LEPTIN TO ADIPONECTIN RATIO IS AN INDEPENDENT PREDICTOR OF COMMON CAROTID ARTERY INTIMA-MEDIA THICKNESS IN OBESE SUBJECTS

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Background: Obesity it is associated with insulin resistance, chronic mild inflammation, type 2 diabetes and vascular disease. Increased production of most adipokines is involved in the development of obesity-related vascular diseases. Adiponectin is an adipokine with insulin-sensitising and anti-atheroslcerotic effects. Plasma adiponectin levels are reduced in obese subjects and in patients with type 2 diabetes, metabolic syndrome and cardiovascular diseases. In the present study we evaluated the association of traditional cardiovascular risk factors, adipokines, inflammation and insulin resistance with intima-media thickness (CIMT) of the common carotid artery, marker of subclinical atherosclerosis.
Methods: The study included 117 healthy subjects (64 men and 53 women), who were classified according to their body mass index (BMI) into three groups: lean (BMI<25kg/m^2), overweight (25≤ BMI<30kg/m^2) and obese (BMI≥ 30kg/m^2). All participants underwent anthropometrical and blood pressure evaluation. The following biomarkers were analyzed: fasting glucose, HbA1c, fasting insulin, fasting proinsulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, adiponectin, leptin, hs-CRP. B-mode ultrasound imaging of the common carotid arteries was used to measure common carotid IMT.
Results: In obese men hs-CRP, fasting insulin, HOMA-IR, fasting proinsulin, leptin and leptin/adiponectin ratio levels were higher and adiponectin levels were lower compared to lean men. In obese women hs-CRP, fasting insulin, leptin and leptin/adiponectin ratio levels were higher and adiponectin levels were lower compared to lean women. Carotid intima-media thickness (CIMT) was higher in obese, healthy men and women compared to overweight and lean men and women (men 0.91±0.17mm *vs.* 0.76±0.14mm *vs*. 0.68±0.09mm, p=0.0003; women 0.86±0.14mm *vs*. 0.74±0.12 *vs*. 0.6±0.08mm, p=0.0001). Determinants of carotid intima-media thickness (CIMT) in obese men were age (β=0.628, p<0.0001), leptin to adiponectin ratio (β=0.307, p=0.013) and hs-CRP (β=0.299, p=0.028) and in obese women were leptin to adiponectin ratio (β=0.386, p=0.035) and systolic blood pressure (β=0.408, p=0.027). Determinants of CIMT in non-obese men and women were systolic blood pressure (men β=0.334, p=0.039; women β=0.352, p=0.025) and age (men β=0.382, p=0.019; women β=0.321, p=0.03).
Conclusions: Obesity is associated with increased CIMT. Leptin to adiponectin ratio is independently associated with CIMT in obese, healthy, middle-aged men and women.

Key words: obesity, adiponectin, leptin, adiponectin/leptin ratio, intima-media thickness.

INTRODUCTION

The prevalence of obesity has increased dramatically in recent years[1]. It is commonly associated with insulin resistance, chronic mild inflammation, type 2 diabetes and vascular disease[2,3]. Adipose tissue is not only a major site for energy storage, important for energy homeostasis, but also an important endocrine organ that secrets a number of biologically active "adipokines"[4,5]. These adipocitokines are involved in overall metabolic regulation and influence a various

systemic phenomena[6]. In obesity, increased production of most adipokines (including tumor necrosis factor-α, interleukins, plasminogen activator inhibitor type 1, resistin, leptin) has been found to be involved in the development of obesity-related vascular diseases[7]. Adiponectin is an adipokine that is specifically and abundantly expressed in adipose tissue and directly sensitizes the body to insulin by activating AMP kinase and PPARα in the skeletal muscle and liver (decrease triglyceride content and increase insulin sensitivity)[8,9]. Adiponectin was demonstrated to have anti-inflammatory, anti-atherogenic and antidiabetic effects[10]. Adiponectin was demonstrated to inhibit various mechanisms contributing to atherogenesis: 1) expression of adhesion molecules (intracellular adhesion molecule-1, vascular cellular adhesion molecule-1, E-selectin) in endothelial cells; 2) foam cell formation by decreasing uptake of oxidized LDL by macrophages; 3) to inhibit proliferation and migration of smooth muscle cells[11,12]. Plasma adiponectin levels are reduced in obese subjects and in patients with type 2 diabetes, metabolic syndrome, hypertension and cardiovascular diseases[8,10,13]. Weyer *et al.*[14] show that plasma adiponectin concentration is closely related to insulin sensitivity and fasting insulinemia.

