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The role of fibrinogen and CRP in cardiovascular risk in patients with acromegaly

Znaczenie fibrynogenu i CRP dla ryzyka krążeniowo-naczyniowego u chorych na akromegalię

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Abstract

Introduction: Patients with active acromegaly have 2- to 3-fold increased cardiovascular mortality. Alterations of acute phase proteins, observed in acromegaly, could lead to cardiovascular diseases. Aim of the study was to evaluate fibrinogen and C-reactive protein (CRP) secretion in patients with acromegaly.

Material and methods: Seventy-seven patients were divided into groups with active (AA, n = 56) and controlled acromegaly (CA, n = 21). Twenty age- and sex-matched healthy subjects served as controls. Serum fibrinogen, CRP, fasting glucose, insulin, total cholesterol, LDL and HDL cholesterol, and triglycerides were measured, and body mass index (BMI) was calculated.

Results: Comparison between the groups revealed: higher fibrinogen, triglycerides, glucose levels, and BMI values in AA than in the controls; higher CRP, fibrinogen, triglyceride levels, and BMI values in CA than in the controls; higher LDL cholesterol and insulin levels and lower CRP levels and BMI values in the AA group than in the CA group. Fibrinogen concentration was highest in the AA group and lowest in the control group. Fibrinogen levels were high in all patients with acromegaly, irrespective of disease status, and they were significantly higher than in healthy subjects. CRP concentration was highest in the CA group and lowest in the control group. CRP levels were significantly and paradoxically lower in patients with AA than in patients with well-controlled disease and did not explain the increased cardiovascular mortality in acromegaly.

Conclusions: Fibrinogen plays an important role as a cardiovascular risk factor in acromegaly, irrespective of the cure of the disease. The role of CRP as a cardiovascular risk factor in patients with uncontrolled acromegaly should be better explained in future studies.

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Key words: *acromegaly, fibrinogen, CRP, cardiovascular risk*

Streszczenie

Wstęp: U chorych na akromegalię stwierdza się 2–3-krotnie zwiększoną śmiertelność z przyczyn sercowo-naczyniowych. Zmiany stężeń białek ostrej fazy, obserwowane w akromegalii, mogą prowadzić do chorób układu krążenia. Celem pracy była ocena wydzielania fibrynogenu i białka C-reaktywnego (CRP, *C-reactive protein*) u chorych na akromegalię.

Materiał i metody: Siedemdziesiąt siedem osób chorych podzielono na grupy z aktywną (AA, n = 56) i kontrolowaną akromegalią (CA, n = 21), 20 zdrowych osób dopasowanych pod względem płci i wieku stanowiło grupę kontrolną. Oznaczono stężenia fibrynogenu, CRP, glukozy na czczo, insuliny, cholesterolu całkowitego, cholesterolu frakcji LDL i frakcji HDL, triglicerydów w surowicy, oraz wyliczono wskaźnik masy ciała (BMI, *body mass index*).

Wyniki: Porównanie badanych grup wykazało: większe stężenia fibrynogenu, triglicerydów, glukozy i wartości BMI w grupie AA niż kontrolnej; większe stężenia CRP, fibrynogenu, triglicerydów i wartości BMI w grupie CA niż kontrolnej; większe stężenia cholesterolu frakcji LDL i insuliny oraz mniejsze CRP i wartości BMI w grupie AA niż CA. Stężenie fibrynogenu było największe w grupie AA, a najmniejsze w grupie kontrolnej. Było ono wysokie u wszystkich chorych na akromegalię, niezależnie od stadium choroby i istotnie większe niż u osób zdrowych. Stężenie CRP było największe w grupie CA, a najmniejsze w grupie kontrolnej. Stężenia CRP były paradoksalnie istotnie mniejsze w grupie AA niż w grupie CA i nie tłumaczą przyczyny zwiększonej śmiertelności z przyczyn krążeniowych w akromegalii.

