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Original Research

PTX3 as a biomarker of lowered arterial stiffness due to weight loss in overweight and obese Japanese men

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Abstract

Background: Obesity, an independent cardiovascular disease risk factor, is the leading cause of death in the world. It has been previously shown that arterial stiffness,which is an index of cardiovascular disease, is significantly higher in Japanese overweight and obese men. Increased levels of pentraxin3 (PTX3), a novel anti-inflammatory substance mainly produced in the atherosclerotic region, due to weight reduction has been proposed to reflect an improvement in arterial stiffness. However, this has not been investigated. **Methods**: Here, we elucidate whether an individual who has significantly increased plasma PTX3 concentration result in a significantly decreased arterial stiffness compared to a smaller change in PTX3 level after a 12-week dietary modified weight reduction program in twenty overweight or obese Japanese men. A well-balanced dietary modification weight-loss program was implemented for overweight and obese men over a course of 12-week. **Results**: Prior to and after the program, we measured anthropometric variables, blood pressure, arterial stiffness, and circulating biochemistry, including plasma PTX3 concentrations. We then compared the differences in arterial stiffness between two groups, low or high ΔPTX3 groups, based on the median of delta of plasma PTX3 levels before and after weight reduction via modified diet habit in men with overweight and obesity. Carotid-femoral pulse wave velocity (PWV) as index of central arterial stiifness and brachial-ankle PWV as index of whole body arterial stiffness were significantly decreased in the high ΔPTX3 group after dietary modification. **Conclusions**: Our present results suggest that PTX3 could be a clinically useful biochemical index for monitoring appropriate arterial function maintenance in obese weight control.

Keywords: Inflammation; Obesity; PTX3; Weight loss; Men

1. Introduction

One of the leading cause of death is cardiovascular disease (CVD) in the world, and obesity is an independent risk factor for CVD [1]. We have previously shown that arterial stiffness is significantly higher in Japanese men with obesity versus those with normal body weight [2], having reported as in other races [3]. In people with obesity, lowering the body mass and reducing CVD risk factors (i.e., high blood pressure and arterial stiffness etc.) are necessary to prevent the development of CVD. We have previously demonstrated that dietary modification-induced weight reduction decreased arterial stiffness and is one of the most effective ways to improve arterial stiffness [4–6]. However, an excessive weight reduction may cause certain side effects, such as weakened immune system and increased risk for severe infectious diseases. For example, most of Judo players need to reduce their weight several times in a year during each game. A recent study demonstrated that overweight Judo players who experienced weight loss of over 5% from baseline had a higher frequency of positive symptoms of upper respiratory tract infection and a lowered mental condition at the same time [7]. Indeed, people who are lean or obese are suggested to have a higher mortality risk for coronavirus disease 2019 (COVID-19), one of the most common severe infectious diseases at present [8]. Therefore, establishing an effective biomarker of improvement in CVD risk and prevention of excessive weight loss is necessary for contemporary society.

It is well established that obesity is characterized by chronic and increased systemic inflammation which lead to several diseases, including CVD [9]. Pentraxin3 (PTX3) is a novel anti-inflammatory substance, produced mainly in endothelial cells, macrophages, and smooth muscle cells at the atherosclerotic parts [10]. In a cross-sectional study, we have reported that PTX3 levels in Japanese normal-weight men were significantly higher than those in overweight and obese people who have been matched with gender and nationality [2]. Interestingly, we have previously demonstrated that weight reduction programs improved both circulating PTX3 levels and arterial stiffness in individuals with obesity [6]. Therefore, increased PTX3 levels due to the weight reduction program may reflect an improvement in arterial stiffness. However, this association has not yet been clarified.

The purpose of this study was to elucidate whether an individual who has significantly increased plasma PTX3 concentration leads to a significantly decreased arterial stiffness compared to a smaller change in PTX3 level after a 12-week dietary modification weight-loss program in overweight or obese Japanese men. We hypothesized that the decreased amount of arterial stiffness is greater in overweight and obese adult men with increased plasma PTX3 concentration after weight loss. To validate our hypothesis, we performed a well-balanced weight-loss program by dietary modification in overweight and obese men. Prior to and after the program, we measured plasma PTX3 concentrations and other physiological characteristics, including pulse wave velocity (PWV), as an index of arterial stiffness. We then compared the differences in arterial stiffness between the two groups, low or high ΔPTX3 groups, based on the median of delta of plasma PTX3 levels before and after dietary modified weight reduction in overweight and obese men.