Leptin is secrete by adipocytes in direct proportion to adipose tissue mass and is a modulator of the appetite and the energetic balance[7]. There are data which suggest that leptin promotes atherogenesis through the following effects: induction of endothelial dysfunction, stimulation of inflammatory reaction, oxidative stress, decrease in paraoxonase activity, platelet aggregation, migration, hypertrophy and proliferation of vascular smooth muscle cells[15]. Wallance *et al.*[16] showed in men participating in West of Scotland Coronary Prevention Study (WOSCOPS) that leptin is an independent risk factor for coronary heart disease. Welsh *et al.*[17] showed in an eldery population, men and women included in PROspective Study of Pravastatin in the Elderly at Risk trial (PROSPER) that leptin is more strongly related to risk of diabetes than cardiovascular events.

Recent studies have shown that leptin to adiponectin ratio is a useful measure of insulin resistance both in diabetic and non-diabetic subjects[18–22] and predict the presence of the metabolic syndrome[23,24].

Carotid intima-media thickness (CIMT) is a measure of subclinical atherosclerosis and is predictive of future cardiovascular events[25–27]. Numerous studies have demonstrated that CIMT correlate with traditional risk factors of cardiovascular disease[28]. There are data which show that obesity[29] and metabolic syndrome[30,31] are associated with increased CIMT and there is a negative correlation between adiponectin and CIMT [29,32,33]. In this study we examined the relationship between traditional cardiovascular risk factors, adipokines (adiponectin, leptin), inflammation (hs-CRP), insulin resistance (HOMA-IR, fasting insulin) and beta cell secretion (proinsulin) to CIMT in healthy men and women.

MATERIALS AND METHODS

Subjects

A total of 117 healthy subjects (64 men and 53 women), mean age 53,8 years, were recruited in Clinical Hospital Colentina, Department of Diabetes, Nutrition, Metabolic Diseases, from February 2009 to January 2010. All participants gave written informed consent. Subjects with diabetes, currently smoking, history of cardiovascular diseases, use of drugs for dyslipidemia and hypertension, presence of viral hepatitis, renal disease or thyroid dysfunction were excluded. Participating subjects were classified by BMI (lean 18.5<BMI<25 kg/m^2, overweight 25.0<BMI<30.0 kg/m^2, obese BMI≥30.0 kg/m^2); 56 were defined as obese (31 men and 25 women), 43 were defined as overweight (24 men and 19 women) and 18 were defined as lean (9 men and 9 women). Percent body fat (%) was measured using a bioelectrical impedance analyzer (Omron BF500).

Carotid artery ultrasound

CIMT was determined using a B-mode ultrasound scanner (Siemens Sonoline Sienna) and a 7,5MHz linear probe with subjects in the supine position, by a trained specialist with no knowledge of the subjects clinical characteristics. Longitudinal scan of both the right and left common carotid artery was recorded. Measurement of IMT was made on the near (anterior) and far (posterior) wall of the common carotid artery at 1 cm proximal to the bifurcation, in segments that were free of plaque, plaque being defined as the presence of wall thickening at least 50% greater than the adjacent thickness. For each individual, the CIMT was determined as the average of near and far-wall measurements of both the left and right arteries.

Laboratory assay

The samples of blood were taken after 12 hours of overnight fasting. Total adiponectin, leptin, hs-CRP, insulin and proinsulin were measured by ELISA (DRG International, Inc.) on a Dynex analyzer. Low-density lipoprotein (LDL)

cholesterol was calculated using the Friedewald formula. Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides and glucose were measured using standard techniques. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as the product of the fasting plasma insulin value (in microunits per liter) and the fasting plasma glucose value (in mg per deciliter) divided by 405.

