Clinical and Biological Study on the Relevance of Hiperfibrinogenemyme in Cardiovascular Pathology of the Obez Patient

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Obesity is a major public health problem, being the second leading cause of death that can be prevented after smoking. Currently, more than 1 billion people have body mass overweight (overweight) and over 300 million suffer from obesity. In the next two decades, the number may double, which will lead to a significant increase in associated pathology, and the average life span of obese patients is 8-10 years shorter than normal subjects [1, 2]. The prevalence of obesity and overweight increases practically in all countries and age groups in the world, and the economic cost of obesity is estimated to be 2-7% of all health expenditure [4]. Adipose tissue, and in particular visceral intraabdominal adipose tissue, is a metabolic active endocrine organ capable of synthesizing and releasing into the blood a wide variety of peptidic and non-peptidic compounds that may play a role in cardiovascular homeostasis.

Keywords obesity, coronary heart disease, hiperfibrinogenemyme, pro-inflammatory status

Excessive adipose tissue is associated with an increase in the production of free fatty acids with hyperinsulinism, insulin resistance, hypertension and dyslipidemia [3, 6].

Increased body weight is associated with increased mortality and total morbidity due to cardiovascular disease, partly mediated by increased blood pressure and cholesterol, lowering HDL-cholesterol and increasing the likelihood of diabetes.

Voluntary weight loss in obese patients may prevent or reduce risk factors associated with cardiovascular disease.

A weight reduction is required in all obese people (BMI $\geq$ 30 kg / m^2) and should be considered in overweight persons (BMI $\geq$ 25 and $<$30 kg / m^2).

Men with a waist circumference of 94-102 cm and women with a waist circumference of 80-88 cm should not increase in extra weight.

At a waist circumference of over 102 cm in men and over 88 cm in women we recommend a weight loss [3, 7]

Epidemiological studies have confirmed in recent years that patients with elevated basal plasma levels of fibrinogen are at high risk of developing coronary artery disease and myocardial infarction [10, 12].

The predictive value of fibrinogenemia determinations on cardiovascular risk in men and women was demonstrated by prospective studies in the US and European countries

Increased plasma fibrinogen is an indirect risk factor for coronary artery disease [12]

Elevated levels may reflect some of the following: coronary artery inflammation in response to infectious agents, the severity of inflammatory response in atherosclerotic vessels, the extent of inflammation associated with myocardial ischaemia, the extent of inflammation associated with myocardial necrosis, the amount and activity of circulating proinflammatory cytokines [8, 9] .

Experimental part

The group studied comprised 172 obese patients, to which we evaluated the degree of obesity (depending on CMA and BMI), we compared gender, age, we evaluated cardiovascular function (presence of hypertension, ischemic coronary artery disease, arteriopathy (by blood glucose, uric acid, total cholesterol, LDL and HDL cholesterol and triglycerides) and we also evaluated the thyroid and corticotropic axis by TSH, FT4, ACTH dosing and cortisol.

To assess cardiovascular risk in both women and men, we determined fibrinogen, knowing that many epidemiological studies have shown that patients with elevated plasma levels are at increased risk of coronary artery disease and myocardial infarction.

Methods of statistical and mathematical processing

For data processing, SPSS, specialized in statistical statistical calculations, produced by SPSS and the Data Analysis module of MICROSOFT EXCEL, together with the XLSTAT suite for MS Excel.

EXCEL patient data recording produced the baseline database from which the significant aspects of this study were extracted.

The actual processing was done with the help of:

-CrossTab, BasicTables, General Tables, Correlate, Regression, and Analyzer Factor, SPSS

- Pivot Tables, Functions-Statistical and Chart commands from MS Excel, and commands from the XLSTAT module for the ANOVA and Cramer tests.

Qu square test was used to interpret incidence tables; the data were appreciated from the point of view of the dependence between the two classification factors, retaining only the results below 5%, considered a sufficient materiality threshold.

