

Obesity is Linked with Inflammation-Evaluation of Subclinical Inflammatory Status in Obese Patients

Roxana Maria Livadariu^{1,2}, Daniel Timofte^{1,2*}, Radu Dănilă^{1,2}, Ana Maria Sîngeap^{2,3}, Daniela Constantinescu^{2,4} and Anca Trifan^{2,3}

¹Department of Surgery, "St. Spiridon" Hospital, Iași, Romania

²Grigore T. Popa University of Medicine and Pharmacy, Iași, Romania

³Department of Gastroenterology, "St. Spiridon" Hospital, Iași, Romania

⁴Department of Immunology, "St. Spiridon" Hospital, Iași, Romania

Abstract

Background: Obesity is one of the most important public health; it seems that inflammation is a pathogenic pathway between obesity and its associated comorbidities. The aim of the study was to evaluate the status of serum inflammatory markers in a group of obese patients hospitalized for bariatric surgery.

Materials and methods: We performed a retrospective study on 64 obese patients successively hospitalised in our Surgical Unit between November 2014 and November 2016. All patients received a full evaluation including medical and personal history, complete clinical examination, and anthropometric measurements as well as general and special biological tests. The inflammatory status of each patient was evaluated by serum values of fibrinogen, CRP, Leptin and NLR and PLR scores. Insulin resistance was assessed by the homeostasis model assessment of insulin resistance index. We noted the presence of metabolic syndrome and its components and also the presence of obstructive sleep apnea syndrome.

Results: 62.5% of patients had ≤ 45 years and the number of male patients was significantly lower (23.4%) than the number of females. The mean value of BMI was 45.06 ± 6.67 SD and the mean value of waist circumference was $133.39 \text{ cm} \pm 17.47$ SD. The mean values of serum inflammatory markers (fibrinogen, CRP and leptin) were abnormally elevated. There was a directly proportional relationship between the increasing of waist circumference and serum fibrinogen ($p=0.04$) and CRP ($p=0.003$) variation. Elevated fibrinogen values correlated with MS, DM II and OSA. Increased leptin values correlated with BMI, HOMA IR and OSA.

Conclusion: Elevated serum values of fibrinogen and CRP correlate especially with abdominal obesity, quantified by waist circumference, while increased pathological values of serum leptin correlates also with BMI. Of all inflammatory markers assessed in the study, elevated fibrinogen appear to be most sensitively related to the presence of MS, OSA and DM II.

Keywords: Obesity; Inflammatory markers; Metabolic syndrome; Diabetes type 2; Obstructive sleep apnea

Introduction

Obesity is nowadays one of the most important public health issues around the world, due to its increasing prevalence and its associated comorbidities, which involve important mortality and significant costs. It is already stated that obesity associates a low grade chronic inflammation although the pathogenic mechanisms underlying this phenomenon are not fully elucidated. The importance of the inflammatory status in obese patients is primarily related to the risk of carcinogenesis, enhanced by the secretion of adipokines and promotion of inflammatory pathways [1]. The central pathogenic phenomenon underlying the link between obesity and inflammation is insulin resistance (IR), as the increased secretion of active adipokines by excessive adipose tissue interfere with the anti-inflammatory effect of insulin, which will promote inflammation [2].

The aim of the study was to evaluate the status of serum inflammatory markers in a group of obese patients with medical indication of bariatric surgery. We also aimed to define to what extent the pathological changes in serum markers of inflammation are influenced by anthropometric indices and by the presence of associated comorbidities to obesity, such as metabolic syndrome and its components (MS) and obstructive sleep apnea (OSA).

Materials and Methods

We performed a retrospective study on 64 obese patients successively hospitalised for bariatric surgery in our Surgical Unit between November 2014 and November 2016. We only included patients over 18 years with

medical indication of bariatric surgery. Patients diagnosed with acute or chronic infections were excluded; we also excluded the patients known to have chronic medical conditions that could affect the inflammatory status. All patients signed the Informed Consent approved by the Ethics Committees of the University of Medicine and Pharmacy "Gr.T. Popa" Iași before joining the study. All patients received a full evaluation including medical and personal history, complete clinical examination, anthropometric measurements (BMI calculated by formula $G \text{ (kg)}/T^2 \text{ (cm)}$) and waist circumference measured in centimeters-half point between the last coast and iliac crest) as well as general and special biological tests.