Wnioski: Fibrynogen odgrywa ważną rolę jako czynnik ryzyka sercowo-naczyniowego w akromegalii, niezależnie od wyleczenia choroby. Znaczenie CRP jako czynnika ryzyka krążeniowego u chorych z niewyrównaną akromegalią powinno być dokładniej wyjaśnione w dalszych badaniach. **(Endokrynol Pol 2010; 61 (1): 83–88)**

Słowa kluczowe: *akromegalia, fibrynogen, CRP, ryzyko sercowo-naczyniowe*

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Introduction

Acromegaly is a rare disease leading to a 2- to 3-fold increased in mortality from cardiovascular complications. It is associated with elevated growth hormone (GH) levels [1–3]. Different metabolic changes, secondary to GH and insulin-like growth factor 1 (IGF-1) hypersecretion, favour atherogenic processes. Dyslipidaemia, diabetes mellitus, insulin resistance, and hypophyseal hormone changes might initiate atherosclerotic plaque creation, accelerate its progression, and cause earlier occurrence of cardiovascular complications [4]. An arterial wall low-grade inflammation, rising before structural changes, is believed to be the first step of atherogenesis [5].

Acute phase reactants, like fibrinogen and high sensitivity C-reactive protein (hs-CRP), are well-known cardiovascular risk (CVR) factors. CRP exerts ability of direct initiation and development of both atheromatosis and endothelial inflammation, by the influence on nitric oxide and cytokines secretion, and on adhesive molecules expression [6, 7]. Fibrinogen and other factors involved in the clotting process are associated with cardiovascular diseases. Fibrinogen has an atherogenic effect, although there is a question whether chronic inflammation and atheromatosis also cause hyperfibrinogenaemia [8, 9].

There are limited data on the influence of GH and IGF-1 excess on acute phase reactants. The data on both CRP [10, 11] and fibrinogen [10, 12-14] levels in acromegaly are controversial.

The aim of the study was to evaluate selected acute phase proteins levels: fibrinogen and C-reactive protein (CRP), in patients with acromegaly.

Material and methods

Subjects

Seventy-seven acromegalic patients were included in the study. They were divided into two groups according to minimal GH during oral glucose (75 g) tolerance test and IGF-1 concentrations. In the active acromegaly group (AA) 56 patients with GH concentration ≥ 1 μg/L or/and IGF-1 concentration above normal for their age and sex range were included. In the well-controlled acromegalic group (CA) 21 patients with GH concentration < 1 μg/L and normal IGF-1 concentration for their age and sex range were included. Twenty sex-matched healthy subjects served as the control group. The clinical characteristics of the studied subjects are shown in Table I.

Methods

All study participants were examined for their body mass and height, and body mass index (BMI) was calculated. In all subjects blood samples were taken for hormonal and laboratory analyses after an overnight fast. The following parameters were measured: fibrino-

Table I. *Clinical characteristics of the subjects*

Tabela I. *Kliniczna charakterystyka badanych*

Parameter	Group	Mean	SD	Median	Quartiles 25%/75%
Age (years)	AA	51.42	14.56	53.00	38.00/65.00
	CA	53.19	8.98	54.00	51.00/60.00
	CG	45.65	11.58	50.50	35.00/55.00
Height [cm]	AA	169.00	0.10	167.50	162.00/165.00
	CA	165.00	0.10	164.00	159.00/170.00
	CG	168.00	0.10	168.00	158.50/176.00
Body mass [kg]	AA	81.80	15.99	83.50	71.00/94.00
	CA	84.58	16.90	78.70	75.00/91.00
	CG	70.95	13.16	73.00	56.50/82.00
BMI [kg/m^2]	AA	28.39	3.99	28.62	25.82/31.71
	CA	30.95	5.81	29.41	26.22/34.41
	CG	24.88	3.45	25.10	21.37/27.75
Time since first symptoms (years)	AA	15.91	9.58	15.00	10.00/20.00
	CA	15.61	9.15	13.50	10.00/21.00
Time since diagnosis (years)	AA	8.89	8.76	7.00	1.00/13.00
	CA	8.27	7.33	7.50	3.00/11.50

SD — standard deviation; BMI — body mass index; AA — active acromegaly; CA — controlled acromegaly; CG — control group

gen, CRP, fasting glucose, insulin, total cholesterol, LDL and HDL cholesterol, and triglycerides. Patients were asked to report the period of the symptoms and the time from diagnosis.

