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ORIGINAL ARTICLE

Lifestyle intervention is associated with decreased concentrations of circulating pentraxin 3 independent of CRP decrease

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Abstract

Objectives. Pentraxin 3 (PTX3) is an acute phase marker, which is produced at the site of infection or inflammation in contrast to CRP that is mainly synthesized by the liver. The aim of the present study was to see if lifestyle interventions/weight loss would lead to decreased blood plasma concentrations of PTX3.

Methods. Study subjects (n = 31) were recruited to a lifestyle intervention program aiming at increased physical activity, improved eating habits, and weight loss. High-sensitivity C-reactive protein (CRP) and PTX3 methods were used for analysis of CRP and PTX3 in plasma samples collected at inclusion and after 4 and 8 weeks of treatment.

Results. Wilcoxon paired samples test showed a significant decrease in PTX3 concentrations from 2068 pg/mL at start to 2007 pg/mL at 4 weeks ($P = 0.002$) and 1748 pg/mL at 8 weeks ($P = 0.003$). The PTX3 decrease was not significantly correlated with a corresponding decrease in CRP or weight reduction.

Conclusions. The lifestyle intervention program resulted in a significant reduction of circulating concentrations of pentraxin 3 already after 4 and 8 weeks of treatment.

Key words: *Adult, body weight, CRP, human, inflammation, pentraxin 3, plasma*

Introduction

Pentraxin 3 (PTX3) is an acute phase protein consisting of 381 amino-acids and with a molecular weight of 42 kDa. PTX3 belongs to the same family as the well-established cardiovascular biomarker C-reactive protein (CRP) (1). CRP is probably the most well-known representative of the short pentraxins of this superfamily, while PTX3 is the most studied representative of the long pentraxin arm (2). Pentraxins are important components for innate humoral immunity (2) and thus significant for protection against microorganisms. PTX3 was first identified in vascular endothelial cells and monocytes, but was subsequently shown to be produced by monocytes, macrophages, polymorphonucelar cells, dendritic cells, endothelial cells, fibroblasts, and epithelial cells (3).

PTX3 was suggested to be a candidate marker for inflammatory, infectious, and cardiovascular diseases (4), and elevated expression of PTX3 was found in a number of cardiovascular diseases. For instance, elevated plasma PTX3 concentrations were observed in patients with acute myocardial infarction (AMI) at admission (5). The peak plasma PTX3 concentrations in this study were registered at 7.5 h after AMI. Elevated concentrations were also typical in patients with unstable angina (6,7). PTX3 concentrations turned out to be predictive of the occurrence of cardiovascular (8) and adverse events in patients with heart failure (9). PTX3 is elevated in sleep apnea syndrome, while treatment reduced the plasma concentrations (10). This association between PTX3 expression and CVD has been confirmed in animal models (11).

Obesity and overweight are strong risk factors for cardiovascular morbidity and mortality. Lifestyle intervention programs and weight reduction were effective to reduce cardiovascular risk. The aim of

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the present study was to examine if a lifestyle intervention program could reduce PTX3 concentrations in blood plasma, thereby indicating that PTX3 could form a link between lifestyle changes and CVD risk.

Materials and methods

Study subjects

The study subjects were recruited among the staff at the Department of Clinical Chemistry and Pharmacology, Uppsala University Hospital, Sweden. Inclusion criteria imply that the study subjects volunteered to be part of the weight reduction/fitness program and to donate blood samples. Blood samples were collected in heparinized vacutainer tubes prior to the start of the program and after 4 and 8 weeks. The blood was centrifugated at 2300 *g* for 5 min within 1 hour after sampling, and the samples were immediately frozen and kept frozen until analysis. The subjects' height and weight were measured and BMI calculated at start and after 4 and 8 weeks. Data on height were lacking in two subjects. The study complied with the declaration of Helsinki.

