

Effects of febuxostat on platelet-derived microparticles and adiponectin in patients with hyperuricemia

Tohru Nishizawa^a, Takehito Taniura^b, Shosaku Nomura^{a*}

^a First Department of Internal Medicine, Kansai Medical University

^b Division of Internal Medicine, Daiwa Hospital

Running head: Febuxostat acts on PDMP and Adiponectin

*Address for reprints : Professor, Shosaku Nomura, M.D., Ph.D.

First Department of Internal medicine,

Kansai Medical University,

2-3-1 Shinmachi, Hirakata

Osaka 573-1191, JAPAN

Tel : + 81 724 45 1000

Fax : + 81 725 32 1113

E-mail : shosaku-n@mbp.ocn.ne.jp

Abstract: (OBJECTIVES) Platelet-derived microparticles (PDMPs) and adiponectin play an important role in the development of atherothrombosis. We investigated the effect of febuxostat on circulating PDMP levels and adiponectin in hyperuricemic patients. (METHODS) Levels of PDMP and biomarkers were measured using an ELISA at baseline and after 2 and 6 months of treatment. (RESULTS) Plasma levels of PDMPs and biomarkers were higher, while those of adiponectin were lower in hyperuricemic patients than in normouricemic controls. Uric acid and IL-6 levels decreased significantly in hyperuricemic patients after 2 months of febuxostat treatment. However, PDMP and biomarkers decreased significantly in hyperuricemic patients after only 6 months of febuxostat treatment and adiponectin increased significantly. (CONCLUSIONS) These results suggest that the effects of febuxostat for PDMPs seen may be the effect on xanthine oxidase but not the decrease of Uric acid, and febuxostat may be beneficial for primary prevention of atherothrombosis in hyperuricemic patients.

Key words: hyperuricemia, febuxostat, sP-selectin, adiponectin,

PDMP

Introduction

A high level of serum uric acid (UA) is a risk factor for coronary artery atherosclerosis and hyperuricemia promotes the development of chronic kidney disease [1,2]. Increased serum UA is also closely associated with systemic inflammation [3]. Inflammation is characterized by elevated levels of acute phase proteins, such as fibrinogen and C-reactive protein, and elevated levels of cytokines such as interleukin (IL)-6 and tumor necrosis factor- α . All these biomarkers, which are cardiovascular risk factors simultaneously, are markedly elevated in patients with metabolic syndrome and diabetes mellitus (DM)[4].

Platelet-derived microparticles (PDMPs) play roles in normal hemostatic responses to vascular injury because they possess prothrombotic activity [5,6]. PDMPs are also released from platelets following physical stimulation under various conditions [5-8] and it is considered that PDMPs contribute to thrombin generation and thrombus formation by generating tissue factors [6,8]. Therefore, PDMPs ultimately cause vascular complications with the participation of the blood coagulation system.

Adiponectin, the most abundant adipose tissue-specific protein, is exclusively expressed in and secreted by adipose tissue [9]. Plasma

adiponectin concentrations have been shown to be decreased in obese individuals with type 2 diabetes and to be closely related to whole-body insulin sensitivity [10,11]. The protein occurs in abundance in the circulation and stimulates nitric oxide (NO) production in vascular endothelial cells, which ameliorates endothelial cell function [12-14]. These observations suggest that the antiatherogenic properties of adiponectin may involve its NO-dependent antiplatelet effects.

Febuxostat was developed in Japan as a treatment for hyperuricemia because it was shown to decrease serum UA to therapeutic target levels and maintain these levels over the long term [15]. Unlike allopurinol, this drug does not inhibit nucleic acid metabolizing enzymes other than xanthine oxidase (XO)[16-18]. XO is one of the major enzymatic sources of reactive oxygen species (ROS) and it catalyzes the oxidation of purine substrates, producing UA and ROS [16]. XO has been reported to be upregulated by various inflammatory stimuli [17,18] and augmented XO eventually causes excess ROS formation leading to tissue damage. Furthermore, clinical studies, comparing allopurinol with febuxostat, have shown that febuxostat has a more potent UA-lowering effect [19,20], and can potentially prevent XO-dependent tissue dysfunction. However, the effects of febuxostat on PDMPs and adiponectin are poorly understood. In this study, we have

investigated the effects of febuxostat treatment on plasma levels of PDMPs, soluble (s)P-selectin and adiponectin in hyperuricemic patients, to determine whether febuxostat affects development of platelet-associated atherothrombosis.

Materials and methods

Patients

The study group included 51 normouricemic controls and 69 hyperuricemic patients. However, seven patients dropped out because of disease aggravation or patient removal. Therefore, 62 patients were analyzed in this study (Table 1 baseline data). From September 2011 to June 2014, normouricemic controls and hyperuricemic patients were selected from patients admitted to our hospitals. The protocol of this study was approved by the Institutional Review Board (IRB) of the medical institution, and written informed consent was obtained from each subject prior to the start of the trial in accordance with the guideline for Good Clinical Practice (GCP).

