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ORIGINAL ARTICLE

Association between insulin like growth factor-1 and lipoprotein metabolism in stable angina patients on statin therapy: a pilot study

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Abstract

Background and aim: The aim of this study was to test whether there was an association between systemic levels of insulin like growth factor-1 (IGF-1), IGF-1 binding protein-3 (IGFBP3) and selected parameters of lipid metabolism depending on the lipid-lowering therapy. This work was conducted in patients described by us previously who had either highly probable, or documented, coronary artery disease, and controlled serum lipids with prolonged statin therapy.

Methods: The study was conducted among 140 patients undergoing coronary angiography. The following parameters were measured: LDL- and HDL-cholesterol levels, TG, TC, apoB-100, apoA1, Lp(a) and IGF-1 and IGFBP3, as well as the level of oxidation products of proteins and lipids.

Results and conclusions: In the group of patients with LDL target up to 100 mg/dl and statins use, as well as in the entire population, IGF-1 and IGFBP3 were associated with protein oxidation products and Lp(a). Additionally, in the whole studied group, IGF-1 was associated with TG and LDL. More differences were observed when we used multivariate analysis. Even then, IGF-1 and IGFBP3 in the group with LDL up to 100 mg/dL, as well as in the entire group, were associated with protein oxidation products, Lp(a) and with quantitative arteriosclerosis scale (Gensini score). These results seem to confirm our previous findings, wherein significantly higher levels of systemic IGF-1 were found in patients with advanced coronary atherosclerosis.

Key words: IGF-1, coronary artery disease, lipoprotein metabolism

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INTRODUCTION

Insulin-like growth factor (IGF-1) is involved in the metabolism of carbohydrates and lipids [1] by increasing the insulin sensitivity of tissues and by influencing the transformation of high-density lipoprotein (HDL). Accordingly, several clinical trials have investigated the relationship between systemic levels of IGF-1 and known cardiovascular (coronary atherosclerosis and peripheral vascular atherosclerosis) risk factors [1].

It has been found that low levels of systemic IGF-1 correlate with increased cardiovascular disease risk in the general population. Decreased IGF-1 is considered a independent risk factor for myocardial infarction and coronary artery disease (CAD). Additionally, it has been shown that there is a relationship between low levels of IGF-1 and a poor prognosis for myocardial infarction patients. Finally, IGF-1 has been found to be negatively correlated with the thickness of the intima-media in the carotid arteries [2–7]. Surprisingly, in several large clinical trials, patients with ischaemic heart disease had higher serum levels of IGF-1 compared to matched non-CAD subjects [8, 9]. We have reported a similar association of higher levels of IGF-1 in patients

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with advanced coronary atherosclerosis compared to patients with haemodynamically insignificant coronary artery stenosis [10].

High concentrations of IGF-1, its receptor, and its binding proteins (IGFBP3), protect the plaque against destabilisation and rupture [11]. The mechanism of this phenomenon is not clear at present. Firstly, there have been reports that IGF-1 interferes with known cardiovascular risk factors such as obesity, endothelial dysfunction, insulin resistance, impaired glucose tolerance, or left ventricular hypertrophy [1]. In addition, IGF-1 affects the metabolism of HDL, although the literature data regarding this issue is contradictory. On the one hand, in a healthy population, a positive correlation between IGF-1 and HDL levels was observed, whereas in a group with CAD it was reversed [12, 13]. Nevertheless, it seems that among subjects with low levels of IGF-1, the chronic insulin resistance which in turn affects the metabolism of HDL is responsible for vascular homeostasis disturbances. Serum levels of HDL seem to be the best predictor for vascular risk among patients treated with optimum lipid-lowering therapy who reach the level of low density lipoprotein (LDL) defined by the European Society of Cardiology (ESC) guidelines. We undertook to investigate the effects of IGF-1 and IGFBP3 on lipid metabolism due to the paucity of data on this subject in the general population with CAD, and to the complete lack of such reports in patients using lipid-lowering therapy with statins. We believe that better understanding of IGF-1 and IGFBP3 contribution in patients with advanced CAD and controlled with statins will lead to treatment improvements, resulting in decreased morbidity and mortality.

