Clinical Report 3 (Japan)

Treatment of Obesity with Bofutsushosan: Obesity is inflammation

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Introduction

C-creative protein (CRP) identified by *Tilet* and *Francis* in 1930 in the plasma of pneumococcus-infected patients with pneumonia is a member of the class of acute phase proteins that precipitate with C-polysaccharide. As is well known, CRP has been widely used as a marker for the presence of inflammation and its activity factor, especially in infectious diseases among inflammatory diseases. With the recent development of a high-sensitive technique for CRP determination, however, the levels of as low as 0.02mg/dl can be traced, leading to disclosure of sub-clinical inflammatory conditions. Thus, disorders that previously were not in the category of inflammation, like hypertension, hyperlipidemia, diabetes, and obesity, and even metabolic syndrome that is a complex of these disorders, are now regarded as chronic inflammation of vascular endothelium and adipose tissue. In fact, it has been demonstrated that high-sensitive CRP (hsCRP) correlates with BMI, waist circumference measurement, and amount of visceral fat. The hsCRP is also considered as an independent risk factor in the events of cardiovascular diseases and type 2 diabetes mellitus, and is associated with the onset of hypertension. The hsCRP level is an important indicator in managing lifestyle-related diseases inclusive of metabolic syndrome. Meanwhile, *bofutsushosan,* a herbal medicine Liu wuan-su originally prescribed to "rid of stagnation and depression of all the wind-heat" is now often used for the treatment of obesity rather than for that of infectious diseases. In this paper, I would like to take up the theme of "obesity is inflammation" through the therapy of *bofutsushosan* for the treatment of a patient who was obese with fatty liver.

Clinical Report

Patient: Male, 44-years old (school teacher for handicapped children)

Chief complaint: Obesity and fatty liver

Present illness

The patient had been identified with liver function abnormalities (ALT67IU/L) in the medical examination of July, 2004 and made his first visit to us. In his initial visit, obesity (weight 85 kg, BMI 29.4) and moderate fatty liver were observed, and the extract of *bofutsushosan* was administered, resulting in no reduction in weight. Three months later, the treatment was discontinued on his own judgment. On July 2005, the patient had a weight increase by 3 kg with the elevated ALT to 85IU/L and returned to the clinic.

Physical findings

The patient's height was 170cm, weight 88kg (BMI30.4), and blood pressure 142/92mmHg. There were no abnormalities in cardiopulmonary auscultation. Pulse palpitation was somewhat empty but deep at the rate of 76/min. The tongue was bright red colored, engorged, and somewhat excessively wet without no scars of teeth, spots and dilation of sublingual veins. The coating of the tongue was yellowish white and moderately thick. There were no resistance and tenderness in the abdomen. The waist circumference measured 94cm and obesity of visceral fat type was observed.

Laboratory findings

Laboratory tests revealed the following values: peripheral erythrocyte count $470x10^6/mm^3$, Hb 14.1g/dl, Ht 41%, total bilirubin 0.4mg/dl, AST 41 IU/L, ALT 85 IU/L, γ-GTP 48 IU/L, total cholesterol 204mg/dl, LDL cholesterol 105mg/dl, HDL cholesterol 62mg/dl, triglyceride 94mg/dl, uric acid 7.5mg/dl, FBS 90mg/dl, HbA_{1c} 4.8%, hsCRP 0.158mg/dl, HBs antigen (-), and HCV antibody (-).

Clinical Course

The patient was not eager to play sports/do workout. He liked sweet goods although he did not drink alcohol. The therapy of *bofutsushosan* was resumed under his usual diet and living habit. As previously, no decreases were observed in weight and ALT levels for three months after the resumption of the treatment. Meanwhile, the levels of hsCRP

dropped sharply. Subsequently, the oral administration was continued, resulting in gradual decreases in the weight and ALT levels. In July 2006, improvement was achieved in the weight to 84kg, ALT to 31 IU/L and hsCRP to 0.039mg/dl (Chart 1).