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The test shows whether there is any relationship (mutual influence) between the two factors analyzed by the scorecard.

The quadratic test for the dependence between two factors, the test result for the data from the incidence tables was calculated, a result that was compared to the threshold value indicating a significant dependence (95% or 99% threshold) or a high significant dependence threshold of 99.9%) between the two classification factors.

$$\chi^2 = \sum_{i=1}^{n} \frac{(|O_i - E_i|)^2}{E_i}$$

O- observed frequency, E- theoretical frequency

The Chi square test is valid if at least 80% of the probable frequencies exceed 5 and all probable frequencies exceed 1.

For small samples, the Yates correction, also known as Continuity Correction, may be used, which involves subtracting 0.5 units of the difference between observed and probable frequencies in the Chi square counter (of the formula) before lifting at square; thus, the Chi square value decreases.

Chi square (of formula) before picking up square; thus, the Chi square value decreases. By subtracting the value of Chi square, the chance that the null hypothesis will be rejected decreases, so the risk of making a type I mistake (rejecting the null hypothesis when it is actually true) drops significantly.

However, it increases the risk of a type II error (accepting a false assumption when it is in fact false).

Some statisticians recommend using the continuity correction for a 2x2 contingency table.

Others are opposed to correction. In the medical literature, the Chi square test applies both with and without correction.

We used the following interpretation of the p values, provided directly by the program with which statistical data processing is performed, by applying the above test.

- p <0.05, the difference between the two media is significant (S).
- p <0.01, the difference between the two media is highly significant (HS).
- p <0.001, the difference between the two media is very high (VHS).
- p> 0.05, the difference between the two media is insignificant (NS).

The Cramer test verifies the association power between two nominal factors and is used for tables with multiple rows and columns (for tables 2x2 the phi coefficient is preferred), more precisely measures if each category of one of the factors is preferentially associated with one of the categories of the other factors.

The result of this test is recorded with V.

$$V = \sqrt{\chi^2 / \min(r-1, c-1)}$$

where r and c are no. of rows and columns in the table of incidence studied.

The Student t test of averaging for two batches proposes two statistical assumptions:

- H0 hypothesis (or null hypothesis): the difference between environments is incidental
- hypothesis H1: the difference between environments is statistically significant

The p result of the test is probability of making an error if the H0 hypothesis of the test is rejected, a result provided as a number between 0 and 1

If p is less than 0.05, we reject the hypothesis H0, the null, and admit that the hypothesis H1 is true.

In the media comparison test *t* (Student test), we used the following interpretation of the values of p, provided directly by the program with which the statistical processing of the data is performed, by applying the above test

- p <0.05, the difference between the two media is significant (S).
- p <0.001, the difference between the two media is very high (VHS).
- p> 0.05, the difference between the two media is insignificant (NS).

Dosing of fibrinogen

Patient preparation - junket (fast);

Specimen harvested - venous blood;

Vacuum container with 0.105 M sodium citrate (sodium citrate / blood ratio = 1: 9);

the pressure given by the garage must be between systolic pressure and diastolic pressure and should not exceed 1 min.

If venous puncture fails, a new attempt on the same vein can only be done after 10 min.

Processing required after harvesting - the sample will be centrifuged for 15 min at 2500g, followed immediately by plasma separation;

Sample Volume - Whatever Vacuum Allows; to prevent partial coagulation of the sample, the correct mixture of blood with the anticoagulant will be ensured by inversion of the tube

Causes of sample rejection - vacutainer that is not full; hemolyzed or coagulated sample;

Coagulometric method (Clauss): In the presence of an excess of thrombin, the coagulation time of a 1/10 diluted, low-platelet-bound citrate plasma is inversely proportional to the fibrinogen concentration;

Reference values: varies with age.

over 18 years: 200-400 mg / dL;

Critical values: <100 mg / dL; at values below 50 mg / dL, haemorrhagic events may occur after traumatic surgery. At values greater than 700 mg / dL repeated determinations after remitting the acute inflammatory process indicates an increased risk for coronary and cerebrovascular disease.

