Chronic inflammation and lipid profile parameters in obese subjects with normal and disturbed glucose metabolism

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SUMMARY
Introduction/Objective In different states of increased chronic inflammation, like obesity and diabetes, early changes in lipid metabolism could represent an adaptive response aimed at diminishing the elevated inflammatory reaction. The aim of study was to investigate the impact of glucose tolerance status on relationship between chronic inflammation and lipid metabolism parameters.

Methods The study consisted of four groups (n = 30 for each group): obese individuals with disturbed glucose metabolism (subjects with newly diagnosed type 2 diabetes (T2DM)) before and after metformin treatment initiation, obese subjects with normal glucose tolerance (NGT) and a control group of healthy normal weight subjects. Appropriate anthropometric measurements and laboratory tests were carried out in all participants.

Results Among the sub-group of obese subjects, the association of highly sensitive C reactive protein (hsCRP) with triglycerides and lipoprotein (a) (Lp(a)) was especially pronounced in the group of T2DM subjects before treatment initiation. In this group, the level of inflammation was the highest and correlation coefficients of triglycerides and Lp(a) with hsCRP were significantly different compared with the group of obese without diabetes (r = 0.21 vs r = -0.36; p = 0.0172) for triglycerides and (r = -0.17 vs r = 0.36, p = 0.0324) for Lp(a). Correlations of hsCRP with triglycerides and Lp(a) in groups of NGT obese subjects and T2DM subjects after treatment initiation did not differ significantly. Treatment with metformin changed the relationship of hsCRP with triglycerides and Lp(a) to the one which is similar to the relationship observed in obese NGT subjects (r = 0.21 vs r = 0.38; p = 0.2449) for triglycerides and (r = -0.17 vs r = -0.27, p = 0.3562) for Lp(a).

Conclusion In subjects with newly diagnosed T2DM, who have the highest level of inflammation, it is probable that the increase in triglycerides is a part of the anti-inflammatory response, whereas Lp(a) is probably produced and used in the reduction of elevated inflammation.

Keywords: C reactive protein; lipoprotein (a); triglycerides; metformin, obesity; type 2 diabetes

INTRODUCTION

Increased inflammation causes changes in the lipid metabolism, which might represent the adaptive response aimed at the reduction of toxicity of different harmful microbiological agents and at a repair of the tissue occurring during the acute inflammatory response. In such conditions, the most frequent changes related to lipid metabolism are a decrease in high density lipoprotein cholesterol (HDL-C) and an increase in triglyceride levels [1].

Chronic inflammation may lead to the development of conditions like atherosclerosis and metabolic syndrome (MetS). It also regulates the gene expression responsible for a scavenger receptor function and foam cell formation. Oxidative stress, by the excess of free radicals’ formation, activates the immune system through the redox-sensitive transcription factors such as nuclear factor-kB [2]. Although this chronic stress does not cause reaction such strong as the acute inflammation does, it is still involved in a development of various degenerative diseases including diabetes and cardiovascular diseases (CVD). Lipoprotein (a) (Lp(a)) levels are associated with CVD, as Lp(a) may play a role in atherothrombosis and in activation of acute inflammation [3]. It is also involved in the activation of endothelial reaction, oxidative modification and formation of foam cells, processes involved in atherosclerosis progression [3, 4].

The aim of our study was to investigate the impact of glucose tolerance status on the relationship between chronic inflammation and lipid metabolism parameters. Additionally, we analyzed the influence of metformin therapy on this relationship among newly diagnosed type 2 diabetes (T2DM) patients.
METHODS

The study was conducted at the Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Center Novi Sad, Serbia. Thirty obese patients with newly diagnosed T2DM before and after the three months metformin treatment (daily dose of 1000 mg), 30 obese individuals with normal glucose tolerance (NGT) and 30 normal weight healthy control subjects were enrolled. All four groups were age- and sex-matched. Subjects suffering from diseases and habits that could influence the oxidative status were not included.

Body mass index (BMI) was calculated as BM (kg)/BH (m)². Body composition was determined by the bio-electrical impedance method, using Tanita apparatus (TANITA BC-418 Segmental Body Composition Analyzer, Tokyo, Japan), measuring the tissue resistance to an alternating current, thus providing the calculation of body fat mass (BFM, kg), lean body mass (LBM, kg) and total body water (TBW, kg).