METHODS

This study was conducted in 140 Caucasians (aged 36–80 years) with suspected (clinical symptoms) or confirmed (by positive ECG-exercise test or in previously made coronary angiographies) CAD qualified for coronary angiography [1]. Venous blood was collected at 8:00 am and allowed to clot. The serum was determined for LDL, triglycerides (TG), HDL, total cholesterol (TC), apoprotein B100 (apoB-100), apoprotein A1 (apoA1), and lipoprotein (a) (Lp(a)). Determination of the apoA1, apoB-100, and Lp(a) levels were performed using the immunonephelometric method using a Nephelometer II system (Dade-Behring).

Determination of TC, HDL, LDL and TG was carried out by the enzymatic method using the Architect system by Abbott. The serum concentrations of IGFBP3 and IGF-1 were established by radioisotope and radioimmunoisotope methods using reagents of Biosource (Nivelles, Belgium) [10]. Concentrations of oxidised proteins were made by the spectrophotometric method using an ELISA reader according to [14].

Assessments of lipid peroxidation

The level of lipid peroxidation was evaluated spectrophotometrically using the oxidation of iron ions ROOH in the presence of xylenol orange and has been described elsewhere [15].

Angiographic studies

The angiographies were performed and analysed by the same invasive cardiologist who assessed the significance of the stenosis by quantitative coronary angiography and calculated the Gensini score using the calculator by Sriram & Svirbely available on the website www.medal.org. The study design was approved by the local Bioethics Commission.

Univariate analysis

Normality was tested in Shapiro-Wilk's W test. At normal distribution of variables, we used T-Student test (for two independent variables). Mann-Whitney test (for two independent variables) were used at abnormal distribution of variables. For some tests, simple regression was also used as well as correlation matrices.

Multivariate analysis

Multivariate was done using (mostly) multiple regression and analysis of covariance. Statistical significance was established when $p < 0.05$. Statistical analysis was conducted using STATISTICA 7.0 software.

RESULTS

Statins were used by 68% (n = 91) of all studied patients (n = = 140) with the following agents: simvastatin 57%, atorvastatin 7.85%, fluvastatin 1.42%, and fibrates 1.42%. The average doses of simvastatin and atorvastatin were 22.92 ± 7.61 mg and 20.0 ± 8.16 mg, respectively. The fibrates were combined only in polytherapy with statins. Patients who received hypolipemic treatment had been treated with statin for more than three months before catheterisation. LDL concentration below 100 mg/dL in the overall population reached a total of 54 people (34% of all respondents).

IGF-1 in the entire study population (Table 1)

IGF-1 levels were positively correlated with TC: r = 0.19, oxidatively modified proteins: r = 0.26, TG: r = 0.23, Lp(a): r = 0.2, and negatively with HDL/LDL: r = –0.18, and age: r = –0.38. In univariate regression analysis, a significant association of IGF-1 with Lp(a): p = 0.003, TG: p =0.003 (Fig. 1), with the products of protein oxidation: p = 0.007, LDL cholesterol: p = 0.02 and the TC: p = 0.006 were found. Multivariate regression analysis showed that independent factors influencing systemic levels of IGF-1 were: age: p = 0.000043, Gensini score: p = 0.008, protein oxidation products: p = 0.002. Analysis of covariance showed that independent factors influencing systemic levels of IGF-1 were Gensini score: p = 0.049 and TG levels: p = 0.002.