Results and discussions

The study was conducted at the County Emergency Hospital of Craiova, in the Diabetes and Nutrition Diseases Clinic, with a retrospective (observation sheet) and a prospective one (through direct supervision) over a 6-year period (2011-2017).

The casuistry presented is based on a number of 172 patients admitted to the Diabetes Clinic and Nutrition Diseases and subsequently monitored (all patients presented different degrees of obesity

Cases have been investigated by anamnesis, clinical examination based on a type-sheet and paraclinical examination (laboratory - usual tests, hormonal dosing, fibrinogen, Rx cordon pulmonary, ECG, cardiac ultrasound).

In all 172 patients, endocrine status was assessed, and after hormonal dosing the patients were grouped in 3 groups: group I - 89 patients did not have endocrine changes, group II - 61 were found with primary hypothyroidism (TSH increased by low FT4) and group III - 22 were detected with reactive hypercholesterolemia and secondary hypothyroidism (elevated ACTH and cotizole and low TSH and FT4).

Table 1

THE MEAN VALUES OF THE PARAMETERS STUDIED IN THE 172 PATIENTS INCLUDED IN THE STUDY

Parameter	Age	Uric acid	cholesterol	LDL	HDL	triglycerides	HS protein C	fibrinogen	TSH	FT4	Cortizol	ACTH	Glicemie	Insulinemie
Age														
Uric acid														
cholesterol	0.202	0.371												
LDL	0.221	**0.561**	**0.772**											
HDL		-0.327	-0.388	**-0.531**										
triglycerides		0.467	**0.571**	**0.694**	-0.403									
fibrinogen	0.388	0.428	**0.554**	**0.678**	-0.473	**0.609**	0.845							
TSH			0.218			-0.215								
FT4			-0.376						-0.247					
cortisol		0.260	0.354	0.374		**0.579**	0.294	0.328	-0.354					
ACTH		0.296	0.424	0.408		**0.545**	0.273	0.309			**0.720**			
glucose	0.323	0.218	0.384	0.456	-0.249	0.417	0.415	0.412	-0.238		0.257	0.232		

Age	Lot 1	Lot 2	Lot 3	Total
No	89	61	22	172
Minimum	42	48	47	42
Maximum	81	80	66	81
Average	60.65	61.28	55.55	60.22
Dev.std.	9.98	7.59	5.52	8.86
C.V.	16.46%	12.38%	9.93%	14.71%
Test Student	L1-L2	L1-L3	L2-L3	ANOVA
p=	0.67866	0.02285	0.00172	0.02632

Table 2
DISTRIBUTION OF PATIENT BATCHES BY AGE

Distribution by age group of patients in the three groups

In group I the mean age of patients was 60.65 years with a minimum of 42 years and a maximum of 81 years at a standard deviation of 9.98 (table 2).

In group II the average age was 61.28 years, with a minimum of 48 years and a maximum of 80 years at a standard deviation of 7.59.

In group III the mean age was 55.55 years with a minimum of 47 years and a maximum of 66 years at a standard deviation of 5.52.

Distribution by sex to the three lots

The gender distribution in the three lots was the following (tables 3.4):

-In group I we had 50 women (56.18%) and 39 men (43.82%),

-in lot II we had 50 women (81.97%) and 11 men (18.03%),

-in lot III we had 18 women (81.82%) and 4 males (18.18%).

So we had a total of 118 women (68.60%) and 54 men (31.40%) enrolled in the study

The Chi square test (at a square square of 25,753) showed that there is no different gender distribution between the three lots, and the Cramer test showed that there is no preferential association between batches and a given sex (table 3, fig. 1).

