Nutrition, Metabolism & Cardiovascular Diseases (2014) **24**, 447–453

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Systemic inflammation is related to coronary microvascular dysfunction in obese patients without obstructive coronary disease

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Received 2 April 2013; received in revised form 23 September 2013; accepted 30 September 2013
Available online 6 November 2013

KEYWORDS
Obesity;
Microvascular dysfunction;
Coronary flow reserve;
Inflammation;
Prevention

Abstract *Background and Aims:* Obesity, systemic inflammation and changes in the heart functions are associated with increased cardiovascular risk. This study aimed to investigate coronary microvascular dysfunction as an early marker of atherosclerosis in obese patients without any evidence of cardiovascular disease.
Methods and results: 86 obese subjects (aged 44 ± 12 years, body mass index (BMI) 41 ± 8 kg m^{-2}), without evidence of heart disease, and 48 lean controls were studied using transthoracic Doppler echocardiography for detecting coronary flow reserve (CFR). A value of CFR ≤ 2.5 was considered abnormal. We measured interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and adiponectin in all patients. Patients with abnormal CFR underwent coronary multislice computed tomography (MSCT) in order to exclude an epicardial stenosis. CFR in obese subjects was lower than in lean subjects (3.2 ± 0.8 vs. 3.7 ± 0.7, $p = 0.02$) and was abnormal in 27 (31%) obese patients and in one (2%) control ($p < 0.0001$). All subjects with abnormal CFR showed no coronary stenosis at MSCT. At multivariable analysis, IL-6 and TNF-α were the only determinants of CFR ($p < 0.02$ and $p < 0.02$, respectively). At multivariable logistic regression analysis, IL-6 and TNF-α were the only determinants of CFR ≤ 2.5 ($p < 0.03$ and $p < 0.03$, respectively).
Conclusions: CFR is often reduced in obese subjects without clinical evidence of heart disease, suggesting a coronary microvascular impairment. This microvascular dysfunction seems to be related to a chronic inflammation mediated by adipocytokines. Our findings may explain the increased cardiovascular risk in obesity, independently of BMI.

The prevalence of obesity is reaching epidemic proportions [1]. Obesity is associated with structural and functional changes in the heart increasing cardiovascular risk [2]. However, whether obesity, independently of its complications, might affect coronary circulatory function early remains uncertain.

Epidemiological data showed an association between circulating levels of inflammatory cytokines and long-term cardiovascular risk [3,4] suggesting that obesity is associated with a systemic inflammation with endothelial cell dysfunction, oxidative stress and immune system activation [5]. Adipocytes produce several cytokines (e.g.,

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http://dx.doi.org/10.1016/j.numecd.2013.09.021

interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α)) and cytokine-like molecules (e.g., leptin) mediating the inflammatory response in obesity [6].

The assessment of coronary microvascular reactivity is a validated tool to identify the presence of coronary microvascular dysfunction [7–10]. In patients without evidence of obstructive coronary artery disease, impaired endothelium-dependent coronary microvascular function represents an early marker of atherosclerosis. However, myocardial-endothelium-independent perfusion alterations during adenosine-induced vasodilation are not infrequent in the absence of significant epicardial coronary disease. Although there has been long interest in microvascular ischaemia, most work has focussed on the endothelium-dependent component; but, adenosine-related vascular smooth muscle alterations do not necessarily correlate with dysfunctional endothelium [8]. Coronary flow reserve (CFR) by transthoracic Doppler echocardiography may provide functional non-invasive assessment of the endothelium-independent microvascular function, related to vascular smooth muscle alterations [11,12].

Alterations in microvascular function could contribute to the increased cardiovascular morbidity and mortality in obesity. However, the influence of obesity on coronary microvessels has been poorly investigated [13,14]. We evaluated the relationship between coronary microvascular dysfunction, inflammation and obesity without evidence of epicardial coronary disease.

Methods

Study population and clinical parameters included in the analysis

We enrolled 86 asymptomatic consecutive subjects (62 male, aged 44 ± 12 years, body mass index (BMI) 41 ± 8 kg m^{-2}) referred to the Bariatric Unit of the University Hospital of Padua for clinical evaluation. Baseline evaluation included physical examination and collection of clinical and laboratory data (Table 1). Patients with thyroid dysfunction and/or systemic inflammatory diseases were excluded from the study. The non-randomised control group consisted of 48 lean, normal volunteers recruited from institutional personnel matched for age and sex. The absence of coronary artery disease was evaluated by clinical history, physical examination and electrocardiogram. The homeostasis model assessment (HOMA) was used to estimate insulin sensitivity. The Framingham Risk Score (FRS) was based on the Third Report of the Expert

Table 1 Characteristics of study population (n = 134).

	Controls (n = 48)	Obeses (n = 86)	p
BMI, kg/m^2	23 ± 1	41 ± 8	<0.0001
Waist, cm	72 ± 3	119 ± 15	<0.0001
Waist-hip ratio	0.75 ± 0.1	0.93 ± 0.09	<0.0001
Age, years	43 ± 10	44 ± 12	0.6
Female gender, n (%)	31 (65)	62 (72)	0.4
Serum cholesterol levels, mg/dl	178 ± 35	210 ± 46	0.5
Serum LDL level, mg/dl	128 ± 20	133 ± 33	0.3
Serum HDL level, mg/dl	49 ± 9	47 ± 13	0.7
Triglyceride level, mg/dl	98 ± 41	137 ± 71	<0.05
Glucose level, mg/dl	88 ± 14	98 ± 13	<0.05
Insulin, μUI/ml	9 (5–13)	14 (9–20)	<0.001
HOMA index	1.4 (1–2)	3.44 (1.8–5.3)	<0.001
hsCRP levels, mg/l	0.7 (0.4–0.9)	5.7 (1.7–7.5)	<0.0001
Leptin, ng/ml	10.1 ± 2.1	27 ± 12	<0.0001
IL-6 level, ng/l	1.1 (0.5–1.4)	3.8 (2.5–5)	<0.0001
TNF-α level, ng/l	3.1 (2–6.3)	11.4 (9.9–13.9)	<0.0001
Adiponectin, μg/ml	3.4 (1.5–6)	2.4 (1.2–3.4)	0.06
Current smokers, n (%)	12 (25)	19 (22)	0.6
Hypertension, n (%)	20 (42)	40 (46)	0.3
Diabetes, n (%)	9 (18)	21 (24)	0.2
Hypercholesterolaemia, n (%)	13 (28)	24 (28)	0.9
Metabolic syndrome, n (%)	7 (14)	45 (52)	1
FRS	2 (1–6)	1 (1–6)	0.8
End-diastolic diameter, mm	48 ± 5	45 ± 5	0.8
End-systolic diameter, mm	26 ± 5	24 ± 2	0.7
LVEF (%)	68 ± 5	66 ± 3	0.8
Interventricular septum thickness, mm	10 ± 0.3	13 ± 0.1	0.03
Posterior wall thickness, mm	10 ± 0.3	13 ± 0.3	0.03
Left ventricular mass index, g/m^2	87 ± 16	134 ± 27	<0.01
Diastolic dysfunction, n (%)	18 (37)	39 (45)	<0.01

Unless specified otherwise, the values are means ± SD or median (IQR).
BMI = Body mass index; FRS = Framingham risk score; HOMA = Homeostasis model assessment; hsCRP = high sensitive C-reactive protein; IL-6 = Interleukin-6; LVEF = left ventricular ejection fraction; TNF-α = Tumour necrosis factor-α.