

Risk factors of subclinical atherosclerosis in obesity and overweight

Alexescu Teodora Gabriela¹, Ciumarnean Lorena², Negrean Vasile³, Pfingstgraf Iulia Olimpia⁴, Lencu Codruta Claudia⁵, Toganel Razvan Dan⁶, Ioana Para⁷, Ionela Popovici⁸, Cornel Cheregi⁹

Abstract

Objective: To examine the relationship of carotid intima-media thickness with weight-gain, overweight and obesity.

Methods: The experimental, analytical study was conducted at the CF University Hospital, Cluj-Napoca, Romania, from 2012 to 2014, and comprised randomly selected in-patients from the Medical Ward. The patients were divided into normal-weight subjects in Group I and overweight and obese subjects in Group II. Intima-media thickness was measured by carotid Doppler ultrasound. Data was analysed using SPSS 13.

Results: Of the 111 subjects, Group I had 27(%) and Group II had 84(%) subjects. Mean carotid intima-media thickness was significantly greater ($p < 0.001$) in Group II compared to Group I, especially in those with metabolic syndrome ($p < 0.001$) and higher high-sensitivity C-reactive protein ($p < 0.05$). With the exception of Group II where there was a direct correlation ($p < 0.05$) between triglycerides and intima-media thickness, and an inverse correlation ($p < 0.05$) between high-density lipoprotein and intima-media thickness, no significant correlations were recorded ($p > 0.05$).

Conclusion: Intima-media thickness was found to be increased in asymptomatic overweight and obese subjects, significantly higher in those with associated metabolic syndrome and high levels of high-sensitivity C-reactive protein, as an indication of the presence of early, subclinical atherosclerosis.

Keywords: Carotid intima-media thickness, Obesity, Overweight, Cytokines, Subclinical atherosclerosis. (JPMA 70: 840; 2020). <https://doi.org/10.5455/JPMA.12075>

Introduction

In time, weight-gain leads to overweight and obesity, and the latter has become an increasingly frequent occurrence. The prevalence of obesity has doubled or even tripled in less than two decades, which is alarming in children where it reaches a percentage of 36% in some regions of Europe.¹ In 2008, approximately 1.5 billion people were overweight, about 500 million were obese, with an average, by gender, of 205 million men (193-217 million) and 297 million women (280-315 million);^{2,3} in 2013, two-thirds of adults were overweight, one-third being obese.⁴ Epidemiological data from 2016 look extremely worrying: over 1.9 billion adults were overweight (39%), over 650 million are obese (13%), 41 million children under 5 years old, and over 340 million children and adolescents aged 5-19 years were overweight or obese.⁴

Over the last few decades, a large number of studies have reported a direct relationship between increased intima-media thickness (IMT) and a higher cardiovascular risk. Two studies concluded that carotidian intima-media thickness is an independent predictor of coronary heart disease and stroke.^{5,6} The multi-ethnic study of atherosclerosis demonstrated that a significant and positive association existed between yearly mean common carotid artery IMT progression and risk of stroke.⁷ In a cohort study of 6453 men, the metabolically healthy obesity phenotype was associated with an increased risk of subclinical carotid atherosclerosis.⁸ In a 2015 study, a larger waist circumference (WC) and a higher diastolic blood pressure (DBP) were parameters independently associated with higher IMT in healthy young adult males.⁹ Adding carotid IMT measurement to the known cardiovascular risk factors has been proposed as a strategy to improve cardiovascular risk prediction for an individual.¹⁰

¹⁻⁸ University of Medicine and Pharmacy, Cluj Napoca, Romania;

⁹ University of Oradea, Romania.

Correspondence: Alexescu Teodora Gabriela. e-mail: teodora.alexescu@gmail.com

The current study was planned to examine the relationship of carotid IMT with weight-gain, overweight and obesity.