Statistical analysis

Statistical analysis was performing using the program SPSS 12.0 for Windows. Continuous variables were tested for normality of distribution with the use of the Wilk-Shapiro test. Data normally distributed were expressed as mean±standard deviation (SD) and data skewed distributed were expressed as median (interquartlile range). Normally distributed variables were compared among the three obesity categories by the ANOVA test with Bonferroni post-test for multiple comparisons and not normally distributed variables were compared among the three obesity categories by the nonparametric Kruskal-Wallis test with Dunn post-test for multiple comparisons. Variables not normally distributed (insulin, proinsulin, HOMA-IR, adiponectin, leptin, leptin to adiponectin ratio and hs-CRP) were log transformed before evaluating the associations. Associations between CIMT and traditional risk factors, adipokines (adiponectin, leptin and leptin to adiponectin ratio), insulin resistance markers (HOMA-IR and insulin), beta cell secretion marker (proinsulin) and inflammation marker (hs-CRP) were examined using linear regression analysis. These associations were further examined, separately for women (obese and non-obese) and men (obese and non-obese), by multiple stepwise regression analysis. The multiple regression analysis were performed with IMT as the dependent variable by entering the independent variables with the highest partial correlation coefficient at each step with an F value probability for inclusion of 0.05 and 0.01 for removal. P value <0.05 was considered statistically significant for all analyses.

RESULTS

Characteristics of study subjects

The clinical and biochemical characteristics of the subjects selected for this study are shown in Table 1. Obese women compared to lean women had significantly higher mean levels of systolic blood pressure, triglyceride and fasting glucose, significantly higher median levels of hs-CRP, fasting insulinemia, leptin and leptin/adiponectin ratio, significantly lower mean levels of HDL-colesterol and significantly lower median levels of adiponectin. Obese men compared to lean men had significantly higher mean levels of systolic blood pressure, diastolic blood pressure, triglyceride and fasting glucose, significantly higher median levels of hs-CRP, fasting insulinemia, HOMA-IR, fasting proinsulin, leptin and leptin/adiponectin ratio, significantly lower mean levels of HDL-cholesterol and significantly lower median levels of adiponectin. CIMT was higher in obese women compared to overweight women (0.86±0.14 mm *vs.* 0.74±0.12 mm, p=0.031) and in comparison to normalweight women (0.86±0,14 mm *vs.* 0.6±0.08 mm, p=0.0004). Also, CIMT was higher in overweight women compared to normalweight women (0.74±0.12 mm *vs.* 0.6±0,08 mm, p=0.028). CIMT was higher in obese men compared to overweight men (0.91±0.17 mm *vs.* 0.76±0,14 mm) and in comparison to normalweight men (0.91±0.17 mm *vs.* 0.68±0.09 mm, p=0.0008).

Univariate analysis between CIMT and various variables

In univariate analysis in obese men CIMT significantly correlated to age (CIMT = 0.0175 × age – 0.0148, r^2=0.65, p<0.0001), hs-CRP (CIMT = 0.3753 × log(hs-CRP) + 0.75, r^2=0.19, p=0.0009), systolic blood pressure (CIMT = 0.0073 × SBP – 0.1453, r^2=0.4, p=0.002), leptin/adiponectin ratio (CIMT = 0.1714 × log(leptin/adiponectin) + 0.7818, r^2=0.21, p=0.0006), proinsulin (CIMT = 0.4039 × log(proinsulin) + 0.5224, r^2=0.15, p=0.029), HOMA-IR (CIMT = 0.2591 × log(HOMA-IR) + 0.7444, r^2=0.14, p=0.035) and in non-obese men IMT significantly correlated to age (CIMT = 0.0059 × age + 0.4539, r^2=0.18, p=0.014), systolic blood pressure (CIMT = 0.0043 × SBP + 0.1457, r^2=0.14, p=0.028) and hs-CRP (CIMT = 0.187 × log(hs-CRP) + 0.7108, r^2=0.12, p=0.033). In univariate analysis in obese women IMT significantly correlated to systolic blood pressure (CIMT = 0.008 × SBP – 0.233, r^2=0.27, p=0.001), leptin/adiponectin ratio (CIMT = 0.0243 × log(leptin/adiponectin) + 0.7041, r^2=0.25, p=0.016), age (CIMT = 0.0098 × age + 0.3322, r^2=0.23, p=0.029), HOMA-IR (CIMT = 0.2895 × log(HOMA-IR) + 0.7267, r^2=0.19, p=0.031), leptin (CIMT = 0.2263 × log(leptin) + 0.4972, r^2=0.16, p=0.047) and in non-obese women IMT significantly correlated to systolic blood pressure (CIMT = 0.0045 × SBP + 0.1015, r^2=0.24, p=0.007), age (CIMT = 0.0071 × age + 0.3107, r^2=0.22, p=0.011).