The following analytical methods were applied: GH — DPC Biermann GmbH, Bad Nauheim, Germany — ELISA; IGF-1 — BioSource IGF-I-D-RIA-CT Kit, BioSource Europe, Nivelles, Belgium —– RIA; Fibrinogen — Dade Behring Marburg GmbH, Marburg, Germany — Claus modified method; hs-CRP — DPC Biermann GmbH, Bad Nauheim, Germany — ELISA; glucose — hexokinase method; Insulin — DPC Biermann GmbH, Bad Nauheim, Germany — ELISA; Total cholesterol — Cholesterol RTU BioMerieux, Lyon, France — enzymatic method; LDL cholesterol — calculated from Friedewald's formula; HDL cholesterol — HDL Cholesterol Direct, BioMerieux, Lyon, France — enzymatic method; Triglycerides — Triglycerides Enzymatique PAP 150, BioMerieux, Lyon, France — enzymatic method.

Statistical analysis

Parameter distribution was assessed using Shapiro-Wilk's W-test. Mann-Whitney's U-test was used for calculation of the statistically significant differences. Pearson's test was used for calculation of the correlations. The level of statistical significance was set at a level of p-value < 0.05. In some cases, the borderline statistical significance at p-value level between 0.10 and 0.05 was considered.

Results

We observed statistically significant: higher fibrinogen, triglycerides, glucose levels, and BMI values in the AA group than in the controls ($p < 0.00001$, 0.002, 0.01, and 0.001, respectively); higher CRP, fibrinogen, triglycerides levels, and BMI values in the CA group than in the controls ($p < 0.01$, 0.002, 0.04, and 0.001, respectively); higher LDL cholesterol and insulin levels and lower CRP levels and BMI values in the AA group than in the CA groups ($p < 0.04$, 0.02, 0.05, and 0.03, respectively).

Mean serum fibrinogen concentration was highest in the AA group and lowest in the control group. The differences in fibrinogen concentrations between the AA and control groups, and between the CA and control group, were statistically significant ($p < 0.00001$ and $p < 0.002$, respectively). There was no difference between the AA and CA groups (Table II, Fig. 1).

Mean serum hs-CRP concentration was highest in the CA group and lowest in the control group. The differences in hs-CRP concentrations between the AA and CA groups, and between the CA and control groups, were statistically significant ($p < 0.05$, $p < 0.01$, respectively). There was no difference between the AA and control groups (Table II, Fig. 2).

Positive, statistically significant correlation between minimal GH (after OGTT) and concentrations of glucose, insulin, triglycerides, and body mass was documented in the AA group. Borderline positive correlation between minimal GH and fibrinogen concentrations was observed in this group. Negative correlations in the AA group were shown between minimal GH and HDL cholesterol concentration. There was a borderline negative correlation between minimal GH and hs-CRP concentrations in this group (Table III).

In the AA group, positive correlations between IGF-1 and insulin, triglycerides concentrations, and body mass were shown, and negative correlations between IGF-1 and HDL cholesterol and hs-CRP (Table IV). In the CA group, negative correlations between IGF-1 and hs-CRP and age were shown (Table IV).

Moreover, in the AA group, positive correlations between body mass and insulin and fibrinogen concentrations were observed (not shown). Both in the AA and CA groups, a positive correlation between BMI and fibrinogen was observed (not shown).

Discussion

Fibrinogen is a well-known and widely described acute phase reactant and cardiovascular risk factor. Its metabolites can cause endothelium damage and dysfunction. Fibrinogen can initiate atherosclerotic plaque creation, accelerates its progression, and causes earlier cardiovascular complications to arise [8, 9].