2. Materials and methods

2.1 Participants and experimental design

Twenty overweight and obese adult Japanese men (age: 39–64 years, BMI: 25.0–37.5 kg/m^2) were included in the study; those with a history of CVD and other chronic diseases were excluded. All participants were measured for anthropometric variables, PWV, an index of arterial stiffness, blood pressure, and blood biochemistry included in plasma PTX3 concentrations, before and after a 12-week weight-loss program (i.e., energy-restricted diet). All measurements were performed after overnight fasting, including abstinence from caffeine and alcohol. The participants were studied in a quiet and temperature-controlled between 24–26 °C room under supine resting conditions. All measurements were performed after a resting period of at least 20 min. This study was reviewed and approved by the Institutional Review Board of Ryutsu Keizai University (#H27-6). Procedures and risks of the present study were explained to the subjects, and they agreed to the study concept and methods via provided written informed consent to participate in the study. In accordance with the World Health Organization definitions, classifications of overweight and obese were defined by Body Mass Index (BMI) values. Especially, participants with BMI $\geq$25 kg/m^2 and $<$30 kg/m^2 were categorized in overweight, and the others with BMI $\geq$30 kg/m^2 were as obese.

2.2 Dietary modification program, dietary records, and physical activity assessment

The protocol used in our previous study [4] has been shown as a low-calorie diet intervention with effects on body composition and risk factors for cardiovascular disease [11]. Based on the diet protocol in the previous study, all participants were instructed to consume meals containing an average of 840 kcal of carbohydrate and 420 kcal each of protein and fat per day (total: 1680 kcal/day) in the present study [4]. Daily food diaries were kept during the intervention term in all participants, and were educated about proper daily nutrition through weekly lectures and counseling by skilled dietitians and trained diet support staff. The participants were asked to record their daily food intake for three days prior to the dietary modification intervention term until the end of the study. As energy intake results of dietary records and assessment before and after the program, we compared the difference before the average 3-day records and that of 12th-week. The total daily energy intake was estimated by a dietitian from food intake records using Excel Eiyo-Kun version 4 software (Kenpakusya, Tokyo, Japan). The participants were instructed to maintain their daily physical activities. Using an activity monitor (Kenz Lifecorder GS; Suzuken Co., Ltd., Nagoya, Japan) as data of physical activity was monitored according to our previous study [4]. All participants wore the accelerometer for 14 days before starting and until the end of the weight-loss program.

2.3 Anthropometric variables

Body mass was measured using a digital scale to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer, which was metal measuring tool. BMI was calculated as weight (kg) divided by the square of the height (m). Waist circumference (WC) at the level of the umbilicus with the participant standing was measured to the nearest 0.1 cm.

2.4 Arterial stiffness, heart rate, and blood pressure

Using a noninvasive vascular profiling system (form PWV/ABI; Colin Medical Technology, Komaki, Japan), Carotid-femoral PWV (cfPWV), brachial-ankle PWV (baPWV), heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured as described previously [4]. Especially, PWV was calculated as the distance divided by the transit time and assessed in duplicate.

2.5 Blood biochemistry

Serum concentrations of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), and plasma concentrations of glucose at fasting (FBG) and hemoglobin A1c (HbA1c) were analyzed and measured using standard enzymatic techniques. Plasma PTX3 levels were measured using a commercial enzyme immunoassay kit as performed in previous study (DPTX30; R&D Systems, Minneapolis, MN, USA) [2,6].

2.6 Statistical analyses

The data of values are expressed as the average $\pm$ standard deviation (SD). All subjects were divided into two groups based on whether their circulating PTX3 levels were higher or lower than the median value of change of them be-

Table 1. Changes of characteristics before and after lifestyle modification in low-ΔPTX3 and high-ΔPTX3 groups. Mean ± SD. $^{**}p < 0.01$, $^{*}p < 0.05$ vs. baseline; †$p < 0.05$ vs. baseline of low-ΔPTX3.