Table 1

The general charecteristics of the study subjects

	Lean (L)			**Overweight (OW)**			**Obese (OB)**			**P total**	**P men**	**P women**
	T	M	W	T	M	W	T	M	W			
Number	18	9	9	43	24	19	56	31	25			
Age (years)	54.6±7.1	55.4±7.5	53.8±7.1	54.5±9.4	55.6±9.1	52.9±11.6	52.9±8.7	51.6±9.1	54.5±8.1	0.67	0.09	0.73
BMI (kg/m2)	24±0.5	24.3±0.5	23.7±0.6	27.2±2.9[a]	27.1±2.24[d]	27.3±3.5[g]	34.1±3.3[bc]	33.8±3.1[e,f]	34.6±3.6[hi]	<0.0001	<0.0001	<0.0001
Waist (cm)	84.2±3.9	93.3±4.6[*]	79.8±3.1	99.7±13.4[a]	102.8±11.1[d,*]	92±9.1[g]	108.8±13.5[bc]	118.26±8.03[e,f,*]	97±5.67[hi]	<0.0001	<0.0001	<0.0001
Body fat (%)	22.7±0.6	21.6±0.5[*]	24.8±0.4	27.7±0.8[a.]	25.9±0.9[d,*]	30.8±0.5[g]	34.9±0.8[bc]	32.55±1.1[e,f]	37.84±0.7[h,i]	<0.0001	<0.0001	<0.0001
SBP (mmHg)	123.6±10.7	125.6±10.1	118.7±11.5	136.5±13.6[a]	141.2±10.7[d]	132.9±13.8[g]	140.5±14.5[b]	145.8±13.8[e]	138.2±13.8[h,i]	0.02	0.037	0.003
DBP (mmHg)	75.8±8.1	78.9±7.8	72.8±7.6	78.9±9.4	82.8±8.7	75.4±9	83.4±6[b]	87.3±12[e]	77.4±8.8	0.038	0.044	0.36
Total cholesterol (mg/dl)	212.5±36.2	217.3±38.1	208.8±33.5	223.2±40.8	228.1±42.3	217±36.9	234.5±41.2	237.5±44.3	230.2±39.1	0.74	0.21	0.69
HDL-cholesterol (mg/dl)	51.3±6.6	46.2±5.7	56.3±6.2	41.9±7.1[a]	38.7±6.5[d]	51.1±6.3[g]	38.7±6.2[b]	34.±6.8[e]	47.2±7.3[h]	0.034	0.038	0.047
LDL-cholesterol (mg/dl)	126.4±35	131.2±29.7	114.9±38.1	132.9±36.7	145.7±33.73	117.79±34.7	141.6±31.2	148.32±24.83	129.8±29.3	0.09	0.65	0.58
Triglyceride (mg/dl)	97.6±27.5	101.4±29.1	91.7±25.5	126.7±34.5	128.9±32.6	125.4±60.7	176.2±53.1[bc]	181.4±47.5[ef]	168.4±52.9[hi]	0.03	0.027	0.041
Hs-CRP (mg/l)	1.4 (0.78-1.83)	0.9 (0.6-1.7)	1.5 (0.95-1.95)	2.35 (1.33-3.53)[a]	2.2 (1.23-2.93)	3 (1.68-4.83)	2.95 (1.75-6.55)[b]	2.4 (1.4-4)[e]	3.2 (1.8-7.35)[h]	<0.0001	0.0062	0.0087
Fasting glucose	80.3±10.2	81.1±9.8	79.2±9.1	87.5±14.2	91.2±10.2	85.5±17.6	96.2±15.3[b]	97.5±17.5[e]	94.2±18.6[h]	0.044	0.047	0.04
HbA_{1c} (%)	4.8±0.6	4.9±0.5	4.6±0.4	5.1±0.8	5.2±0.6	5±0.7	5.4±0.9	5.5±0.7	5.3±1	0.21	0.33	0.26
Fasting Insulinemia (µU/ml)	6.4 (4.97-8.79)	6.6 (5.32-10.35)	5.48 (4.3-8.05)	13.9 (9.75-19.53)[a]	14.5 (10.05-24.93)	12.2 (8.7-18.17.93)[g]	15.8 (10.04-27.35)[b]	18.2 (10.23-35.8)[e,*]	14.3 (9.51-19.46)[h]	0.0002	0.011	0.0008
HOMA-IR	1.77 (1.48-2.91)	1.63 (1.43-2.5)	2.21 (1.56-3.19)	3.16 (2.17-5.34)	3.16 (2.17-5.34)	2.91 (1.56-3.81)	3.86 (2.31-8.43)[b]	3.86 (2.31-8.43)[e]	3.19 (2.02-4.56)	0.0052	0.047	0.15