Patients and Methods

The experimental, analytical study was conducted at the CF University Hospital, Cluj-Napoca, Romania, from 2012 to 2014. After getting approval from the institutional ethics committee, subjects were randomly selected from about 7500 patients admitted to the Medical Ward of the hospital. A simple random method generated a starting point as the first patient (the 9th patient) and then every fifth number from this starting point was selected (the 14th patient, the 19th patient, and so on). All the patients selected by this method were included in the study after they furnished an informed consent and the absence of a diagnosis and/or clinical complaints of heart disease or any diagnosis interfering with survival over the next 2 years was ensured. The patients were divided into normal-weight (NW) subjects in Group I and overweight (OW) and obese (O) subjects in Group II. For each participant, a research sheet was prepared containing personal data like age and gender, personal and family medical history, anthropometric data, like weight, height and abdominal circumference, medication used, smoking and drinking status, daily physical activity, food habits, internet usage; objective exam and blood tests; carbohydrate metabolism-related data, like fasting blood glucose (normal rate [NR] = 80-100mg%), glucose tolerance test in suspected subjects performed with the KONELAB 60i device (an analyzer fully automated, with random access photometric system. It is the latest and most sophisticated model in the range of random access, fully automated photometric analyzers. Its advanced technology and new design offer efficiency and accuracy in analysis as well as convenience in use), using the enzymatic method, data on lipid metabolism, like total cholesterol (TC) (NR <200 mg%), high-density lipoprotein (HDL) (NR >40mg% for women and >50mg% for men), low-density lipoprotein (LDL) (NR <100mg%), non-HDL cholesterol (NR ≤130mg%), serum triglycerides (TG) (NR <150mg%) determined with the KONELAB 60i device using the enzymatic method, BP performed in both the arms and the ankles (NR <140/90mmHg), and carotid Doppler ultrasound with ALOKA PROSOUND SSD 4000 (pure-HD with 3 probes; Linear Probe UST-5524-7.5 of 7.5 MHz, with pulsed Doppler).

Patients with body mass index (BMI) 18.5-24.9kg/m² were

considered NW, BMI 25.0-29.9 kg/m² as OW and BMI ≥30kg/m² as O.¹¹

IMT was measured by carotid Doppler ultrasound using an ALOKA S4000 ultrasound machine in B mode, with a 7.5 MHz linear transducer, by scanning the circumference of the bilateral carotid artery and calculating the average of the maximum values obtained.¹²⁻¹⁴

Data was analysed using SPSS 13. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to verify the normality of distribution of continuous numerical variables. The differences between the mean values of continuous quantitative variables were assessed with the Student t-test, or the analysis of variance (ANOVA) test when several categories were present. The analysis of differences between the mean values of continuous variables whose distribution did not comply with the normality condition was carried out with the Mann-Whitney U test, or the Kruskal Wallis test when several categories were present. In order to analyse the difference between qualitative variables, the Z-test and chi-squared test were used. P<0.05 was considered statistically significant.

Results

Of the 111 subjects, Group I had 27(24.3%) and Group II had 84(75.7%) subjects. In Group II, there were 36(43%) OW patients, 33(39.2%) obesity grade I (O-I), 13(15.5%) O-II, and 2(2.3%) O-III patients.

The relationship between carotid IMT and weight-gain status was highly significant (p<0.001) between NW compared to both OW and O.

The mean value of IMT was significantly higher in OW, O-I and O-II patients compared to NW (Figure 1).

In patients with metabolic syndrome, mean ITM was significantly higher (p< 0.001).

An analysis of the average values of the studied serum cytokines (hsCRP, E-selectin, MCP-1) in metabolic syndrome patients with carotid intima-media thickness ≥ 0.9 mm (a cut-off value that is recognized as a definite cardiovascular risk factor) evidenced the fact that these were higher among overweight and obese patients compared to normal weight patients, with a highly significant statistical difference (p<0.001) in the case of the highly sensitive C-reactive protein (NW-SM vs SM with IMT>0.9/ 15 vs 37) (Figure 2).