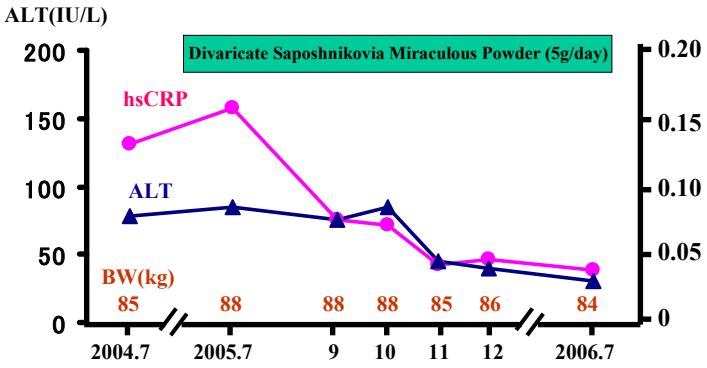

Chart 1: Clinical course (Male, 44 years old)

Discussion

Obesity is a condition in which excessive fat is accumulated in the body. As well as storing energy surplus in cells in the form of triglycerides, enlarged adipocytes in obese subjects secrete inflammatory cytokines (TNFα, etc), kemokines (monocyte chemoattractant protein-1: MCP-1, etc.) and hormones (adiponectin, leptin, etc.). Adipose tissue is comprised of mature adipocytes and stromata (stromal-vascular fraction: SVF). SVF contains monocytes, macrophages, preadipocytes, blood vessel components, and fibroblasts, presumably regulating reproduction / differentiation of adipocytes, and inflammation in the adipose tissue. In fact, Anty et al.[1] have reported that in obese patients there is a positive relation between the amount of IL-6 and the amount of CRP mRNA and that IL-6 and CRP exist in both mature adipose cells and SVF, more of them existing in the latter five to eight folds. It is assumed that in obese subjects, TNFα and MCP-1 secreted from enlarged adipocytes allow monocytes/macrophages to infiltrate into adipose tissue, where IL-6 is released. And I consider that the released IL-6 enhances CRP secretion from preadipocytes at local adipose tissue and from liver cells at remote organs (Chart 2). There is a recent report that CRP mediates LDL uptake by macrophages; attenuates synthesis of NO while increasing production of endothelin-1 (ET-1) and plasminogen activator inhibitor-1 (PAI-1) from vascular endothelium; and induces secretion of IL-6 and MCP-1 from endothelium. CRP is not merely an inflammation marker but also one of important factors directly linked to the events of atherosclerosis and thrombosis.

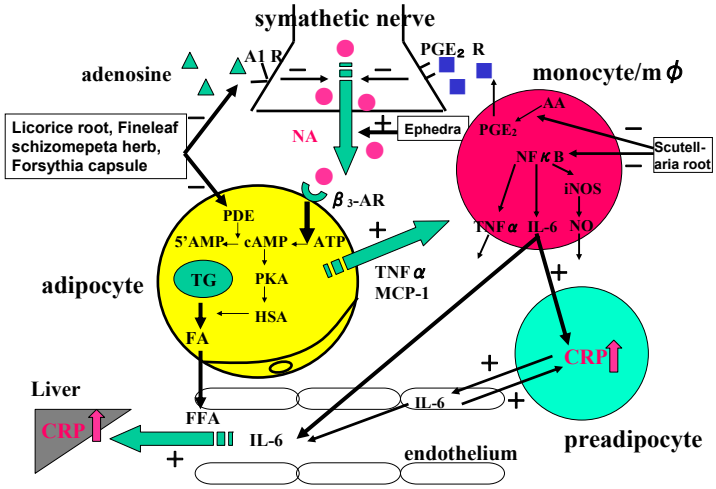

Chart 2: Mechanism of CRP increase in obesity (assumption)

To prevent cardiovascular events in patients with obesity, losing 5% of the current weight is the initial treatment goal to be achieved. It should, however, be remembered to reduce the levels of hsCRP. It is beyond any doubt that weight control by diet/exercise therapy alone can lower the hsCRP concentration. This is probably because burning of tryglycerides accumulated in adipocytes contributes to lower the secretion of TNFα and MCP-1 from adipose tissue, accompanying the reduced secretion of IL-6 from monocytes/macrophages. For middle-aged working people who are busy and have no exercise habit, like the subject case in this report, however, weight reduction through diet/exercise is often extremely difficult. In this case with obesity, treatment was performed only with *bofutsushosan* without employing diet/exercise, and the reduced hsCRP/ALT and weight loss were encountered. The ingredients making up the *bofutsushosan* are *Ephedorae* Herba, *Saposhnikoviae* Radix, *Schizonepetae* Spica, and wild mint to expel heat that does not diffuse from the body surface; *Rhei* Radix and *Natrii Sulfas* that are excreted in stool; *Kasseki*(talc) that is excreted in urine; *Gypsum* Fibrosum, *Scutellariae* Radix, *Gardeniae* Fructus, *Forsythiae* Fructus, and *Platycodi* Radix for internal