Table 1 (continued)

Proinsulin (pmol/l)	5.43 (3.26-6.52)	5.91 (5.05-7.29)*	3.66 (2.06-5.59)	6.8 (4.41-8.51)	7.28 (6.78-9.52)*	3.53 (1.52-5.71)	8.19 (4.8-11.74)[b,c]	9.64 (5.78-13.66)[e, f, *]	4.87 (3.36-10.69)	0.0019	0.0049	0.13
Adiponectin (µg/dl)	6.26 (4.51-8.34)	4.52 (3.72-8.61)	7.24 (5.45-8.47)	4.31 (2.15-5.46)[a]	2.66 (1.63-4.69)[d, **]	5.42 (3.33-6.4)	3.48 (1.54-5.43)[b]	2.01 (1.42-3.54)[e, **]	5.13 (3.75-6.76)[h]	0.0004	0.0015	0.042
Leptin (ng/ml)	25.4 (10.8-37.1)	10.8 (9.95-15.55)**	33.15 (25.93-52.65)	30 (19.18-48.18)	29 (17.09-42.38)	41.5 (22.43-54.43)	40.05 (20.07-73.65)	32.1 (16.2-75.4)[e]	54 (27-73.1)[h]	0.042	0.047	0.039
Leptin/Adiponectin	4.21 (3.17-6.37)	3.2 (1.87-5.06)	5.12 (3.8-8.81)	6.46 (2.7-10.11)	5.49 (2.65-12.08)	6.73 (2.71-7.65)	8.12 (3.59-9.79)	7.28 (2.57-12.51)[e]	9.11 (4.76-13.75)[h]	0.029	0.024	0.039
CIMT (mm)	0.64±0.11	0.68±0.09*	0.6±0.08	0.75±0.16	0.76±0.14	0.74±0.12[g]	0.89±0.18[bc]	0.91±0.17[e,f]	0.86±0.14[h,i]	0.0005	0.0003	0.0001

*Values are means±SD and median (interquartile range). T–total, M–men, W–women; BMI–body mass index; SBP–systolic blood pressure; DBP–diastolic blood pressure; a) p<0,05 ,OW vs. L (total); b) p<0.05, OB vs. L (total); c) p<0.05, OB vs. OW (total); d) p<0.05,OW vs. L (men); e) p<0.05, OB vs. L (men); f) p<0.05 OB vs.OW (men); g) p<0.05, OW vs. L (women); h) p<0.05, OB vs. L (women); i) p<0.05 OB vs. OW (women); *-p<0.05 men vs. women; **-p<0.01 men vs. Women.*

Multiple regression analysis with CIMT as the dependent variable

We performed multiple regression analysis stepwise separately for obese and non-obese men and women. The following independent variables were included in the analysis: age, systolic blood pressure, leptin, adiponectin, leptin/adiponectin ratio, hs-CRP, HOMA-IR, fasting proinsulin, triglycerides, HDL-cholesterol, LDL-cholesterol, BMI. In obese men age (β=0.628, p<0.0001), leptin/adiponectin ratio (β=0.307, p=0.013) and hs-CRP (β=0.299, p=0.028) were independent predictors of IMT (R^2=0.577, R^2 adjusted=0.536) (table 2). In non-obese men age (β=0.382, p=0.019) and systolic blood pressure (β=0.334, p=0.039) were independent predictors of IMT (R^2=0.538, R^2 adjusted=0.39). In obese women leptin/adiponectin ratio (β=0.386, p=0.035) and systolic blood pressure (β=0.408, p=0.027) were independent predictors of IMT (R^2=0.408, R^2 adjusted=0.354) (Table 3). In non-obese women age (β=0.321, p=0.031) and systolic blood pressure (β=0.352, p=0.025) were independent predictors of IMT (R^2=0.491, R^2 adjusted=0.354).