Blood samples were collected in the morning of surgery in order to measure routine and special biological tests. Insulin resistance was assessed by the homeostasis model assessment of insulin resistance index ($\text{HOMA-IR} = \text{fasting blood glucose (mg/dl)} \times \text{fasting insulinemia}$

***Corresponding author:** Daniel Timofte, MD, PhD, Department of Surgery, 3rd Surgical Unit, "St. Spiridon" Hospital, Bd. Independenței, No 1 Iași, România, Tel: +40(0)232240822; E-mail: dantimofte@yahoo.com

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(mU/L)/405). The values of C Reactive Protein (CRP) and serum fibrinogen, NLR and PLR scores (obtained by dividing the number of neutrophils and platelet counts by the number of lymphocytes) were noted. Leptin dosing was performed by the enzyme-linked immunosorbent assay (ELISA) using an SANOFI Pasteur ELISA, with HRP-labelled antibody sandwich ELISA, with 7.36 ± 3.73 ng/ml and for men 3.84 ± 1.79 ng/ml. Among the comorbidities, we noted the presence of type II diabetes (DM II), dyslipidemia and hypertension-as constitutive parts of the metabolic syndrome, but also the presence of obstructive sleep apnea syndrome-according to the pneumological reports.

The database was completed using Microsoft Excel 2013 version and the statistical analysis was performed in SPSS V.19.0. Continuous variables were expressed using mean, median and standard deviation (SD) values. Significance level (p-value) was considered to be 0.05 (5%) with 95% probability (confidence interval). The regression analysis was used for estimating the relationships among different variables; the statistical significance of every model was verified using the t-Student, the ANOVA test or chi-square test.

Results

Considering age as a categorical variable with 45 years threshold, in our study group there was a higher percentage (62.5%) of patients aged ≤ 45 years. The number of male patients was significantly lower (23.4%) than the number of females (76.6%). All patients enrolled in the study had BMI >35 , with a mean value of 45.06 ± 6.67 SD, ranging between 35 and 67 kg/m². The mean value of waist circumference was 133.39 cm ± 17.47 SD, ranging between 89 and 159 cm.

The inflammatory status of each patient was evaluated by serum values of fibrinogen, CRP, Leptin and NLR and PLR scores. As showed in Table I, the mean values of serum inflammatory markers were abnormally elevated. Leptin: 54.017 ng/ml ± 37.32 SD, Fibrinogen: 403.64 mg/dl ± 48.53 SD, CRP: 0.89 mg/dl ± 0.86 SD, suggesting the existence of a subclinical inflammatory state in our group of patients.

We used the regression analysis to evaluate the possible influence of anthropometric indexes on serum values of inflammatory markers (Figure 1) and the results showed that there is a directly proportional relationship between variation of waist circumference and serum

fibrinogen ($p=0.04$) and between waist circumference and CRP values variation ($p=0.003$). As showed in Figure 2, there is also a direct proportional relationship between the value of the serum leptin and the waist circumference, statistically significant when tested using ANOVA test ($p=0.01$). Concerning the BMI value, the regression analysis showed that there is a directly proportional relation between serum fibrinogen and PCR values variation and BMI, with no statistical significance in the studied group. The only statistically significance ($p=0.05$) was noted in the directly correlation between BMI and leptin serum values (Figure 3). The results also showed that the increased values of anthropometric indexes have no influence on PLR and NLR variation.