Glucose (Architect analyzer C8000, Abbott Laboratories, IL, USA), total cholesterol and triglycerides (Architect ci4100 analyzer, Abbott Laboratories) were assayed by the standard enzymatic procedure, and HDL-C were analyzed with a direct enzymatic colorimetric test (Architect ci4100 analyzer, Abbott Laboratories), while LDL cholesterol was calculated indirectly, using the Friedewald formula. Insulin (Advia Centaur XP Siemens, Erlangen, Germany), apolipoprotein B, apolipoprotein AL, Lp(a) (Architect ci4100 analyzer, Abbott Laboratories), and high sensitivity C reactive protein (hsCRP) (Siemens Healthcare Diagnostic Inc., Camberley, UK) were assayed by the immunoturbidimetric method. The Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) index, an indirect indicator of mainly hepatic IR. HOMA-IR index was calculated from the values of fasting blood glucose (FBG) and fasting insulinaemia according the formula:

\[ \text{HOMA-IR} = \frac{\text{FBG} \times \text{fasting insulinaemia (mIU/l)}}{22.5} \]

Lp(a) was analyzed by the immunoturbidimetric method (QUANTIA Lp(a), BIOKIT, S.A., Barcelona, Spain) (Architect ci4100 analyzer, Abbott Laboratories), and Hgb A1c levels were determined by Abbott Architect analyzer C8000.

Recommendations for specific reference values were: The Guide to Good Clinical Practice recommendations for lipids and lipoproteins by the Ministry of Health of Serbia, ADA recommendations for the value of the glycemic status and the International Federation of Clinical Chemistry, as well as recommendations from producers of reagents. The study was done in accord with standards of the institutional Committee on Ethics.

Statistical analysis

The verification was performed with the statistical probability distribution sets. Statistical tests of parameter sets and corresponding tests of dispersive analysis (ANOVA statistical test) were used. Linear correlations test was performed using the Pearson's product-moment correlation coefficient. For the analytical expression of the relationship between parameters in obese T2DM patients before and after the treatment initiation regression analysis was applied. Linear regression had the highest correlation coefficients. The effect of an onset of diabetes and treatment initiation was expressed by the changes in regression equations, and the value of changes was verified by the Pearson's correlation coefficient test. Duncan's multiple range test (post-hoc ANOVA test) was used to directly highlight statistically significant differences in BMI, triglycerides, Lp(a), HOMA-IR and hsCRP between the groups (control, NGT obese, obese T2DM before and after the metformin treatment). This test was selected due to its tolerance to type I error in the small samples.

RESULTS

Basic characteristics of the study groups are shown in Table 1. As expected, obese subjects with T2DM before and after treatment and NGT obese individuals had a significantly higher BMI compared with the control group, without significant inter-group differences (Table 2). Also, the level of serum triglycerides was the highest in T2DM patients before the treatment, with significant difference compared with the control and NGT obese group (Table 2). Con-
Table 2. Analysis of the relationships of BMI, serum triglycerides, Lp(a), hsCRP, serum creatinine, HOMA-IR index values among studied groups

| Parameters and relations | BMI (kg/m²) | Triglycerides (mmol/l) | Lp(a) (g/l) | HOMA-IR | Hs CRP (mg/l) | Creatinine (µmol/l) |
|--------------------------|-------------|------------------------|------------|---------|--------------|-------------------|
| A                        | 23.9 (19.2–24.8) | 1.3 (0.4–8.5) | 0.27 (0.02–1.17) | 1.55 (0.46–3.20) | 1.3 (0.1–9.7) | 75.22 ± 11.33     |
| B                        | 36.6 (30.1–54.1) | 1.4 (0.4–5.6) | 0.16 (0.01–0.57) | 3.44 (1.69–9.30) | 5.2 (0.1–63.1)  | 78.82 ± 15.19     |
| C                        | 36.6 (30.1–43.7) | 3.3 (0.8–9.1) | 0.09 (0.01–0.86) | 8.57 (1.49–29.08) | 7.2 (0.3–28.9)  | 79.25 ± 16.50     |
| D                        | 35.5 (30.3–42.2) | 2.3 (0.6–6.4) | 0.13 (0.01–0.98) | 5.01 (1.16–13.80) | 5.3 (0.3–14.3)  | 78.42 ± 16.52     |
| A vs. B                  | p = 0.0001   | p = 0.80             | p = 0.16   | p = 0.14 | p = 0.02     | p = 0.30          |
| A vs. C                  | p = 0.0001   | p = 0.004            | p = 0.04   | p = 0.005 | p = 0.002    | p = 0.26          |
| A vs. D                  | p = 0.0001   | p = 0.14             | p = 0.09   | p = 0.01  | p = 0.02     | p = 0.39          |
| B vs. C                  | p = 0.99     | p = 0.007            | p = 0.43   | p = 0.002 | p = 0.27     | p = 0.91          |
| B vs. D                  | p = 0.57     | p = 0.19             | p = 0.70   | p = 0.22  | p = 0.92     | p = 0.92          |
| C vs. D                  | p = 0.55     | p = 0.12             | p = 0.65   | p = 0.006 | p = 0.29     | p = 0.85          |