We observed statistically significant higher fibrinogen levels both in active and cured acromegaly patients than in controls. This could suggest exaggerated thrombo- and atherogenic processes in acromegaly, but it is yet to be clarified whether higher fibrinogen level is a primary cause or is secondary to atheromatosis and endothelial dysfunction [8, 9]. The weak, borderline correlation between minimal GH and fibrinogen levels in active acromegaly indicates the possible influence of elevated GH concentrations on fibrinogen concentrations; no such correlation was found in cured acromegaly patients. In our study, fibrinogen levels were highest in active acromegaly patients, but they did not differ significantly from those in cured acromegaly patients.

There is some controversy regarding fibrinogen concentrations in acromegaly. In some studies fibrinogen levels were higher in patients with acromegaly than in healthy subjects [12–14]. They were lower in cured than in non-cured acromegalics, but they were higher than in healthy controls [12]. By way of contrast, in another study fibrinogen concentrations did not differ between active and cured acromegalics [10].

Table II. *Concentrations of minimal GH, IGF-1, hsCRP, fibrinogen, lipids, insulin, and glucose in the groups studied*

Tabela II. *Stężenie GH, IGF-1, hs-CRP, fibrynogenu, lipidów, insuliny i glukozy w badanych grupach*

Parameter	Group	Mean	SD	Median	Quartiles 25%/75%
Minimal GH [μg/L]	AA	5.15	7.61	2.75	1.01/6.86
	CA	0.43	0.29	0.43	0.18/0.55
	CG	0.34	0.36	0.14	0.07/0.64
IGF-1 [ng/ml]	AA	818.85	510.99	644.90	412.95/1120.20
	CA	260.83	83.61	259.65	231.30/285.90
	CG	315.00	70.59	308.20	267.80/365.40
hs-CRP [mg/L]	AA	0.78	0.95	0.35	0.16/0.96
	CA	1.16	0.89	0.96	0.67/1.31
	CG	0.67	0.74	0.41	0.16/0.66
Fibrinogen [mg/dL]	AA	409.00	88.57	435.00	335.00/480.00
	CA	398.24	108.12	380.00	330.00/500.00
	CG	289.50	62.45	285.00	245.00/325.00
Fasting glucose [mg/dL]	AA	98.78	16.62	95.00	88.00/106.00
	CA	94.75	21.07	88.50	81.50/105.50
	CG	88.95	6.48	88.50	84.50/94.00
Insulin (μIU/ml)	AA	9.37	6.76	7.60	4.85/11.10
	CA	5.86	2.90	6.30	3.50/7.60
	CG	7.16	2.13	7.65	5.80/8.65
Total cholesterol [mg/dL]	AA	217.33	42.68	213.50	195.00/227.00
	CA	214.72	37.37	210.00	187.00/239.00
	CG	212.45	27.26	213.5	195.00/227.00
LDL cholesterol [mg/dL]	AA	136.6	33.11	130.50	115.50/158.50
	CA	126.94	40.55	121.00	91.00/138.00
	CG	132.75	28.44	131.50	109.5/146.00
HDL cholesterol [mg/dL]	AA	58.16	14.80	57.50	47.00/66.50
	CA	66.41	27.91	65.00	53.00/76.00
	CG	66.15	20.91	57.00	55.50/70.00
Triglycerides [mg/dL]	AA	124.91	55.10	112.00	86.00/160.00
	CA	117.50	67.88	100.00	80.00/138.00
	CG	87.85	42.89	74.50	60.50/101.50

GH — growth hormone; IGF-1 — insulin growth factor 1; hs-CRP — high selection C-reactive protein; AA — active acromegaly; CA — controlled acromegaly; CG — control group

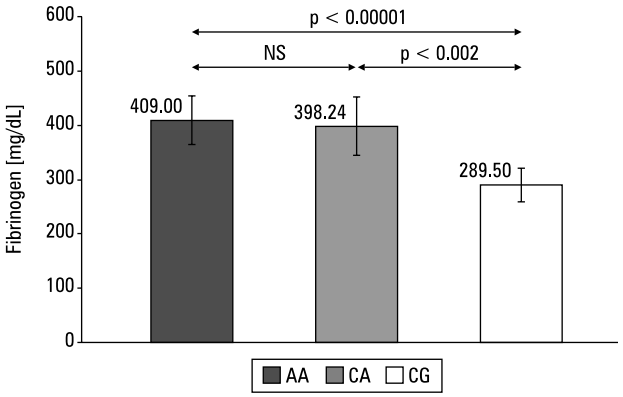

Figure 1. *Mean serum fibrinogen concentrations in the groups studied. AA — active acromegaly; CA — controlled acromegaly; CG — control group*