	low-ΔPTX3		high-ΔPTX3		Main Effect		Interaction Effect
	Pre	Post	Pre	Post	Time	Group	
Body mass, kg	81.9 ± 7.3	74.0 ± 6.9**	87.9 ± 10.5	76.0 ± 8.6**	**<0.001**	0.384	0.135
BMI, kg/m^2	27.6 ± 0.4	25.0 ± 0.4**	29.8 ± 1.1	23.4 ± 2.8**	**<0.001**	0.191	0.120
Waist circumference, cm	96.0 ± 1.8	87.2 ± 1.5**	101.1 ± 2.2	89.1 ± 2.2**	**<0.001**	0.197	0.093
SBP, mmHg	125 ± 3	116 ± 2**	134 ± 6	120 ± 4*	**<0.01**	0.243	0.424
DBP, mmHg	81 ± 2	77 ± 2*	87 ± 4	77 ± 3**	**<0.001**	0.400	0.060
Heart rate, bpm	57 ± 1	54 ± 2*	64 ± 3†	55 ± 2**			
Total cholesterol, mg/dL	206 ± 7	178 ± 5**	207 ± 10	175 ± 9**	**<0.001**	0.927	0.664
HDL cholesterol, mg/dL	50 ± 4	51 ± 4	49 ± 4	51 ± 4	0.386	0.942	0.942
Triglyceride, mg/dL	113 ± 14	80 ± 9*	116 ± 10	66 ± 6**	**<0.001**	0.689	0.255
Fasting glucose, mg/dL	91 ± 1	89 ± 2	96 ± 3	86 ± 2**	**<0.01**	0.625	0.098
HbA1c, %	5.1 ± 0.3	5.0 ± 0.3	5.3 ± 0.3	5.1 ± 0.3	0.106	0.501	0.799
HOMA-IR, IU/mL	1.54 ± 0.22	0.98 ± 0.12**	2.41 ± 0.41	1.14 ± 0.26**	**<0.01**	0.100	0.158
Energy intake, kcal/day	2249 ± 81	1607 ± 47**	2549 ± 163	1528 ± 29**	**<0.001**	0.217	0.101
Physical activity, kcal/day	283 ± 34	313 ± 58	318 ± 38	316 ± 38	0.520	0.742	0.483

fore and after the dietary modification. Baseline differences in each characteristic between the two groups were confirmed by an unpaired *t*-test. Statistical analysis was performed using a two-way (time-by-group) analysis of variance with repeated measures to determine the intergroup differences in the effects of the intervention. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS software v23 (IBM, Tokyo, Japan).

3. Results

Based on values higher or lower than the median value of changes in circulating PTX3 levels before and after dietary modification intervention, we compared all characteristics in the two groups as shown in Table 1. Energy intake showed significant main effects of time but not any group × time interaction effects. No significant baseline difference was found in any of the characteristics between the groups, excluding heart rate. Most of the characteristics, excluding HDL cholesterol, HbA1c, and physical activity levels, showed significant main effects of time but not any group × time interaction effects. There was no significant interaction in BMI between groups. Moreover, there was no significant interaction in the indices of metabolic syndrome, WC, SBP and DBP, TG, HDLC, and FBG levels after the intervention. Circulating PTX3 levels were significantly increased in the high ΔPTX3 group, as shown in Fig. 1. By contrast, cfPWV and baPWV were significantly decreased in the high ΔPTX3 group after dietary modification, as shown in Fig. 2 (interaction effect, $p < 0.05$ and $p < 0.01$ respectively).

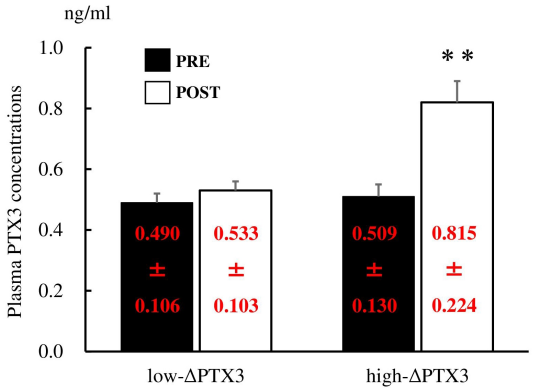

Fig. 1. Changes in plasma PTX3 concentrations before and after dietary modification program in the high and low ΔPTX3 groups. $^{**}p < 0.01$ vs. Pre.

4. Discussion

The present study tried to elucidate whether PTX3 is a biomarker of improvement in arterial stiffness induced by dietary modification-induced weight reduction in overweight and obese men. We observed significant reductions in baPWV and cfPWV in the high ΔPTX3 group but not the low ΔPTX3 group. Our results propose PTX3 as a novel biomarker of improvement in arterial stiffness as a result of weight reduction in overweight and obese men.