A – Control; B – NGT obese; C – T2DM before treatment; D – T2DM after treatment

Figure 1. The linear correlations between hsCRP and triglycerides in studied groups; T2DM – type 2 diabetes mellitus; hsCRP – high sensitive C-reactive protein
versely, Lp(a) was the highest in control subjects and the difference compared to T2DM patients before the start of metformin treatment reached statistical significance (Table 2). Not surprisingly, those with T2DM were the most insulin resistant before the initiation of metformin treatment. Their HOMA-IR index was significantly higher than in all the other groups, and after the treatment period, their HOMA-IR index was significantly higher only compared with the control group (Table 2). Their hsCRP was also the highest in T2DM patients prior to treatment. Significant differences were observed between the control group and all groups of obese patients, and values in the group of obese subjects were not significantly different from those in patients with newly diagnosed T2DM before and after initiation (Table 2). There were no significant differences in the levels of serum creatinine between the examined groups (Table 2).

We performed a sub-analysis including NGT obese subjects as well as obese T2DM patients before and after metformin treatment. The correlation analysis including hsCRP and triglycerides pointed out that correlations of these two parameters differed significantly between the NGT obese group and the T2DM patients prior to the initiation of metformin treatment (r = 0.21 vs. r = -0.36; p = 0.0172) (Figure 1). Therefore, among obese NGT individuals, an increase in triglyceride levels was accompa-
nied by an increase in hsCRP level, while this relation was completely opposite in T2DM patient before the start of metformin treatment. The similar findings were during the comparison of correlations of these two parameters in T2DM patients before and after the initiation of metformin treatment. ($r = -0.36$ vs. $r = 0.38$; $p = 0.0037$) (Figure 1). Finally, the correlation coefficient of these two parameters did not differ significantly between NGT obese subjects and T2DM patients after the treatment initiation ($r = 0.21$ vs. $r = 0.38$; $p = 0.2449$) (Figure 1). Namely, after the initiation of metformin therapy, a pattern of relation between hsCRP and triglycerides became similar to the one observed among NGT obese individuals (Figure 1).

The similar results but in the opposite direction were found during the sub-analysis of correlations between hsCRP and Lp(a) in obese subjects. Correlation coefficients between two parameters in NGT obese group and in T2DM patients prior to the metformin treatment differed significantly ($r = -0.17$ vs. $p = 0.36$, $p = 0.0324$) (Figure 2). In other words, while the higher levels of hsCRP were followed by a decrease in Lp(a) in NGT obese group, this relation was direct in T2DM patients before they started the metformin treatment. The same was during the comparison of correlation coefficients between hsCRP and Lp(a) in T2DM patients before and after the metformin treatment period ($p = 0.36$ vs. $p = -0.27$; $p = 0.0168$) (Figure 2). After the initiation of metformin therapy, the pattern of relation between hsCRP and Lp(a) became similar to the one observed among NGT obese individuals: a decrease in hsCRP level was accompanied by an increase in Lp(a) level. This was also supported by the calculation of probability for the hypothesis on the coincidence of the linear coefficients in two sets which showed that there were no significant differences in correlation coefficient between hsCRP and Lp(a) in groups of NGT obese subjects and T2DM patients after the metformin treatment initiation ($r = -0.17$ vs. $p = -0.27$, $p = 0.3562$) (Figure 2).

Although there was no significant change in the level of triglycerides prior and after the metformin therapy initiation, the shift in type of distribution should be emphasized, so albeit the effect of metformin initiation was not quantitatively verified, the qualitative effect of a therapy was apparent (Figure 3).

Likewise, metformin therapy did not significantly change the Lp(a) levels, but it has not caused the qualitative change either, since the distribution remained unchanged (Figure 4).

**DISCUSSION**

HsCRP is an acute phase reactant which is responsible for quick response in the case of stress, infection, injury or malignancy. Although chronic stress does not cause excessive
reactions, prolonged low-grade inflammation leads to the development of different degenerative diseases [5].