IGF-1 in the group with LDL < 100 mg/dL (Table 1)

IGF-1 correlated negatively with age (r = –0.33). In univariate regression analysis, the association of IGF-1 with oxidatively

Table 1. Significant relation of various parameters with insulin like growth factor-1 (IGF-1)

Parameter	Total cholesterol	Triglycerides	Lipoprotein (a)	HDL/LDL	LDL	Apoprotein B100	Protein oxidation products	Gensini score	Body mass index	Blood pressure	Age
IGF-1 in 1	r = 0.19	r = 0.23	r = 0.2	r = –0.18	p = 0.02a		r = 0.26	p = 0.008b			r = –0.38
	p = 0.02a	p = 0.003a	p = 0.003a				p = 0.007a				p = 0.000043b
							p = 0.002b				
IGF-1 in 2	p = 0.002b		p = 0.035a		p = 0.01b	p = 0.048b	p = 0.02a	p = 0.0005b	p = 0.0002b	p = 0.01b	r = –0.33
			p = 0.006b				p = 0.00004b				p = 0.002b

1 — entire population; 2 — group with LDL < 100 mg/dL; HDL/LDL — high/low density lipoprotein; p — significant association; r — significant correlation; a — univariate analysis; b — multivariate analysis

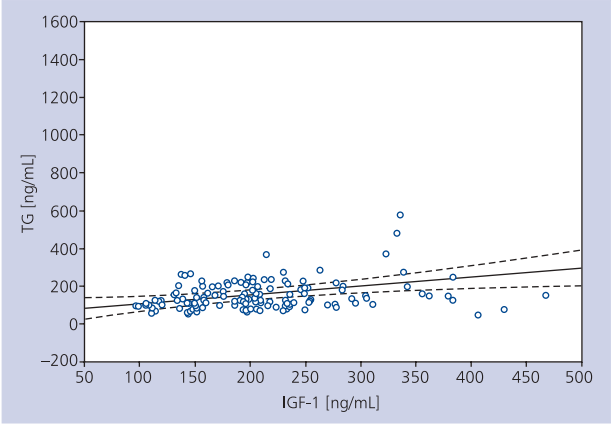

Figure 1. Association between insulin like growth factor-1 (IGF-1) and triglycerides (TG) in whole studied group

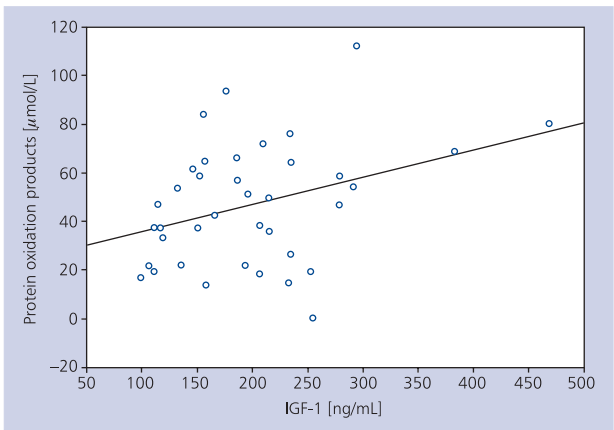

Figure 2. Association between insulin like growth factor-1 (IGF-1) and protein oxidation products in group of patients with low density lipoprotein goal < 100 mg/dL

modified proteins (p = 0.02) (Fig. 2), and Lp(a) (p = 0.0035) were observed. Multiple regression showed that independent factors influencing systemic levels of IGF-1 (among such parameters as: age, sex, hypertension, diabetes mellitus, body mass index [BMI], Gensini score, TC, LDL, Lp(a), TG, apoA1, apoB100, oxidatively modified proteins and peroxidised lipids), were: age (p = 0.002), BMI (p= 0.0002), Gensini score (p = 0.0005), TC (p = 0.009), LDL (p = 0.01), apoB100 (p = 0.048), protein oxidation products (p = 0.00004), and Lp(a) (p = 0.006). Analysis of covariance (among such parameters as age, sex, hypertension, diabetes mellitus, TC, LDL, Lp(a), TG, apoA1, apoB/apoA, oxidatively modified proteins, and concentration of lipid peroxidation products) showed that independent factors influencing systemic levels of IGF-1 were Lp(a) (p = 0.03), and blood pressure (p = 0.01).