Several previous studies have suggested that PTX3 exerts cardioprotective effects. Circulating PTX3 levels are positively correlated with endothelial function in individuals with chronic diseases [12–14]. It has been suggested that PTX3 has an anti-atherosclerotic role in vascular endothelial cells [15], and it was shown that PTX3 exhib-

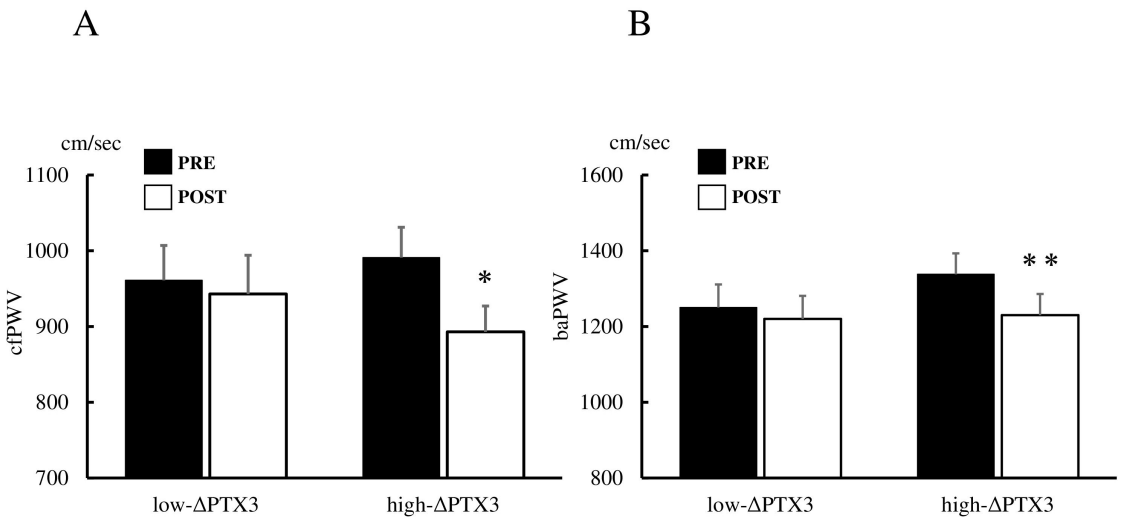

Fig. 2. Changes in (A) baPWV and (B) cfPWV before and after dietary modification program in the high and low ΔPTX3 groups. $^{**}p < 0.01$, $^{*}p < 0.05$ vs. Pre.

ited a cardioprotective effect in an acute myocardial infarction mouse model [16]. For example, *ptx3*-deficient mice showed significantly greater exacerbation of heart damage with increased neutrophil infiltration and number of apoptotic cardiomyocytes than the wild-type controls [16]. We have previously reported that endothelial function assessed by circulating levels of ET-1 and NOx was improved in men who are overweight and obese after the same dietary modification program used in the present study [4]. Although we did not assess endothelial function in the present study, increased plasma PTX3 levels may reflect an improvement in endothelial function.

We recently demonstrated a negative significant relationship between changes in body mass and circulating plasma PTX3 concentrations after lifestyle modification programs [6,17]. In contrast, no significant difference in the change in body mass between the two groups was observed in the present study. One possible explanation is the difference in the method of the weight reduction program. A combination of dietary modification and aerobic exercise training was employed as a weight reduction program in our previous study, whereas only dietary modification was applied in the present study. Since endurance-trained men exhibit a higher plasma PTX3 concentration [18], aerobic exercise itself influences plasma PTX3 levels and may cause a different response. The difference in the amount of weight reduction could be another possibility. We have reported that weight reduction by dietary modification is much larger than that by habitual aerobic exercise in overweight and obese individuals [19], and a combination of these methods showed the largest weight reduction among them. Therefore, the difference in the weight reduction program implemented may have contributed to the different observations.

Improving obesity could be important for increasing plasma PTX3 levels in overweight and obese individuals. Our recent study suggested that the participants who successfully reduced their body mass to the normal range (25 kg/m^2) through a combination of dietary modification and habitual aerobic exercise showed a greater improvement in plasma PTX3 levels than their counterparts. Interestingly, although no significant interaction in the change in BMI between the low and high ΔPTX3 groups, the present study showed that the average BMI after dietary modification in the high ΔPTX3 group was within the normal range. These findings imply that a successful weight reduction and achievement of normal BMI may help improve plasma PTX3 levels, regardless of the weight-loss program.

5. Conclusions

In this study, we demonstrated the relationship an increase in plasma PTX3 concentration after weight-loss via dietary modification in overweight and obese Japanese men with decreasing arterial stiffness.

Author contributions

AZM, KT and SM designed this study. HK, AZM, TY, KT, and SM performed experiments and analyzed the data. AZM, HK and SM made the first draft of the manuscript and all authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Ryutsu Keizai University (#H27-6) and conformed to the principles outlined in the Declaration of

Helsinki. All Participants provided written informed consent before inclusion in the study.

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Conflict of interest

The authors declare no conflict of interest.

References

[1] Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation. 1983; 67: 968–977.

[2] Miyaki A, Maeda S, Choi Y, Akazawa N, Eto M, Tanaka K, *et al*. Association of Plasma Pentraxin 3 with Arterial Stiffness in Overweight and Obese Individuals. American Journal of Hypertension. 2013; 26: 1250–1255.