Strong correlation between inflammation and glycemic control in patients with T2DM suggests that inflammation plays an important role in the pathogenesis of diabetes [6].

Recent studies found that that low hs-CRP (< 2 mg/L) appeared to be associated with reduced risk of incident stroke, incident coronary heart disease and coronary heart disease death, whereas low LDL-C (< 70 mg/dL) was not associated with protective effects [7]. These results support those of the recent CANTOS (The Canakinumab Anti-inflammatory Thrombosis Outcome Study) trial with respect to the importance of inflammatory processes in the pathogenesis of CVD [8].

Recent trials with targeting both LDL-C and hs-CRP by statin therapy in patients with acute coronary syndrome could further reduce the incidence of MACE and the residual cardiovascular risk [9]. Tang et al. [10] found that elevated serum levels of hs-CRP are associated with high levels of uric acid, low levels of HLD cholesterol and superoxide dismutase (SOD) but not levels of serum triglycerides. In the study of Kasukuri et al. [11], there was a moderate positive correlation of hs-CRP with all lipid parameters which was significant except for triglycerides.

Kimak et al. [12] showed recently that the main problem of a stable coronary angina patients is not the high concentration of total cholesterol and LDL-C but the progressive increase of chronic inflammation and the accompanying increase in triglycerides and apo B lipoprotein concentration but did not examine correlations between parameters of inflammation and the lipid status. Some CVD outcome studies with triglyceride-lowering agents have produced inconsistent results, meaning that no convincing evidence is available that lowering triglycerides by any approach can reduce mortality [13].

During the sub-analysis which included only obese subjects, we found significant changes in correlations between hsCRP and triglycerides and Lp(a). In the group with the highest degree of inflammation (T2DM patients before the initiation of metformin treatment), the relation of hsCRP with triglycerides and Lp(a) is completely opposite to the one observed among NGT obese subjects. Namely, in T2DM patients prior to the therapy initiation, hsCRP levels are accompanied by a decrease in triglycerides (inverse correlation) and by an increase in Lp(a) level (direct correlation), while these relations are completely inverse in NGT obese individuals. It can be speculated that this scenario reflects the role of increased triglyceride production in the anti-inflammatory response, while Lp(a) molecules are favorably low during the attempt of reducing the increased inflammation.

Barcia et al. [14] suggested that triglyceride-rich lipoproteins, apart from their known role in the fat transportation, can interact with different endotoxins, acting as the immunomodulatory agent in the liver and other tissues during the immune response to infections or, in this case, in the course of subclinical inflammation. This recent study with 52 dyslipidemic subjects showed a strong and significant positive correlation between the serum hsCRP Levels with the serum triglycerides [15]. Some other studies showed that CRP and IL-6 levels correlated with significance positively with Lp(a) levels in hemodialysis patients [16]. Lp(a) levels showed no significant correlations with glycemic control parameters nor insulin and triglyceride levels in study with diabetic patients [17]. Some authors suggest that levels of hsCRP are associated with a disorder of lipid profile such as an increase in total cholesterol, triglycerides and LDL cholesterol and lower HDL—but the mechanism is not entirely clear [18]. Bermudez and al. [19] found, among individuals with metabolic syndrome, that only subjects with hypertriglyceridemia exhibit a greater risk of presenting with elevated level of Lp(a).

In our study, high hsCRP levels are associated (direct correlation) with high Lp(a) levels, and also low hsCRP levels are associated to low Lp(a) levels in T2DM group before metformin therapy initiation, which might imply that low levels of Lp(a) reduce levels of inflammation and damage of blood vessels. High levels of Lp(a) might also show inability to reduce inflammation and exhaustion of physiological mechanism of lowering hsCRP levels with lowering of Lp(a) (e.g. consumption at blood vessel damage repairing). Similar to our study Munoz-Torrero et al. [20] and Katsiki et al. [21] found that MetS patients with elevated Lp(a) levels also had significantly higher levels of pro-inflammatory cytokines and hsCRP compared with MetS patients with normal Lp(a) levels.