When assessing the correlations between serum markers of inflammation and MS and its components, we noticed that elevated serum fibrinogen values correlated ($p=0.04$) with MS (Table II). We also noted that in patients with DM II, the mean serum levels of fibrinogen, leptin and CRP are within pathological limits and higher than in non-diabetic patients (Table III). Continuing with the evaluation of inflammatory markers in relation to pathological changes of glucose metabolism, the regression analysis showed that between the variation of the serum values of fibrinogen and CRP on the one hand and the variation of HOMA IR value on the other hand there is a directly proportional relationship. Testing the results using the ANOVA test did not reveal statistical significance. In contrast, the directly proportional relationship between increasing in serum leptin and HOMA IR values (Figure 4) was statistically significant in the studied group ($p=0.04$).

In our study, we observed that the mean values of serum Fibrinogen, CRP and leptin are higher in the patients diagnosed with OSA, mean values exceeding the upper limit of normal in this group comparing with the non-OSA group. Both elevated plasma fibrinogen ($p=0.004$) and elevated serum leptin values ($p=0.007$) were positively and significantly correlated with the presence of OSA (Table IV).

Discussion

Chronic inflammation specific to patients with obesity and SM has some special features, as there is no involvement of autoimmune diseases or infectious pathologies that could induce significant damage to an organism.

Table I: Inflammatory markers values in obese patients.

	Mean	95% CI		Median	SD	Min	Max
		Min.	Max.				
Leptin	54.017	44.69	63.34	44.40	37.32	6.70	187.50
PLR	115.87	108.06	123.68	113.20	31.26	52.66	236.00
NLR	2.10	1.91	2.28	2.03	0.74	1.01	5.10
Fibrinogen	403.64	391.52	415.77	406.50	48.53	288.00	500.00
CRP	0.89	0.67	1.10	0.51	0.86	0.20	4.60

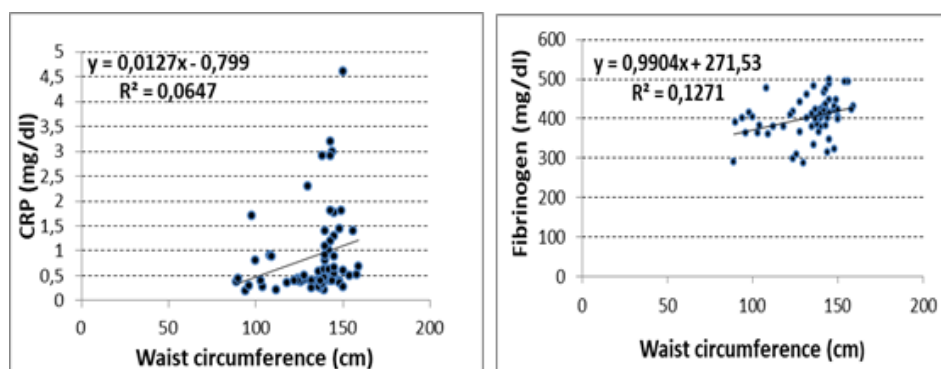


Figure 1: Regression analysis: fibrinogen and CRP values vs. waist circumference.

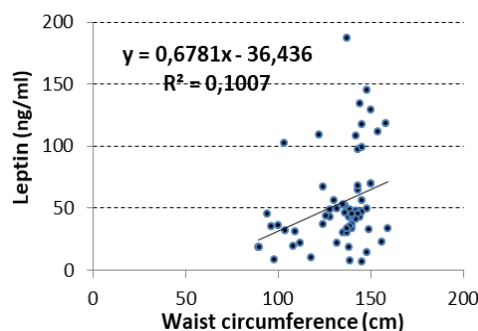


Figure 2: Regression analysis: leptin serum values vs. waist circumference.

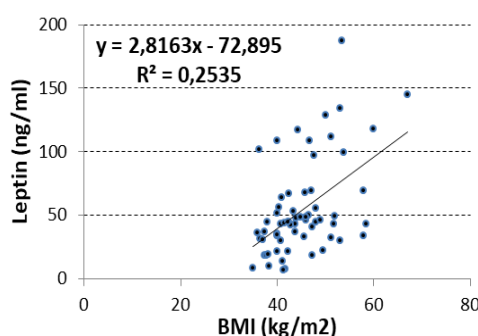


Figure 3: Regression analysis: leptin values vs. BMI values.