Table 2

Multiple regression analysis for IMT with anthropometrical and biochemical parameters in obese men

Variable	Non-standardized regression coefficient	Standardized regression coefficient (β)	95% confidential interval	P
Age (years)	**0.015**	**0.628**	**0.072; 0.0229**	**<0.0001**
Systolic blood pressure	0.004	0.219	-0.0012; 0.0092	0.12
Leptin/adiponectin ratio*	**0.1014**	**0.307**	**0.0065; 0.2104**	**0.013**
Leptin	0.009	0.164	-0.041; 0.268	0.33
Adiponectin	-0.0032	-0.237	-0.0024; 0.0017	0.12
hs-CRP*	**0.2559**	**0.299**	**0.0305; 0.4811**	**0.028**
HOMA-IR*	0.19	0.284	-0.0079; 0.3798	0.062
Fasting proinsulin*	0.2061	0.2	-0.0916; 0.5037	0.17
Triglycerides	0.0006	0.147	-0.0019; 0.0007	0.38
HDL-cholesterol	-0.0048	-0.168	-0.0124; 0.0028	0.2
LDL-cholesterol	0.0009	0.115	-0.0023; 0.0013	0.51
BMI	0.0078	0.144	-0.0221; 0.0187	0.46

*log transformation because of the skewed distribution

Table 3

Multiple regression analysis for IMT with anthropometrical and biochemical parameters in obese women

Variable	Non-standardized regression coefficient	Standardized regression coefficient (β)	95% confidential interval	P
Age (years)	0.0048	0.238	-0.0029; 0.0127	0.21
Systolic blood pressure	**0.0063**	**0.408**	**0.0008; 0.0118**	**0.027**
Leptin/adiponectin ratio*	**0.0186**	**0.386**	**0.0015; 0.0357**	**0.035**
Leptin	0,1577	0,294	-0,036; 0,349	0,08
Adiponectin	-0,0072	-0,138	-0,0041; 0,0025	0,41
Hs-CRP*	0,045	0,117	-0,0267; 0,2216	0,48
HOMA-IR*	0,1157	0.173	-0.1431; 0.3745	0.36
Fasting proinsulin*	0.0091	0.227	-0.0356; 0.4172	0.24
Triglycerides	0.0004	0.103	-0.0011; 0.0017	0.57
HDL-cholesterol	-0.0006	-0.028	-0.0086; 0.0074	0.94
LDL-cholesterol	0.0007	0.124	-0.0014; 0.0052	0.46
BMI	0.007	0.166	-0.2587; 0.0107	0.39

*log transformation because of the skewed distribution

DISCUSSION

Obese women had significantly higher plasma levels of triglyceride, fasting glucose, hs-CRP, insulinemia, leptin, leptin to adiponectin ratio and lower plasma levels of HDL-cholesterol and adiponectin compared to lean women. Obese men had significantly higher plasma levels of triglyceride, fasting glucose, hs-CRP, fasting insulinemia, HOMA-IR, proinsulin, leptin, leptin to adiponectin ratio and lower plasma levels of HDL-cholesterol and adiponectin compared to lean men. In this study we show that CIMT increase with BMI, both in healthy men and women, without known cardiovascular disease. In univariate analysis in non-obese men age, systolic blood pressure and hs-CRP were significantly associated with CIMT and in obese men age, hs-CRP, systolic blood pressure, leptin to adiponectin ratio, proinsulin and HOMA-IR were significantly associated with CIMT. In univariate analysis in non-obese women systolic blood pressure and age were significantly associated with CIMT and in obese women systolic blood pressure, leptin to adiponectin ratio, age, HOMA-IR and leptin were significantly associated with CIMT. In multivariate analysis in obese men age, leptin to adiponectin ratio and hs-CRP are independent predictors of CIMT and in obese women leptin/adiponectin ratio and systolic blood pressure were independent predictors of CIMT. In multivariate analysis in non-obese men and women systolic blood pressure and age were independent predictors of CIMT.

Previous numerous studies have demonstrated a strong correlation between cardiovascular risk factors and common carotid IMT[28,34]. In a recent study, which included 3258 subjects (aged 45,22±3,63 years), 1404 men, participants in the study Coronary Artery Risk Development in Young Adults (CARDIA), Polak *et al.*[34] showed in a multivariate analysis a significant direct associations of CMIT with age, smoking, LDL-cholesterol, hypertension, male gender, fasting glucose. In our study in multivariate analysis in obese men age was an independent predictor of CIMT, in obese women systolic blood pressure was an independent predictor of CIMT, in non-obese men and women age and systolic blood pressure were independent predictors of CIMT.