High levels of hsCRP and low levels of Lp(a) might predict onset of T2DM which represents the state of high inflammation (characterized by elevated hsCRP) and hypothetically the condition of good response in minimizing damage and repairing blood vessels (characterized by low Lp(a)). European Prospective Investigation of Cancer (EPIC)-Norfolk and the Diabetes Genetics Replication and Meta-analysis, reported a strong inverse relationship between Lp(a) and the risk of T2DM [22]. In present study, in all groups, except T2DM group before metformin therapy initiation, we can observe an inverse correlation between hsCRP an Lp(a) (e.g. increase in Lp(a) is accompanied with decrease in hsCRP and vice versa). This finding might represent the result of presence of lower grade oxidative modification and inflammation and different function of these parameters in all other groups compared to T2DM patients prior to metformin therapy.

A Danish population study found an association between low Lp(a) and incident diabetes [23]. Possible etiology may include the production of large VLDL particles that are less optimal for the assembly of Lp(a) due to its lipid content interfering with interactions of apo(a) kringle repeats with apoB-100. This is supported by the general observation that Lp(a) levels are modestly inversely associated with triglyceride levels in all populations, and indeed, high levels of triglycerides might influence the levels of Lp(a) and most probably its function [24].

Convincing evidence has been presented that the pro-inflammatory and pro-atherosclerotic effects of Lp(a) are largely attributed to different oxidation-specific epitopes (produced in response to reactive oxygen species), present in Lp(a) particles [3]. This might explain a significant change in correlation levels before and after the metformin
treatment. Important changes in linear correlations of Lp(a) and triglycerides with hsCRP point out a possible functional relationship between them, but in a completely opposite direction.

Similar to our study, patients with diabetes have been shown to have lower Lp(a) levels than non-diabetics, in patients with suspected coronary artery disease undergoing coronary angiography [25]. Studies have shown the lower Lp(a) levels are associated with increased risk of incident diabetes. The mechanisms behind these observations are not clear, but imply reverse causality [23].

Recent data show that treatment of patients with rheumatoid arthritis with IL-6 antagonists reduces Lp(a) by ~30% [26]. We also observe significant changes in correlations between two acute phase reactants (Lp(a) an hsCRP), supporting previous statement.

The fact that metformin therapy reduces the relationship of these two parameters to the level present in NGT obese individuals could indicate that the reduction in plasma glucose levels reduces the degree of inflammation and oxidative stress in one’s organism, and that the level of damage and the role of Lp(a) varies depending on the level of inflammatory and oxidative damage. Oxidative stress and glycosylation of Lp(a) molecules, in addition to increased levels of triglycerides and insulin, are an assumed explanation for a significant change in the correlation between Lp(a) and hsCRP. Increased plasma levels of Lp(a) have been accepted as an independent, genetically-conditioned risk factor, for the development of CVD in most of the studies. The useful, protective role of low levels of this lipoprotein in the elimination of harmful proinflammatory molecules of oxidative damage, which was hypothetically observed in our research, should be confirmed by the large-scale prospective studies with the long duration of the follow-up.

Considering that Lp(a) was analyzed by the immunoturbidimetric method, its glycosylation could affect the results. However, reviewing the Package insert test (QUAN-TIA Lp(a), BIOKIT, S.A., Barcelona, Spain) and available literature, we found no clear data about Lp(a) epitopes significant for recognition of this protein by antibodies in the kit, nor could we conclude to what extent their possible glycosylation might impact the result of analysis. The interrogation of the possible effect of glycosylation on applied methodology could be a subject of the future research.

CONCLUSION

In this study, for the first time, we found a significant change in linear correlations for triglycerides and Lp (a) with parameter hsCRP with the onset of diabetes in obese patients and also significant effect of metformin therapy. Oxidative stress and glycosylation of Lp(a) molecules, in addition to increased levels of triglycerides and insulin, are an assumed explanation for a significant change in the correlation between Lp(a) and hsCRP.

In our study, high hsCRP levels are directly associated and correlated with high Lp(a) levels, and also low hsCRP levels are associated to low Lp(a) levels in T2DM group before metformin therapy initiation, which might imply that low levels of Lp(a) reduce levels of inflammation and blood vessels damage. The high levels of Lp(a) might also show inability to reduce inflammation and exhaustion of physiological mechanism of lowering hsCRP levels with lowering of Lp(a) (e.g. consumption at blood vessel damage repair).

The useful, protective role of low levels of Lipoprotein (a) in the elimination of harmful proinflammatory molecules of oxidative damage, which was hypothetically observed in our research, should be confirmed by the large-scale prospective studies with the long duration of the follow-up.

Conflict of interest: None declared.

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Хронична инфламација и параметри липидног статуса код гојазних особа са нормалним и поремећеним метаболизmom глукозе

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