Intervention program

Prior to the study all the subjects participated in a class led by one of the authors (T.Å.). The aim of the education was to present different strategies to promote increased daily physical activities, exercise, and healthy eating habits. Focus on the nutritional advice aimed at inciting to food choices that in turn led to increased satiety and thus negative energy balance (such as enhanced protein intake and avoidance of sweet beverages). However, the subjects were free to choose among several suggested strategies to fit their individual needs and preferences. It was voluntary to report what kind of lifestyle intervention was actually undertaken during the study, and since fewer than half of the participants disclosed such a report, we omitted these data.

Anthropometric measurements

The weight of the subjects was measured on a standard scale (KORONA Model 8018507; KORONA Electric GmbH, Sundern, Germany) under consistent conditions (i.e. time point of day and time interval from last meal).

CRP assay

High-sensitivity CRP (reagent: 6K2601) was analyzed by turbidimetry on an Architect Ci8200 analyzer (Abbott Laboratories, Abbott Park, IL, USA). The CRP assay had a total coefficient of variation of 0.8% at 8 mg/L, and the assay calibrator was traceable to CRM 470. The lower limit of detection of the CRP assay was 0.2 mg/L.

Pentraxin 3 ELISA

Pentraxin 3 was analyzed in blood plasma with a commercial sandwich ELISA (DY1826, R&D Systems, Minneapolis, MN, USA). A monoclonal antibody specific for pentraxin 3 was used as a capture antibody. Standards and samples were pipetted into the wells of microtiter plates, and pentraxin 3 was bound to the immobilized antibodies. After washing, a biotinylated antibody was added. After incubation and washing a streptavidine-HRP conjugate was added to the wells. After further incubation and washing steps a substrate solution was added. The development was subsequently stopped, and the absorbance was measured in a SpectraMax 250 (Molecular Devices, Sunnyvale, CA, USA). The pentraxin 3 concentrations in the samples were determined by comparing the optical density of each individual sample with the standard curve. The assays were calibrated against recombinant human pentraxin 3. The intra-assay coefficient of variation (CV) for the assay was 4.5%, and total CV was approximately 7%.

Statistical calculations

Wilcoxon matched pair test (Statistica, StatSoft Inc., Tulsa, OK, USA) was used to compare values at start and after 4 and 8 weeks. Spearman rank correlation was used to investigate associations between PTX3 and CRP, weight, and BMI. Statistical significance was set at $P < 0.05$.

Results

The study population consisted of 29 females and 2 males with a median age of 51.5 years (interquartile range 46–57 years). The mean BMI at start was 26.1 kg/m^2 (range 24.3–30.5), 25.8 kg/m^2 (24.2–29.8) after 4 weeks, and 25.6 kg/m^2 (24.0–29.3) after 8 weeks, while the mean weight at start was 75.2 kg (range 67.1–83.0), 74.9 kg (66.3–80.8) after 4 weeks, and 73.3 kg (66.4–80.2) after 8 weeks.

Median blood plasma CRP decreased from 1.32 mg/L (interquartile range 0.51–2.17) at start to 1.21 mg/L (0.49–1.64; $P = 0.27$) after 4 weeks and 1.08 mg/L (0.62–1.59; $P = 0.66$) after 8 weeks. The CRP decrease after 4 weeks was significantly associated with the concomitant weight reduction

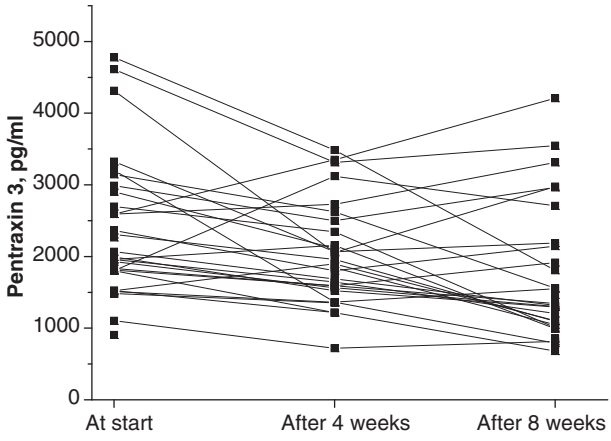

Figure 1. Pentraxin 3 in individual patients at start, and after 4 weeks and 8 weeks of lifestyle intervention.