Table 3
DISTRIBUTION BY GENDER

Sex	Ladies	men	Total
Lot 1	50	39	89
Lot 2	50	11	61
Lot 3	18	4	22
Total	118	54	172

Determining obesity by BMI and CFA

Batch distribution by BMI (table 4):

-In group I we had 36 patients (40.45%) with grade I obesity (BMI = 30-34.9 kg / m^2), 39 patients (43.82%) with grade II obesity (BMI = 35-39, 9 kg / m^2) and 14 patients

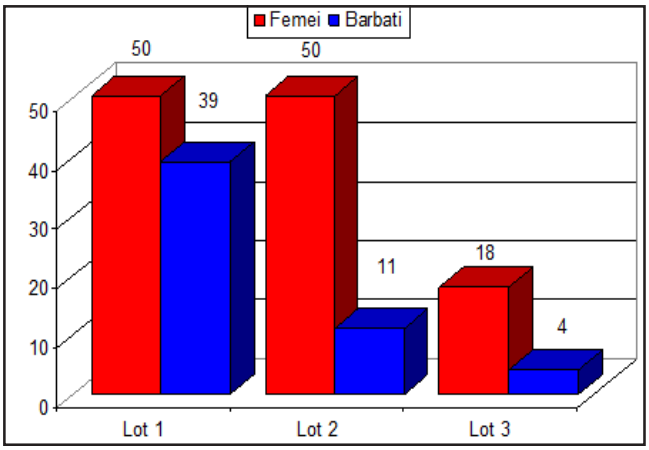

Fig 1. Graphic representation of patients in the three groups by gender

(15.73%) with grade III obesity (BMI greater than or equal to 40 kg / m^2);

- in group II we had 23 patients (37.70%) with the first degree of obesity, 24 patients (39.34%) with grade II obesity and 14 patients (22.95%) with grade III obesity;

- in group III we had no patient with grade I obesity, we had 13 patients (59.09%) with grade II obesity and 9 patients (40.91%) with grade III obesity.

Table 4
THE DISTRIBUTION BY OBESITY OF THE PATIENTS FROM THE 3 GROUPS

IMC	IMC 1	IMC 2	IMC 3	Total
Lot 1	36	39	14	89
Lot 2	23	24	14	61
Lot 3		13	9	22
Total	59	76	37	172

At a square chunk of 15,455 we have a different distribution of the obesity grades in the three lots. In groups I and II, degrees I and II of obesity had an almost equal proportion (40.45% -43.82% and 37.70% -39.34% respectively), in the third group no patient had grade I obesity, with grade II obesity patients (59.09%) and 40.91% of patients with Grade III obesity (fig. 2).

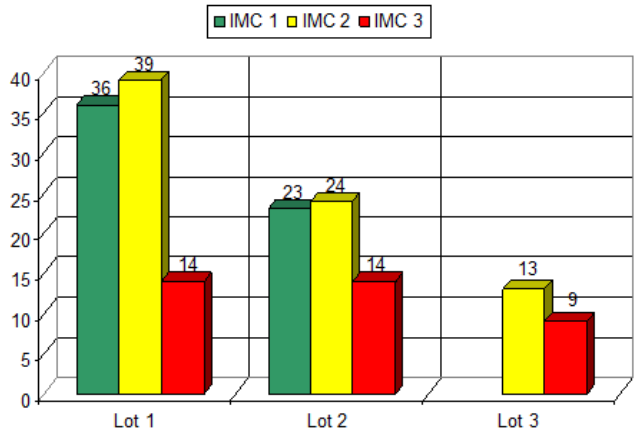

Fig. 2 Graphic representation of patients in the three groups according to BMI

Dosage of fibrinogen

I mention that in the patients included in the study we excluded any possible source of infection.

The values of fibrinogen in the three groups studied were as follows:

-in lot I we had an average fibrinogen value = 377.09 mg / dL, a minimum value of 220 mg / dL and a maximum value of 530 mg / dL at a standard deviation of 91.98;

- in lot II we had an average fibrinogen of 400.52 mg / dL, a minimum value of 225 mg / dL and a maximum value of 560 mg /L;

In group III, the mean value of fibrinogen was 422.09 mg /L, the minimum value was 278 mg /L, and the maximum value was 523 mg / L(table 5).