Table II: Differences between inflammatory serum markers in relation to MS.

Biological inflammatory marker	MS	Mean	95% CI		Std. Dev.	Min	Max	Sig.
			Min.	Max.				
Fibrinogen	Abs.	392.29	374.30	410.29	51.57	288.00	492.00	0.04
	Pres.	416.50	400.79	432.21	42.08	290.00	500.00	
PLR	Abs.	114.82	105.75	123.90	26.01	63.00	188.70	0.77
	Pres.	117.06	103.34	130.78	36.75	52.66	236.00	
NLR	Abs.	2.03	1.82	2.24	0.60	1.03	3.72	0.42
	Pres.	2.18	1.85	2.51	0.89	1.01	5.10	
CRP	Abs.	0.90	0.59	1.21	0.89	0.20	3.20	0.92
	Pres.	0.88	0.56	1.20	0.86	0.22	4.60	
Leptin	Abs.	50.32	38.98	61.67	32.51	7.91	145.20	0.40
	Pres.	58.21	42.41	74.00	42.31	6.72	187.50	

Table III: Differences between serum inflammatory markers in relation to DM II.

Inflammatory marker	DMII	Mean	95% CI		Std. Dev.	Min.	Max.	T-test p-Sig.
			Min.	Max				
Fibrinogen	Abs.	398.17	384.29	412.05	49.85	288	500	0.06
	Pres.	427.33	405.17	449.49	34.88	363	493	
PLR	Abs.	116.15	107.46	124.84	31.20	62.23	236.00	0.88
	Pres.	114.64	93.77	135.52	32.85	52.66	179.40	
NLR	Abs.	2.12	1.9173	2.3396	0.758	1.01	5.10	0.53
	Pres.	1.97	1.5226	2.4341	0.717	1.10	3.50	
PCR	Abs.	0.806	0.5931	1.0207	0.768	0.20	3.20	0.10
	Pres.	1.25	0.4973	2.0127	1.19	0.22	4.60	
Leptin	Abs.	53.60	43.610	63.592	35.88	10.2	187.5	0.85
	Pres.	55.81	27.370	84.264	44.77	6.7	118.0	

The results of our study showed that the increased serum inflammatory markers values (Fibrinogen, CRP and Leptin) directly correlated with obesity, especially abdominal obesity quantified by waist circumference. The variation of the CRP and cytokines serum values (IL 6) proportional to the anthropometric index variation and the distribution of adipose tissue has been demonstrated by other

authors [3]. The pathogenic mechanisms explaining this link are related to the capability of the abdominal excessive adipose tissue to induce chronic inflammation through abnormal production of cytokines, chemokines, acute phase proteins and other mediators of inflammation, and through activating alternative inflammatory pathways [4].

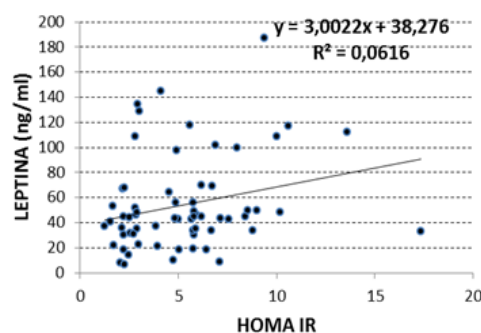


Figure 4: Regression analysis of serum leptin value vs. HOMA-IR value.

Table IV: Mean values of serum fibrinogen, CRP and leptin are higher in the patients diagnosed with OSA.