Serum high-sensitivity C-reactive protein (hsCRP) in patients with carotid IMT ≥ 0.9mm was higher compared

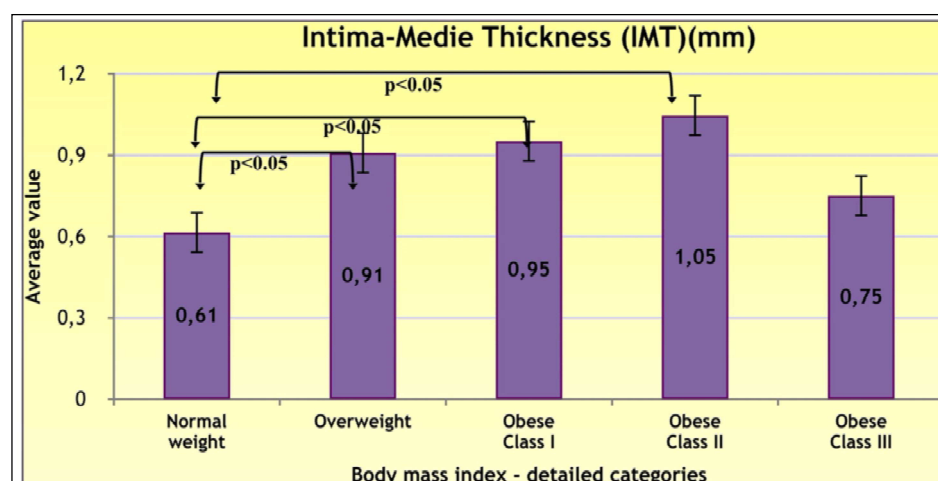


Figure-1: The relationship between intima-media thickness and detailed weight status.

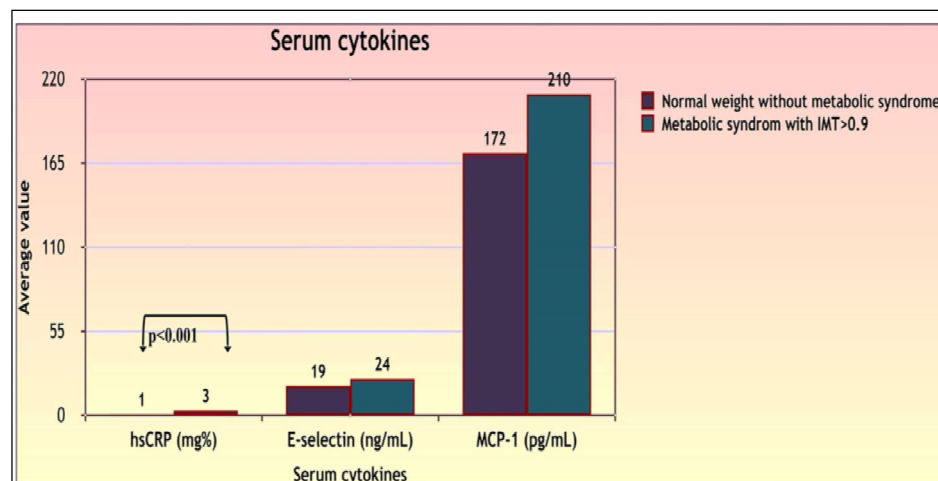


Figure-2: Serum cytokines according to weight status, metabolic syndrome and the mean value of carotid intima-media thickness.

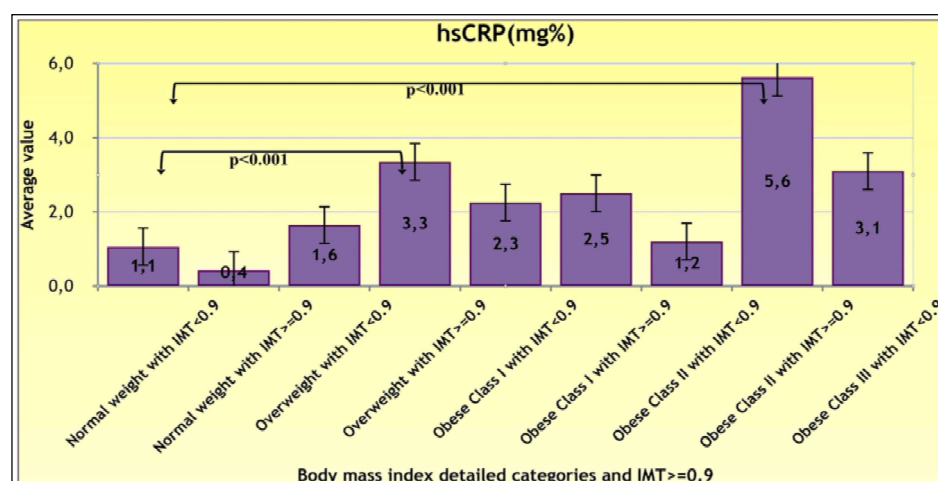


Figure-3: The mean hsCRP value according to detailed weight status and carotid intima-media thickness.

to patients with IMT < 0.9 mm ($p < 0.05$).