heat to subside; *Angelicae* Radix, *Peoniae* Radix, *Cnidii* Rhizoma, *Atractylodis* Rhizoma, *Zingiberis* Processum Rhizoma, and *Glycirrhizae* Radix to increase Qi and blood. Ephedorine in *Ephedorae* Herba promotes the release of noradrenaline (NA) from sympathetic nerve terminals[2]. When NA binds to β_3-adrenaline receptors present in the surface of adipocytes, the concentration of cAMP in adipocytes is elevated and hormone sensitive lipase is activated by catalytic PKA to decompose triglycerides. When adenosine A1 receptors and PGE_2 receptors in the sympathetic nerve terminals are stimulated, the release of NA from nerve terminals is suppressed. Xanthine derivatives included in licorice, fineleaf schizonepeta herb, and forsythia capsule work to inhibit adenosine A1 receptors, and scutellaria root works to inhibit synthesis of PGE_2 through mediation of COX_2 in monocytes/macrophages (aspirin-like action). These two functions indirectly serve to facilitate NA releases from sympathetic nerve terminals. Moreover, since Xanthine derivatives (licorice, fine leaf schizonepeta, and forsythia capsule) inhibit breakdown of cAMP in adipocytes through the inhibition of phosphodiesterase (caffeine-like action)[2], *bofutsushosan* can yield the effect of fat burning even in Japanese people who often have β_3-AR gene mutation. The menthol in wild mint possibly stimulates TRPM8, one of cold receptors, in peripheral nerves and activates the sympathetic nerves through the hypothalamus to promote catabolic action.

In the subject case, however, lowering levels of CRP were observed soon after the start of the administration of *bofutsushosan* and subsequently weight loss and improvement in ALT value were encountered. This cannot be explained sufficiently by the breakdown of triglycerides being accelerated in adipocytes and hepatocytes. Piao et al. [3] have reported that in a rat reperfusion model of focal cerebral ischemia, scutellaria root suppressed the release of TNFα, IL-6 and NO from activated microglia (intracerebral macrophages) by inhibiting the NF-κB signaling pathway. *Daisaikoto*, also frequently used for the treatment of obesity or fatty liver, includes *Scutellariae* Radix. I consider that the reduced levels of CRP induced by the *bofutsushosan* in obesity may be significantly attributed to an important role in direct anti-inflammatory activity of *Scutellariae* Radix against monocytes/macrophages.

Presently for *Natrii* Sulfas, mostly hydrous sodium sulfate ($Na_2SO_4 \cdot 10H_2O$) is used, whereas it is shown by Masutomi [4] that mirabilite is hydrous magnesium sulfate ($MgSO_4 \cdot 7H_2O$). Both compounds have potent purgation, but hydrous sodium sulfate is not desirable to the obese patients who are frequently predisposed to an accompanying hypertension due to a sodium load. Meanwhile, lowered levels of blood magnesium (Mg^{2+}) cause aggravation of the pathologic status of hypertension, hyperlipidemia, and atherosclerosis. In fact, low levels of blood magnesium are observed in obese patients and there is a report that magnesium supplementation can achieve weight reduction. Magnesium is necessary for activating lipoprotein lipase to decompose tryglycerides. Magnesium deficiency can develop hypertriglyceridemia. Presently, magnesium oxide, a laxative agent has been given as an attempt to the obese patients with normal renal function at low dosages. In this sense, it is preferable that mirabilite in the *bofutsushosan* is hydrous magnesium sulfate.

The *bofutsushosan* used this time was an extract drug and administered twice a day, in the morning and at night. At the time of the first treatment, the dosing schedule was conveniently set for the patient due to difficulty taking medication during working hours. It was amazing that the doses in two-thirds of the regular amount yielded sufficient decreases in the levels of hsCRP, ALT and weight with no complementary diet/exercise therapy. Meanwhile, for the initial three months after the administration was started, completely no weight loss was observed regardless of the amount of dosage. Although I had doubts temporarily about the efficacy of the *bofutsushosan*, the observation of a decrease in hsCRP prompted me to continue the treatment.