Table 5

VALUES OF FIBRINOGEN IN THE STUDIED GROUPS

Fibrinogen	Lot 1	Lot 2	Lot 3	Total
No	89	61	22	172
Minimum	220	225	278	220
Maximum	530	560	523	560
Average	377.09	400.52	422.09	391.16
Dev.std.	91.98	86.24	75.39	88.99
C.V.	24.39%	21.53%	17.86%	22.75%
Test Student	L1-L2	L1-L3	L2-L3	ANOVA
p=	0.11813	0.03601	0.30248	0.06127

Performing the Student's t test to highlight the difference between the mean values of fibrinogen values, we obtained the following results:

- there is no statistically significant difference (p = 0.11, greater than the threshold of 0.05) between the mean for the subjects in lot 1 and those in lot 2,

- there is a statistically significant difference (p = 0.036, less than the threshold of 0.05) between the mean for the subjects in lot 1 and those in lot 3,

- there was no statistically significant difference (p = 0.0302, greater than the threshold of 0.05) between the mean for the subjects in lot 2 and those in lot 3

The distribution of fibrinogen values by lots was as follows:

- In group I 45 patients (50.56%) had normal fibrinogen, 44 patients (49.44%) had increased fibrinogen;

- in group II 23 patients (37.70%) had normal fibrinogen, 38 patients (62.30%) had increased fibrinogen;

- in group III 6 patients (27.27%) had fibrinogen within limits and 16 patients (72.73%) had increased fibrinogen.

Correlation BCI-fibrinogen level

Of the 60 patients diagnosed with painful (ECG) resting BCI (table 6):

-52 patients (86.67%) had fibrinogen> 400 mg / dL;

-8 patients (13.33%) had fibrinogen <400 mg / dL.

Table 6

CORRELATION OF PAINFUL BCI-HYPERFIBRINOGENEMIA

	fibrinogen		
BCId	grown	normal	Total
BCId+	52	8	60
BCId-	46	66	112
Total	98	74	172

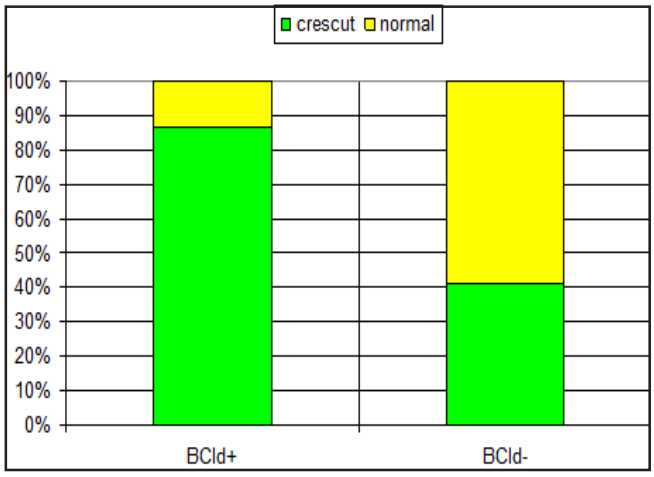

Fig 3.The correlation between elevated fibrinogen levels and the presence of coronary ischemic disease has a statistically high significance (<0.001)

Of the 41 patients diagnosed with painless BCI (ECG-resting) (table 7)

-31 patients (75.61%) had fibrinogen> 400 mg / dL,

- 10 patients (24.39%) serum fibrinogen <400 mg / dL

Following the dosing of fibrinogen in the whole group studied, we had a statistically high correlation (p <0.001) between its elevated levels and the presence of ischemic coronary artery disease (both in patients with painful and painless ischemic coronary disease).