(n = 26; Spearman R = 0.71; P = 0.00005) and after 8 weeks (n = 26; R = 0.67; P = 0.00018). Median plasma PTX3 values decreased from 2068 pg/mL (interquartile range 1800–2904) at start to 2007 pg/mL 1544–2422 after 4 weeks and 1748 pg/mL 1044–2188 after 8 weeks (Figure 1). In comparison with values at start, plasma PTX3 concentration was significantly reduced after 4 weeks (P = 0.002) and after 8 weeks (P = 0.003).

No significant Spearman rank correlations were observed between CRP and PTX3 at start (R = 0.14), after 4 weeks (R = –0.02), and after 8 weeks (R = 0.00), nor were there any significant correlations between PTX3 and BMI at start (R = –0.12), after 4 weeks (R = 0.02), and after 8 weeks (R = –0.09) or weight at start (R = –0.03), after 4 weeks (R = 0.07), and after 8 weeks (R = 0.05). Likewise, there were no significant Spearman rank correlations between the decrease of PTX3 and the decrease of CRP from the start to 4 weeks (R = –0.34) and 8 weeks (R = –0.33) of treatment, nor were there any significant correlations between the PTX3 decrease and BMI at 4 weeks (R = –0.21) and 8 weeks (R = –0.28) or weight decrease at 4 weeks (R = –0.35) and 8 weeks (R = –0.33).

Discussion

The World Health Organization estimated in 2008 that about 1.5 billion adults were overweight while over 200 million men and nearly 300 million women were obese. Obesity was once considered a problem only for citizens in high-income countries, but today it is more or less universal, and obesity rates are increasing worldwide. Obesity is a strong risk factor for morbidity and mortality in all age groups and a major economic burden for the health care providers. Obesity-related disorders are also associated with impaired quality of life for the individual. Reduction of obesity and associated morbidity and mortality is a primary target for the health care system.

CRP is a widely used cardiovascular risk marker. Similarly, PTX3 has been reported to be a biomarker for a number of different clinical conditions such as cardiovascular disease and death (12), atherosclerosis (13), non-alcoholic steatohepatitis (14), pulmonary infections and lung injury (15), systemic lupus erythematosus (16), systemic sclerosis (17), pre-eclampsia (18), and lung cancer (19). In contrast to CRP that is synthesized mainly in the liver, PTX3 is produced at the site of infection or inflammation by macrophages, monocytes, dendritic cells, and tissue cells. Thus, it seems likely that PTX3 could respond differently to CRP in response to lifestyle intervention.

The weight reduction in this study was rather modest with a mean decrease of 0.8 kg after 4 weeks and 1.4 kg after 8 weeks. Nevertheless, we found significantly decreased plasma PTX3 concentrations after 4 and 8 weeks of intervention. A reduction in PTX3 should be a desirable outcome of the intervention program since increased PTX3 concentrations are associated with increased cardiovascular morbidity and mortality (12,13).

As already mentioned, PTX3 and CRP have different sites of production, and this might be reflected by their discriminative relationships against BMI reduction. Hence, in contrast to CRP, we did not find any associations between alterations in PTX3 and BMI over time. Also, the difference between the two markers seems to be in agreement with previous reports that PTX3 is a risk marker for CVD independent of CRP (12). The observed change in PTX3 concentration induced by the lifestyle intervention is not a direct effect of weight reduction, but rather reflects other alterations caused by the intervention.

This study has some important limitations: The study is based on mainly females of northern European descent, so generalizability to other ethnic groups is uncertain. The number of study subjects is small, and we lack data on the actual lifestyle changes chosen by the individual study subjects.

In conclusion, PTX3 in blood plasma seems to reflect other and probably more complex processes than merely a change in weight or BMI, which makes the biomarker even more interesting for monitoring lifestyle interventions. Further studies on the association between lifestyle-induced decreases in PTX3 concentrations in blood plasma, as demonstrated in the present study, and cardiovascular morbidity and mortality would be of great interest.

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