[3] Wildman RP, Mackey RH, Bostom A, Thompson T, Sutton-Tyrrell K. Measures of Obesity are Associated with Vascular Stiffness in Young and Older Adults. Hypertension. 2003; 42: 468–473.

[4] Miyaki A, Maeda S, Yoshizawa M, Misono M, Saito Y, Sasai H, *et al*. Effect of weight reduction with dietary intervention on arterial distensibility and endothelial function in obese men. Angiology. 2009; 60: 351–357.

[5] Miyaki A, Maeda S, Yoshizawa M, Misono M, Saito Y, Sasai H, *et al*. Effect of Habitual Aerobic Exercise on Body Weight and Arterial Function in Overweight and Obese Men. American Journal of Cardiology. 2009; 104: 823–828.

[6] Zempo-Miyaki A, Kumagai H, Yoshikawa T, Myoenzono K, So R, Otsuki T, *et al*. Pentraxin 3 increases in adult overweight and obese men after weight loss by dietary modification with exercise training. Applied Physiology, Nutrition, and Metabolism. 2019; 44: 111–117.

[7] Hiraoka H, Hanaoka Y, Jesmin S, Kimura F, Matsuish Y, Shimizu K, *et al*. Variation of Salivary IgA during Weight Loss Period before a Competition among University Judo Players. Journal of Clinical Medicine Research. 2019; 11: 798–806.

[8] Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, *et al*. Obesity and Mortality among Patients Diagnosed with COVID-19: Results from an Integrated Health Care Organization. Annals of Internal Medicine. 2020; 173: 773–781.

[9] Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S, *et al*. Adipokines: molecular links between obesity and atherosclerosis. American Journal of Physiology-Heart and Circulatory Physiology. 2005; 288: H2031–H2041.

[10] Ristagno G, Fumagalli F, Bottazzi B, Mantovani A, Olivari D, Novelli1 D, *et al*. Pentraxin 3 in cardiovascular disease. Front in Immunology. 2019; 10: 823.

[11] Okura T, Nakata Y, Yamabuki K, Tanaka K. Regional body composition changes exhibit opposing effects on coronary heart disease risk factors. Arteriosclerosis, Thrombosis, and Vascular Biology. 2004; 24: 923–929.

[12] Yasunaga T, Ikeda S, Koga S, Nakata T, Yoshida T, Masuda N, *et al*. Plasma pentraxin 3 is a more potent predictor of endothelial dysfunction than high-sensitive C-reactive protein. International Heart Journal. 2014; 55: 160–164.

[13] Suliman ME, Yilmaz MI, Carrero JJ, Qureshi AR, Saglam M, Ipcioglu OM, *et al*. Novel links between the long pentraxin 3, endothelial dysfunction, and albuminuria in early and advanced chronic kidney disease. Clinical Journal of the American Society of Nephrology. 2008; 3: 976–985.

[14] Kocyigit I, Eroglu E, Orscelik O, Unal A, Gungor O, Ozturk F, *et al*. Pentraxin 3 as a novel bio-marker of inflammation and endothelial dysfunction in autosomal dominant polycystic kidney disease. Journal of Nephrology. 2014; 27: 181–186.

[15] Norata GD, Marchesi P, Pulakazhi Venu VK, Pasqualini F, Anselmo A, Moalli F, *et al*. Deficiency of the Long Pentraxin PTX3 Promotes Vascular Inflammation and Atherosclerosis. Circulation. 2009; 120: 699–708.

[16] Salio M, Chimenti S, De Angelis N, Molla F, Maina V, Nebuloni M, *et al*. Cardioprotective function of the long pentraxin PTX3 in acute myocardial infarction. Circulation. 2008; 117: 1055–1064.

[17] Miyaki A, Maeda S, Choi Y, Akazawa N, Tanabe Y, So R, *et al*. The addition of whole-body vibration to a lifestyle modification on arterial stiffness in overweight and obese women. Artery Research. 2012; 6: 85–91.

[18] Miyaki A, Maeda S, Otsuki T, Ajisaka R. Plasma pentraxin 3 concentration increases in endurance-trained men. Medicine and Science in Sports and Exercise. 2011; 43: 12–17.

[19] Maeda S, Zempo-Miyaki A, Sasai H, Tsujimoto T, So R, Tanaka K. Lifestyle Modification Decreases Arterial Stiffness in Overweight and Obese Men: Dietary Modification vs. Exercise Training. International Journal of Sport Nutrition and Exercise Metabolism. 2015; 25: 69–77.