Mean values of hsCRP had a correlation with carotid IMT ≥ 0.9 mm ($p < 0.001$).

NW patients with IMT < 0.9 mm had a significantly lower mean hsCRP value ($p < 0.001$) compared to OW and O-II patients with IMT ≥ 0.9 mm (Figure 3).

Also, the mean E-selectin value was significantly lower ($p < 0.05$) in NW persons with IMT < 0.9 mm than in O-I and O-II persons with IMT ≥ 0.9 mm. In the case of monocyte chemoattractant protein-1 (MCP-1), although the same trend in conjunction with weight-gain was present, the differences were not statistically significant ($p > 0.05$).

With the exception of OW patients, where there was a direct correlation ($p < 0.05$) between TG levels and IMT, and an inverse correlation ($p < 0.05$) between HDL and IMT, no statistically significant correlations were recorded ($p > 0.05$).

Discussions

Available literature describes the fact that IMT is increased in patients with metabolic syndrome, which is similar to our data.¹⁵⁻¹⁷

A recent study shows that in middle-aged adults, information provided by pulse wave velocity and IMT can be, to some extent, similar with regard to arterial injury or in indicating subclinical atherosclerosis.¹⁸

Data on the association of carotid IMT with traditional cardiovascular risk factors is contradictory.

While some epidemiological studies have established that carotid IMT is a marker of subclinical atherosclerosis and is associated with classical risk factors for cardiovascular disease,¹⁹⁻²¹ other studies, like ours, failed to demonstrate a link between carotid IMT and lipid metabolism.²² The fact that no statistically significant correlations between average carotid IMT and lipid metabolism were recorded in the studied groups suggests that complex mechanisms are involved in the pathophysiology of early atherosclerosis, of which the most important is probably systemic inflammation.

Although since 2003, the European Society of Hypertension has recommended for hypertension management the use of carotid IMT measurements in high-risk patients to help identify damage in the target organs.²³ In 2010, the American Heart Association argued that the use of IMT in patients with intermediate risk is not satisfactory.²⁴

This study demonstrates that overweight and obese people, especially those with more associated components of metabolic syndrome, should be evaluated for subclinical atherosclerosis, and the cheapest way would be the non-invasive measurement of mean carotid IMT, in accordance with earlier data.²⁵

The study has its limitations as the MCP-1 gene polymorphism was not analysed. Also, a small number of morbidly obese subjects were included in the study because of the exclusion criterion that was dictated by a previous diagnosis of heart disease.

Conclusions

IMT was found to be increased in asymptomatic overweight and obese subjects, significantly higher in those with associated metabolic syndrome and high levels of hsCRP, as an indication of the presence of early, subclinical atherosclerosis.

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Conflict of Interest: None.