Table 7

CORRELATION OF BPI PAINLESS - HYPERFIBRINOGENEMIA

	fibrinogen		
BCInd	grown	normal	Total
BCInd+	31	10	41
BCInd-	67	64	131
Total	98	74	172

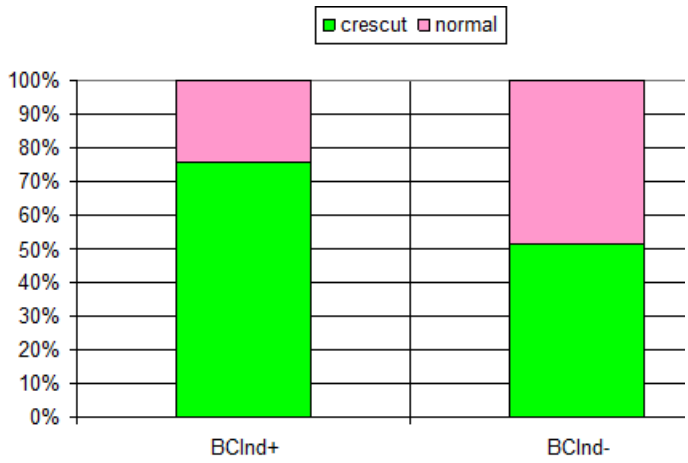

Fig 4 Graphic representation of hyperfibrinogenemia in patients with non-painful BCI

Conclusions

Being the second leading cause of death (after smoking), obesity is a major public health problem. The prevalence of obesity and overweight increases practically in all countries and age groups in the world and the economic cost of obesity is estimated to be 2-7% of all health expenditur

Considering that more than 1 billion people currently have overweight and over 300 million suffer from obesity and over the next two decades the number may double, which will lead to a significant increase in associated pathology, and a shortened life expectancy of 8-10 years obese patients, we considered it necessary to study obesity and the etiopathogenic factors involved in its occurrence.

In Romania, the epidemiological analyzes show that almost 60% of the population has problems with weight (34.60% of Romanians are overweight and 24.70% are obese).

Of the 172 patients enrolled in the study, 89 patients (51.74%) had obesity without endocrine disorder, 61 patients (35.47%) had primary hypothyroidism and 22 patients (12.79%) had reactive hyperchortitis and secondary hypothyroidism.

Plasma fibrinogen is included among the new cardiovascular risk factors because: it greatly influences platelet aggregation; increases the viscosity of the blood; interact with plasminogen binding; in combination with thrombin, mediates the final phase of thrombus formation.

The high level of plasma fibrinogen may occur in the following situations: advanced age, obesity, smoking, diabetes, elevated LDL cholesterol and HDL cholesterol lowering, alcohol consumption, sedentarism [8, 12].

We tried to exclude any possible source of infection in the patients included in the study.

The values of fibrinogen in the three groups studied were as follows: in lot 1 we obtained an average fibrinogen value of 377.09 mg / dL, in lot 2 we recorded an average fibrinogen value of 400.52 mg / dL in group 3 the mean fibrinogen was 422.09 mg / L

By comparing the averages between the three lots, we obtained a value of p = 0.06, which shows that the averages of the three groups do not differ significantly statistically

In lot 1, 50.56% of patients had normal fibrinogen, 49.44% had elevated fibrinogen; in lot 2, 37.70% of patients had normal fibrinogen, 62.30% had elevated fibrinogen; and in lot 3, 27.27% had fibrinogen within limits and 72.73% had increased fibrinogen.

Of the 60 patients diagnosed with painful BCI (EKG): 86.67% had fibrinogen> 400 mg / dL; 13.33% had fibrinogen <400 mg /dL

The correlation between elevated fibrinogen levels and the presence of coronary ischemic disease has a statistically high significance (<0.001).

Of the 41 patients diagnosed with undetectable BCI (EKG at rest): 75.61% had fibrinogen> 400 mg / dL and 24.39% had fibrinogen <400 mg / dL.

Following the dosing of fibrinogen in the whole studied group, a statistically high correlation (p <0.001) between its elevated values and the presence of ischemic coronary artery disease (both in patients with painful and painless ischemic coronary disease) was revealed.

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Manuscript received: 16.08.2018