The subject case of the report is on the borderline of metabolic syndrome from the Japanese criteria for

metabolic syndrome. Among the patients on the borderline, however, some have increased levels of hsCRP. The subject case had the history of no alcoholic drinks with fatty liver, which cannot be discriminated between simple fatty liver (steatosis) and nonalcoholic steatohepatitis (NASH) since liver biopsy was not performed. Even nonalcoholic fatty liver disease (NAFLD), a disease concept covering from non-progressive simple steatosis to progressive NASH, poses a variety of problems of hypercytokinemia, oxidative stress, and insulin resistance with accumulation of visceral fat. Chart 3 and 4 exhibit results of the treatment with the *bofutsushosan* in 6 cases of obesity (5 males and 1 female) with NAFLD, inclusive of the subject case. With the consent of all the patients, they received only *bofutsushosan* without concomitant diet・exercise therapy. In the third month since the therapy started, the levels of hsCRP in blood significantly dropped from 0.237±0.060mg/dl to 0.140±0.065mg/dl ($p < 0.05$), and other profiles indicated decreases but were not statistically significant; weight 86.1±3.0kg to 84.3±3.4kg, blood AST values 37±4IU/L to 30±IU/L, and blood ALT values 56±4IU/L to 50±10IU/L. It can be expected that *bofutsushosan* calms inflammation in the adipose tissue, vascular endothelia and liver not only by the effect of weight reduction as previously mentioned but also by lowering the levels of hsCRP, which prevent progression of atherosclerosis and liver cirrhosis. In the obese patients whose hsCRP values are 0.1mg/dl or more with metabolic syndrome and/or NAFLD, the herbal therapy with *bofutsushosan* as well as diet and or exercise therapy should be attempted in a positive manner.

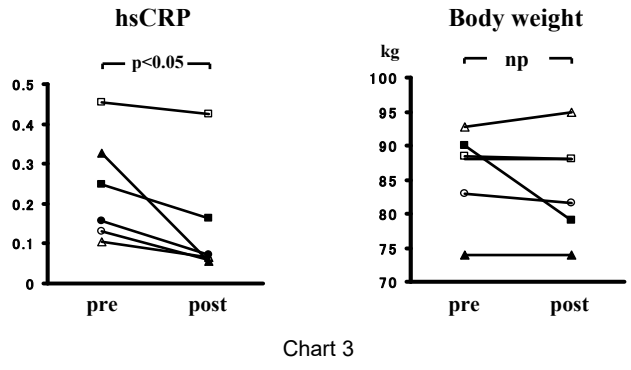

Chart 3

■:Case 1 □:Case 2 ●:Case 3 ○:Case 4 ▲:Case 5 △:Case 6

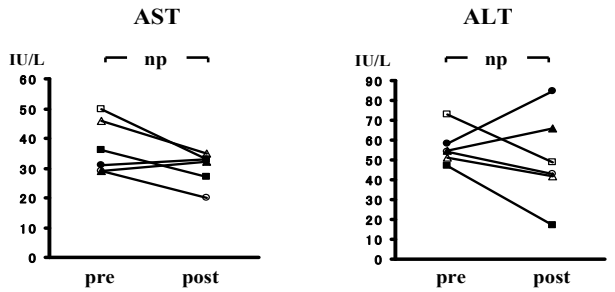

Chart 4

Chart 3, 4: Efficacy of *bofutsushosan* in obesity with nonalcoholic fatty liver disease (NAFLD)

Author's remarks

I have reported the case in which *bofutsushosan* was effective for the obese patients with fatty liver. It was interesting that *bofutsushosan* afforded a decrease in hsCRP levels during an early stage of administration, which, I consider, suggests that obesity is persistent systemic inflammation focused on adipose tissue even if it is at low level. Excessive nutrition becomes "evil *(jya)*" in the body. This evil turns out to be "flame *(hi)*" or "inflammation" that Liu wuan-su refers to. "Obesity is nothing less than inflammation."

Reference

1) Masutomi Y.: Shosoin yakubutsuwo chushintosuru kodaisekki no kennkyu *[Study of ancient stone medicines, mainly focused on Shosoin medicines]*, Nihon kobutsu shumi no kai *[Japan Mineral Hobbyists Group]* 1957