Rycina 1. *Średnie stężenie fibrynogenu w badanych grupach. AA — aktywna akromegalia; CA — kontrolowana akromegalia; CG — grupa kontrolna*

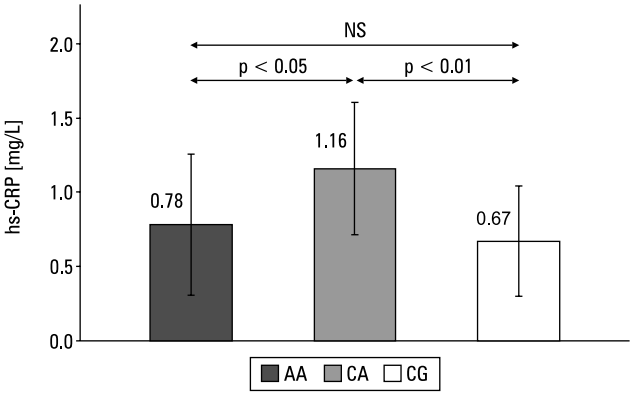

Figure 2. *Mean serum hs-CRP concentrations in the groups studied. AA — active acromegaly; CA — controlled acromegaly; CG — control group*

Rycina 2. *Średnie stężenie hs-CRP w surowicy w badanych grupach. AA — aktywna akromegalia; CA — kontrolowana akromegalia; CG — grupa kontrolna*

Table III. *Correlations between minimal serum GH concentrations and other parameters in patients with active acromegaly (AA)*

Tabela III. *Korelacje między stężeniem GH w surowicy i innymi parametrami u chorych na aktywną akromegalię (AA)*

Group	Parameter	Correlation coefficient r	p-value
AA	Insulin	+0.67	< 0.0001
AA	Glucose	+0.51	< 0.0001
AA	hs-CRP	–0.28	0.08
AA	Fibrinogen	+0.27	0.09
AA	TG	+0.38	< 0.01
AA	HDL	–0.29	< 0.05
AA	Body mass	+0.35	< 0.01

Table IV. *Correlations between serum IGF-1 concentrationand other parameters in patients withacromegaly*

Tabela IV. *Korelacje między stężeniem IGF-1 w surowicy a innymi parametrami u chorych na akromegalię*

Group	Parameter	Correlation coefficient	p value
AA	Body mass	+0.37	< 0.01
AA	Insulin	+0.54	< 0.0001
AA	TG	+0.39	< 0.01
AA	HDL	–0.29	< 0.05
AA	hs-CRP	–0.34	< 0.05
CA	Age	–0.46	< 0.05
CA	hs-CRP	–0.54	< 0.05

TG — triglyceride; AA — active acromegaly; CA — controlled acromegaly

Colao et al. observed a decrease of fibrinogen levels in a smaller group of patients with recently diagnosed acromegaly without lipid disorders and hypertension after 6 months of somatostatin analogue (lanreotide) therapy. Similarly to our study, they showed the highest reduction of fibrinogen levels in patients with better control of acromegaly (greater GH suppression) [12]. Hekimsoy et al. studied biochemical CVR factors, including fibrinogen, in patients with good and weak control of acromegaly. They did not show, like us, any significant differences between fibrinogen concentrations in both groups of patients [10]. On the other hand, Sartorio and co-workers presented higher fibrinogen levels in acromegaly than in GH deficiency (GHD), and higher fibrinogen in GHD than in controls [14].

The latter observation is a very important one, since both GH excess and GHD could have a similar negative and harmful effect on CVR [15, 16]. In the current study, GHD was studied neither in cured acromegaly nor in the control group; we can only speculate that some patients with controlled acromegaly could be GH deficient subjects. The values of minimal GH levels in our cured patients could support this suspicion. Moreover, recent data from literature has documented numerous cases of GHD in patients with successfully treated acromegaly [17].

