP 3 or RBP4 (Table 1).

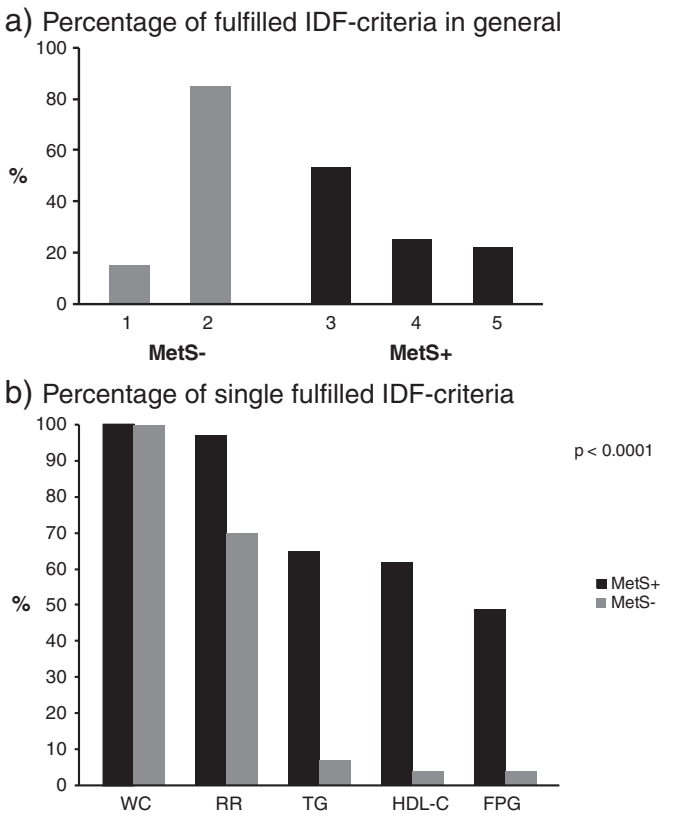

Fig. 1. Characteristics of MetS+ and MetS− regarding the IDF-criteria for the MetS; WC = waist circumference, RR = blood pressure, TG = triglycerides, HDL-C = HDL cholesterol, FPG = fasting plasma glucose. a) Percentage of fulfilled IDF-criteria in general. b) Percentage of single fulfilled IDF-criteria.

To assess the impact of adipokines on retinal ED we then divided the whole group into quartiles of neck circumference, hsCRP, TNFα, IL-6, sICAM, sVCAM, MCP-1, IGF-BP 3, RBP 4 and adiponectin. We observed significant differences in CRVE (−16 μm) and AVR (+0.07) between those patients with neck circumference ≤41 cm (1st quartile) and those with neck circumference ≥48 cm (4th quartile). In addition patients with adiponectin ≥8204 ng/ml (4th quartile) showed wider retinal arterioles (+8 μm) than patients with adiponectin ≤4109 ng/ml (1st quartile). Patients with sVCAM ≤ 706 ng/ml (1st quartile) had lower levels of AVR (−0.06) and wider venules (+10 μm) than those with sVCAM ≥995.5 ng/ml (4th quartile) ($p < 0.05$ for all) (Table 2).

In the univariate regression model using CRAE, CRVE and AVR as dependent variables, we observed a significant association of neck circumference with AVR ($R^2 = 0.08$; $p < 0.01$) and with CRVE ($R^2 = 0.04$; $p < 0.05$) for the whole group. After performing the regression for MetS+ and MetS− separately, the association with neck circumference remained significant for the MetS+ group (Table 3). Within the adipokines a significant association between adiponectin and CRAE was observed among the MetS− group ($R^2 = 0.18$; $p < 0.05$). This association was not significant in the whole group or MetS+. Using MetS present/absent as a dummy variable, no association with parameters of ED was observed. In the multivariate regression model no significant associations were found.