OSA		Mean	95% CI		Dev. Std.	Min	Max	Sig.
			Min	Max				
Fibrinogen	Abs	380.23	359.95	400.51	45.74	288.00	475.00	0.004
	Pres	415.90	401.62	430.19	45.83	290.00	500.00	
PLR	Abs	122.73	110.97	134.48	26.52	77.08	188.70	0.20
	Pres	112.28	101.93	122.63	33.21	52.66	236.00	
NLR	Abs	2.06	1.75	2.36	0.69	1.10	4.20	0.74
	Pres	2.12	1.88	2.37	0.78	1.01	5.10	
PCR	Abs	0.82	0.43	1.21	0.87	0.20	3.20	0.64
	Pres	0.93	0.65	1.20	0.88	0.22	4.60	
Leptin	Abs	44.28	34.71	53.85	21.59	18.20	102.00	0.007
	Pres	59.12	45.81	72.43	42.72	6.72	187.50	

Regarding NLR and PLR scores, literature data supports correlations between these-as markers of inflammation and obesity [5]. Our study results do not confirm the importance of these scores as markers of inflammation in obese patients.

Analyzing the correlations between the presence of MS and the changes in serum markers of inflammation, we found that the mean serum values of fibrinogen and leptin are pathologically elevated in patients with diagnosed MS, and the correlation between elevated fibrinogen and MS was statistically significant ($p=0.04$). Other authors who studied these relationships concluded that the connection between obesity, inflammation and MS is related to the insulin resistant, hypertrophied and dysfunctional adipocytes of the obese patients; the excessive fatty tissue is not metabolically inert, as it is characterized by an enhanced release of proinflammatory factors that will further support chronic inflammation through lipotoxicity and oxidative stress [6]. Elevated serum fibrinogen in connection with MS and obesity is even more important since hyperfibrinogenemia increases the cardiometabolic risk, with authors claiming that this is even a component of SM [7].

Since the glucose metabolic disorders, either in the form of IR or in the form of constituted DM II are important components of MS and involve complex pathogenic mechanisms that interfere with the rest of the SM components, we studied the possible correlations between the imbalance of carbohydrate metabolism and changes in serum inflammatory markers. In our study group, the mean values of fibrinogen ($p=0.06$) and leptin were higher in patients with diagnosed DM II. The regression analysis showed a direct relationship between the increase of fibrinogen and PCR serum values and HOMA IR variation, but no statistical significance was noted. The only statistically significant correlation was recorded for the proportional regression of leptin serum values in relation to those of HOMA-IR ($p=0.04$). Current literature unambiguously supports the link between hyperfibrinogenemia and DM II and this correlation is considered one of the main pathogenic factors involved in micro- and macroangiopathic complications of DM II development [8,9].

OSA is another comorbidity intensively associated to obesity. In this study we tried to find out to what extent the serum values of the studied inflammatory markers are correlated with OSA. Many authors have already demonstrated the link between OSA, its severity and inflammation, using common inflammatory biomarkers such as fibrinogen, PCR, TNF α , IL 6 and even showing reduction in inflammation biological status with OSA treatment [10,11]; also, the evaluation of inflammation by modern biomarkers involved in endothelial dysfunction (Pentraxin 3, Nesfatin 1) revealed the same direct relationship between their increase and the existence of OSA [12]. The results obtained in our study group support the link between the increased inflammatory markers and OSA. The mechanism involved in inflammation induced by OSA is primarily a direct one, related to the episodes of intermittent hypoxia and hypercapnia leading to activation of hypoxia induced factor 1 (HIF1) and nuclear factor κ B (NF- κ B), a transcription factor that participates in the immune response to infection. However, these mechanisms are intricately with other pathways activated by the presence of OSA, such as sympathetic stimulation that will lead to IR installation and increased FFA release, which contributes to the activation of inflammatory pathways to endothelial dysfunction. Thus, a vicious circle is installed in which each of the components is maintained and stimulates by each other [12].

Conclusion

Patients with obesity are characterized by a subclinical inflammatory status. Elevated serum values of fibrinogen and CRP correlate especially with abdominal obesity, quantified by waist circumference, while increased pathological values of serum leptin correlates also with BMI. Of all inflammatory markers assessed in the study, elevated fibrinogen appear to be most sensitively related to the presence of MS, OSA and DM II.

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Conflict of interest

Authors have no conflict of interest to disclose.

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