The discrepancies among the various above-mentioned studies could be also explained by several factors such as lipid levels, hypertension, smoking habits, or other hormonal deficiencies. Another differentiating factor might be the criterion of disease cure. We have, for that reason, applied GH concentration suppression < 1 μg/L following OGTT (75 g) as a very strict criterion of cure, according to the recent European and American standards [18–20]. Data from literature point towards a reduction of mortality in acromegaly when the mean GH was reduced to < 2.5 μg/L [3, 21–24]. Only one study indicated mortality reduction when GH < 1 μg/L, although increased mortality was also associated with GHD [2]. Finally, the application of more strict criteria of acromegaly cure, as used by us, would increase the number of GHD cases that can blur mortality analysis.

High-sensitivity CRP is another well-known, modern, and widely approved CVR factor [6, 7, 25]. It plays a crucial role in arterial wall low-grade inflammation, which is believed to be the first step of atherosclerotic plaque creation, just before structural changes. In the current study, CRP levels were paradoxically lowest in patients with active acromegaly and in healthy subjects from the control group. This could imply low CVR in patients with active acromegaly. Concentrations of hs-CRP in cured acromegalic patients were higher than in patients with active acromegaly and in controls. The presence of lower hs-CRP levels in active than in well-controlled acromegaly, and similar to healthy subjects, is surprising. This needs to be extensively studied in the future.

The results of the CRP studies in acromegaly are still unequivocal. Some authors reported low CRP levels in active acromegaly, and their increase followed acromegaly control during GH receptor antagonist (pegvisomant) therapy [11]. Other studies did not reveal significant differences between patients with active and controlled acromegaly [10].

CRP exacerbates arterial atheromatosis by worsening endothelial function [7], and hs-CRP is considered a strong and independent CVR factor [25]. Nevertheless, the relation of the atheromatosis extent to hs-CRP concentration was not clearly documented [26]. CRP is produced in the liver by activated monocytes under the influence of cytokines [27]. GH acts by means

of GH receptors belonging to the cytokine receptor superfamily, and GH receptor activation induces molecular signalling similar to cytokine signalling [28]. High GH concentrations can compete with proinflammation cytokines, and in such a way can decrease hs-CRP levels [29]. This may lead to the conclusion that GH protects endothelium and arterial wall. The mechanisms of this process remain unexplained. More data and future studies are necessary.

In another study, acute phase reactants were higher in GHD patients than in healthy controls, and their levels decreased following GH administration [30]. In our subjects, GHD was not studied, but we could asume GHD in some of our patients with controlled acromegaly. This might explain higher hs-CRP in this group. Other authors had similar observations to ours, confirmed by the correlations of hs-CRP with GH and IGF-1 [31, 32].

Another explanation of the differences in hs-CRP among our groups could be adipose tissue mass. GH exerts lipolytic activity, and fat mass in cured acromegaly is higher than in active acromegaly. There were negative correlations between hs-CRP and BMI in active acromegaly patients. Adipose tissue possesses GH receptors, and it is a source of IL-6 production, which stimulates CRP synthesis [33]. We can speculate that GH inhibits IL-6 synthesis and decreases CRP secretion. This hypothesis has not been confirmed and should be explained in future studies.

In summary of the presented results, we have clearly documented that fibrinogen concentrations in all patients with acromegaly were significantly higher than in healthy subjects, irrespective of disease status. This could indicate fibrinogen as an important CVR factor in acromegaly. Levels of another widely accepted risk factor — CRP — were significantly and paradoxically lower in patients with active acromegaly than in patients with well controlled disease and did not explain the increased cardiovascular mortality in acromegaly.

Conclusions

Fibrinogen plays an important role as a cardiovascular risk factor in acromegaly, irrespective of the cure of the disease. The role of CRP as a cardiovascular risk factor in patients with uncontrolled acromegaly needs to be better explained in future studies.

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