Table 2. Significant relation of various parameters with insulin like growth factor 1 binding protein 3 (IGFBP3)

Parameter	Total cholesterol	Triglycerides	Lipoprotein (a)	HDL/LDL	LDL	Apoprotein A1	Protein oxidation products	Gensini score	Age
IGFBP3 in 1	r = 0.32		r = 0.25	r = –0.23	r = 0.25		r = 0.26	p = 0.02b	r = –0.34
									p = 0.01b
IGFBP3 in 2	r = 0.45	p = 0.03b	p = 0.01b			p = 0.0018b			r = –0.43
	p = 0.0006b								

1 — entire population; 2 — group with LDL < 100 mg/d; HDL/LDL — high/low density lipoprotein; p — significant association; r — significant correlation; a — univariate analysis; b — multivariate analysis

IGFBP3 in the whole study population (Table 2) [10]

IGFBP3 correlated positively with TC: r = 0.32, LDL: r = = 0.25, Lp(a): r = 0.25, TG: r = 0.33, and oxidatively modified proteins: r = 0.26; it correlated negatively with HDL/ /LDL: r = –0.23 and age: r = –0.34. Multiple regression showed that independent factors influencing systemic levels of IGFBP3 were age (p = 0.01), and Gensini score (p = 0.02).

IGFBP3 in the group with LDL < 100 mg/dL (Table 2)

IGFBP3 correlated positively with TC (r = 0.45), and negatively with age (r = –0.43). Multiple regression analysis (among such parameters as sex, age, weight, height, Gensini score, TC, HDL, TC/TG, oxidatively modified proteins, TG, concentration of lipid peroxidation products, Lp(a), and apoA1) showed that independent factors influencing systemic levels of IGFBP3 were: age (p = 0.03), Gensini score (p = 0.03), level of TC (p = 0.0006), oxidatively modified proteins (p = 0.001), TG (p = 0.03), Lp(a) (p = 0.01), and ApoA1 (p = 0.001).

DISCUSSION

It has been postulated that IGF-1 may affect vascular homeostasis [1] by participating in the metabolism of carbohydrates, mainly by increasing insulin sensitivity and by decreasing tissue expression of hybrid IGF-1/insulin receptors [2–6, 16].

IGF-1 also affects lipid metabolism, again by improving the insulin sensitivity of tissues, inhibition of the expression of cholesterol ester and triglycerides transfer protein, hepatic lipase (which degrades HDL), and by decreasing the endogenous synthesis of very low density lipoproteins (VLDL). IGF-1 also inhibits expression of scavenger receptors (SRB1) on the surface of liver Hep2 B cells, which leads primarily to a reduction of HDL reverse transport as well as secondarily to its lower degradation [17].

In our study, using univariate analysis we found that IGF-1 showed an association with TC, LDL, Lp(a) and TG, but not with HDL. Using both univariate and multivariate analysis, in patients who achieved LDL below 100 mg/dL, IGF-1 was associated with Lp(a) and oxidatively modified proteins as well as with BMI, age and Gensini score.

Based on this study and other publications [16–18], we believe that products of lipid oxidation, oxidised proteins, and high values of Lp(a) could be considered as clinically useful indicators of atherosclerosis progression risk in patients with statin controlled lipids. IGF-1 and IGFBP3 levels showed an association with these parameters and could be potentially used as surrogate markers to further risk stratify patients, as lipid profiles cannot be used.

A positive but weak correlation between IGF-1 and the parameters that provide a persistent plasma lipoprotein oxidation validates our previous results [10], wherein significantly higher levels of systemic IGF-1 were found in patients with advanced coronary atherosclerosis. Therefore, it is not surprising that there is a correlation of IGF-1 with LDL and TC, well recognised coronary risk factors. Our research reveals that

the susceptibility of serum lipoproteins to oxidation is probably higher in patients with advanced atherosclerosis. It is difficult to explain the mechanism of this phenomenon. Additionally, IGF-1 correlated with hypertension, weight, height and age.