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References

- James PT, Rigby N, Leach R. International Obesity Task Force. The obesity epidemic, metabolic syndrome and future prevention strategies. *Eur J Cardiovasc Prev Rehabil* 2004; 11: 3-8.
- O'Riordan M. Global Obesity Rising, But Blood-Pressure and Cholesterol trends Suggest Some Good News. [Online] [Cited 2018 Oct 10]. Available from: URL: <http://www.medscape.com/viewarticle/736886>.
- Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011; 377: 557-67.
- CDC. Overweight and Obesity: adult overweight and obesity. [Online] [Cited 2018 Oct 10]. Available from: URL: <http://www.cdc.gov/obesity/adult/index.html>.
- Simon A, Megnien JL, Chironi G. The value of carotid intima-media thickness for predicting cardiovascular risk. *Arterioscler Thromb Vasc Biol* 2010; 30: 182-5.
- Qu B, Qu T. Causes of changes in carotid-intima thickness: a literature review. *Cardiovascular Ultrasound* 2015; 13: 46.
- Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen TP, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet* 2012; 379: 2053-62.
- Kim TJ, Shin HY, Chang Y, Kang M, Jee J, Choi YH, et al. Metabolically healthy obesity and the risk for subclinical atherosclerosis. *Atherosclerosis* 2017; 262: 191-7.
- Clemente G, Mancini M, Giacco R, Tornatore A, Ragucci M, Riccardi G. Visceral adiposity and subclinical atherosclerosis in healthy young men. *Int J Food Sci Nutr* 2015; 66: 466-70.
- Baldassarre D, Hamsten A, Veglia F, de Faire U, Humphries SE, Smit AJ, et al; IMPROVE Study Group. Measurements of carotid intima-media thickness and of inter-adventitia common carotid diameter improve prediction of cardiovascular events: results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population) study. *J Am Coll Cardiol* 2012; 60:1489-99.
- Tsigos C, Hainer V, Basdevant A, Finer N, Fried M, Mathus-Vliegen E, et al; Obesity Management Task Force of the European Association for the Study of Obesity. Management of obesity in adults: European clinical practice guidelines. *Obesity Facts* 2008; 1: 106-16.
- Bots ML, Evans GW, Riley WA, Grobbee DE. Carotid intima-media thickness measurements in intervention studies: design options, progression rates, and sample size considerations; a point of view. *Stroke* 2003; 34: 2985-94.
- Lane HA, Smith JC, Davies SJ. Noninvasive assessment of preclinical atherosclerosis. *Vasc Health Risk Manag* 2006; 2: 19-30.
- Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim Carotid Intima-Media Thickness Consensus (2004-2006). An Update on Behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium. *Cerebrovasc Dis* 2007; 23: 75-80.
- Min-Soo A, Jang-Young K, Young JY, Seong-Yoon K, Sang-Beak K, Kyoung-hoon L, et al. Cardiovascular Parameters Correlated with Metabolic Syndrome in a Rural Community Cohort of Korea: The ARIRANG Study. *J Korean Med Sci* 2010; 25: 1045-52.
- Alexescu TG, Cozma A, Sitar-Taut A, Negrean V, Handru MI, Motocu M, et al. Cardiac Changes in Overweight and Obese Patients. *Rom J Intern Med* 2016; 54: 161-72.
- Leite A, Santos A, Monteiro M, Gomes L, Veloso M, Costa M. Impact of overweight and obesity in carotid intima-media thickness of Portuguese adolescents. *Acta Paediatr* 2012; 101: e115-21.
- Koivisto T, Virtanen M, Hutri-Kähönen N, Lehtimäki T, Jula A, Juonala M, et al. Arterial pulse wave velocity in relation to carotid intima-media thickness, brachial flow-mediated dilation and carotid artery distensibility: The Cardiovascular Risk in Young Finns Study and the Health 2000 Survey. *Atherosclerosis* 2012; 220: 387-93.
- O'Leary DH, Bots ML. Imaging of atherosclerosis: carotid intima-media thickness. *Eur Heart J* 2010; 31:1682-9.

20. Khan SP, Ahmed KZ, Yaqub Z, Ghani R. Carotid intima-media thickness correlation with lipid profile in patients with familial hypercholesterolemia versus controls. *J Coll Physicians Surg Pak* 2011; 21: 30-3.
 21. Caie Y, Zhiqiang S, Yunpeng L, Junping A, Qiyu S, Yaping T. The correlation between serum lipid profile with carotid intima-media thickness and plaque. *BMC Cardiovasc Disord* 2014; 14: 181.
 22. Abd El-Hafez H, Elrakhawy MM, El-Baiomy AA, El-Eshmawy MM. Carotid Intima Media Thickness Is Independently Associated with Male Gender, Middle Age, and IGF-1 in Metabolically Healthy Obese Individuals. *ISRN Obesity* 2014; 2014: 545804.
 23. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21: 1011-53.
 24. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2010; 122: 2748-64.
 25. Kasliwal RR, Bansal M, Desai D, Sharma M. Carotid intima-media thickness: Current evidence, practices, and Indian experience. *Indian J Endocrinol Metab* 2014; 18: 13-22.
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