There are data which have showed a positive relationship between BMI and CIMT, both in adults and children. De Michele *et al.*[35] showed in 310 middle-aged women a graded and independent association between general and abdominal obesity and preclinical carotid artery structural changes (increased CIMT and cross-sectional IM area). Lo *et al.*[29] found that in 99 healthy women (aged 24-59 year) obesity is associated with increased CIMT. Burke *et al.*[36] demosntrated in 6814 subjects, men and women (aged 45-84 years), from US, free of clinical CVD at baseline, participants in Multi-Ethnic Study of Atherosclerosis (MESA), a higher prevalence of coronary artery calcium, a greater CIMT and a greater left ventricular mass in the obese group compared to the normal body size group. Iannuzi *et al.*[37] showed in 147 healthy children (aged 6-14 year) that obese children have significantly increased CIMT and stiffness compared with control subjects. Urbina *et al.*[38] showed in 318 non-diabetic youth (182-lean and 136-obese), that obese, heathy subjects (age 17,9±3,3 years) have increased thickness of the common carotid artery and bulb compared to lean subjects.

There are studies which observed an independent negative association between adiponectin levels and CIMT. Iglseder *et al.*[32] demonstrated in a large population, without clinical manifestations of atherosclerosis and a small proportion of diabetic patients (4%), an independent negative association of adiponectin levels and CIMT, whereas no relationship with presence of atherosclerotic plaques was found. Lo *et al.*[29] show in healthy young and middle-aged women that adiponectin and sc abdominal adiposity are associated with CIMT. Pils *et al.*[33] described in 240 young subjects, 140 obese subjects (age 13,5±4,4 years) and 100 control subjects (14,4±4,4 years) that serum levels of adiponectin were significantly correlated with CIMT. In the present study in multivariate analysis we found no significantly correlation between adiponectin and CIMT.

Data from recent studies suggest that leptin/adiponectin ratio can serve as a clinical marker of atherosclerosis both in non-diabetic and diabetic subjects. In this study we obtained that leptin/adiponectin ratio is an independent predictor of CIMT in both obese and non-obese subjects. Finucane *et al.*[18] showed in 2097 non-diabetic subjects, 890 men and 1207 women, that the leptin/adiponectin ratio is a useful measure of insulin resistance. Zaletel *et al.*[19] and Oda *et al.*[20] suggest that leptin/adiponecti ratio is a more effective parameter of insulin resistance than

adiponectin, leptin and HOMA-IR in both non-diabetic and type 2 diabetic patients. Norata *et al.*[39] showed that the leptin/adiponectin ratio, together with age and glucose, is an independent predictor of IMT in healthy males and significantly correlated to body mass index, waist-to-hip ratio, systolic blood pressure, high-density lipoprotein, apolipoprotein A-I, glucose, and the homeostasis model of insulin resistance. Also Norata[39] showed that obese subjects had a significantly higher leptin/adiponectin ratio compared with nonobese subjects and subjects with metabolic syndrome had a significantly higher leptin/adiponectin ratio level compared with subjects without. We also noticed that obese subjects have higher leptin to adiponectin ratio, compared to non-obese subjects. Satoh *et al.*[40] suggest that the leptin/adiponectin ratio may serve as a potential atherogenic index in obese type 2 diabetic patients, because in this group of patients leptin/adiponectin ratio is more strongly correlated with pulse wave velocity (PWV) than leptin or adiponectin alone. Kotani *et al.*[41] showed in type 2 diabetic subjects that the leptin/adiponectin ratio, together with age, is an independent predictor of CIMT, especially in those who are 70 years old or younger. Takamura *et al.*[42] showed that leptin/high-molecular-weight adiponectin ratio is independently correlated with CIMT in men, but not in women. Kotani *et al.*[43] shown in a population of healthy older females that in multivariate analysis leptin/adiponectin ratio is not an independent predictor for CIMT.

In conclusion, in present study we identified differences regarding the predictors of CIMT in obese men and women. In our analyze leptin to adiponectin ratio was the only variable, which was an independent predictor of IMT in both obese, healthy middle-aged men and women. Further studies are warranted to evaluate whether modification of the leptin/adiponectin ratio could result in beneficial effects in terms of cardiovascular outcome.

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