Increased levels of IGF-1 should be considered as a physiological regulatory mechanism to provide increased protection in advanced CAD [6]. Ischaemic heart disease in these patients was manifested as a stable angina, rather than acute coronary syndrome. This is confirmed by other authors who had associated a worse prognosis of patients with myocardial infarction with low levels of IGF-1 and growth hormone (GH) [1, 4]. In the context of these findings, the role of GH in IGF-1 biosynthesis and metabolic changes induced by these proteins is still unclear. The results of experimental studies in mice have indicated that the adverse effects of low levels of IGF-1 are rather the result of secondary increased GH secretion by the pituitary, which is part of the feedback with IGF-1 [19, 20]. This hypothesis could explain the nature of anti-insulin metabolic changes observed at low systemic concentrations of IGF-1 and high GH.

However, one limitation of our protocol is that the level of GH was studied only in a few cases, not sufficient in number to perform a thorough statistical analysis.

We could not confirm a relationship between IGF-1 and HDL in the entire study population, but a significant association with apoA1 in the subgroup of subjects achieving LDL levels below 100 mg/dL was observed. This seems to be only partially in agreement with the observations of other authors [1].

CONCLUSIONS

The serum level of IGF-1 in patients taking lipid-lowering therapy was significantly affected by: parameters associated with plasma lipoprotein metabolism, the presence of atherosclerotic changes in the lumen of the coronary arteries [10], as well as by recognised cardiovascular risk factors such as age, weight, and height.

Evaluation of systemic concentrations of IGF-1 could be a useful tool in determining the risk of cardiovascular diseases, but the results would require further verification in a larger study.

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Conflict of interest: *none declared*

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Związek insulinopodobnego czynnika wzrostu 1 z lipidami osocza w grupie osób ze stabilną chorobą wieńcową, leczonych statynami: wyniki wstępne

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Streszczenie

Wstęp i cel: Celem badania było określenie związku między stężeniem insulinopodobnego czynnika wzrostu-1 (IGF-1), białka wiążącego IGF-1 (IGFBP3) a wybranymi parametrami gospodarki lipidowej w zależności od stosowanej terapii hipolipemizującej. Badanie przeprowadzono w opisanej wcześniej grupie osób z wysokim prawdopodobieństwem lub z udokumentowaną chorobą wieńcową, u których monitorowano osoczowe stężenia lipoprotein.

Metody: Badanie przeprowadzono wśród 140 pacjentów poddanych koronarografii. Oznaczano następujące parametry: cholesterol całkowity, lipoproteiny o wysokiej i niskiej gęstości (HDL, LDL), triglicerydy (TG), apoproteinę B100 i A1 (apoB-100, apoA1p), lipoproteinę a (Lp(a)) oraz IGF-1 i IGFBP3, jak również poziomy produktów utleniania białek i lipidów.

Wyniki i wnioski: W grupie chorych z LDL do 100 mg/dl stosujących preparat statyny, jak również w całej badanej populacji IGF-1 oraz IGFBP3 wykazywały związek z produktami utleniania białek i Lp(a). Dodatkowo w całej grupie badanej IGF-1 wykazywał związek z TG i LDL. Więcej różnic zaobserwowano w analizie wieloczynnikowej, w której IGF-1 oraz IGFBP3 u osób z LDL do 100 mg/dl, jak również w całej grupie badanej wykazywały związek z produktami utleniania białek, Lp(a) oraz z miażdżycą (określaną ilościowo w skali Gensiniego). Potwierdza to wcześniejsze wyniki, w których wyższe stężenie ogólnoustrojowego IGF-1 stwierdzono u pacjentów z zaawansowaną miażdżycą tętnic wieńcowych.

Słowa kluczowe: insulinopodobny czynnik wzrostu-1, choroba niedokrwienna serca, lipoproteiny osocza

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