The participation criteria included the absence of a history of inflammatory, coronary artery, or cerebrovascular disease for 3 months prior to enrollment, as well as the absence of clinically detectable renal (serum creatinine ≥ 2.0 mg/dl), hepatic (elevated serum transaminase), infectious (fever or elevated

white blood cell count) or malignant disease (as determined by ultrasonography or computed tomography). Other uric acid-lowering agents were withheld, owing to their potential influence on data interpretation. These medications were stopped at least 2 weeks prior to the initiation of febuxostat therapy. Of the 62-hyperuricemic patients, 43 had type 2 diabetes (Table 1); of these, fourteen were being treated with sulfonylureas, ten with α -glucosidase inhibitors and eight with insulin injections. The age range of eligible patients was 20–90 years.

Study design

The 62 study participants had a serum UA $>8\text{mg/dl}$ and were not on anti-hyperuricemic therapy. The primary endpoint was serum UA level, PDMPs and adiponectin after treatment. Secondary endpoints were as follows: IL-6, sP-selectin, sE-selectin, soluble vascular cell adhesion molecules (VCAM)-1 and monocyte chemoattractant protein 1 (MCP)-1.

The target serum UA level was $<6.0\text{ mg/dl}$ and the dose of the test drug, febuxostat, was increased up to a maximum of 60 mg/day. No other changes to the pharmacologic regimens of the patients were made during the course of the trial. In addition, patient food habits, such as diet, were not altered during the study. Clinical and biochemical data determined before and after

6 months of therapy with febuxostat were analyzed.

Measurement of PDMP, soluble molecules and adiponectin

Fasting blood samples from patient and control subject peripheral veins were collected into vacutainers containing EDTA-ACD (NIPRO Co. Ltd., Osaka, Japan) using 21-gauge needles to minimize platelet activation. Samples were gently mixed by inverting the tubes once or twice and were then kept at room temperature for a maximum period of 2–3 h. Immediately after centrifugation at 8,000 g for 5 min, 200 µl of the upper layer supernatant from the 2 ml samples was collected to avoid contamination with platelets. The collected samples were stored at –40°C until analysis.

PDMP levels were measured twice and mean values were recorded. Furthermore, some basic studies were carried out prior to this assessment using clinical specimens. An enzyme-linked immunosorbent assay (ELISA) kit used for PDMP measurements was obtained from JIMRO Co. Ltd. (Tokyo, Japan)[10,21]. Plasma sP-selectin, sE-selectin, sVCAM-1, MCP-1 and IL-6 were measured using a monoclonal antibody-based ELISA kit purchased from Invitrogen International Inc. (Camarillo, CA, USA), while plasma adiponectin was measured with an Adiponectin ELISA kit purchased from Otsuka Pharmaceuticals Co. Ltd (Tokyo, Japan). Recombinant products and

standard solutions provided with the commercial kits were used as positive controls in each assay. All kits were used in accordance with the manufacturer's instructions.

Effect of UA for PDMPs in normal platelet-rich plasma

Platelet-rich plasma of healthy persons (n=3) were treated with purified UA (Wako Pure Chemical Industries, Ltd, Osak, Japan) of various concentrations (1-32 mg/dL) for 30 min. After treatment, PDMPs were collected by the above mentioned method. PDMP levels were measured five times by ELISA method, and finally mean volumes were recorded.

Statistics

Data were expressed as the mean \pm SD and analyzed using multiregression analysis, as appropriate. Between-group comparison of values was made with the Newman-Keuls test and Scheffe's test. The correlation between uric acid and after continuous-response variables was assessed using multivariate linear regression analysis. P-values less than 0.05 were considered statistically significant. Analysis was performed using the StatFlex program (ver. 6).

Results

Plasma levels of PDMPs, IL-6, sP-selectin, sE-selectin, sVCAM-1 and MCP-1 were higher, while those of adiponectin were lower in hyperuricemic patients than in normouricemic controls (Table 1). We investigated 15 variables for hyperuricemic patients using multiregression analysis (Table 2). Univariate analysis showed that age, HbA1c, diabetes mellitus, PDMP, sP-selectin, sE-selectin, sVCAM-1, MCP-1 and adiponectin were significantly associated with UA (Table 2). In addition, age, PDMP, sP-selectin, MCP-1 and adiponectin were significant factors in the multivariate model with UA (Table 2).

UA and IL-6 levels decreased significantly in hyperuricemic patients after 2 and 6 months of febuxostat treatment (Fig. 1). However, PDMP, sP-selectin, MCP-1, sE-selectin and sVCAM-1 decreased significantly in hyperuricemic patients after only 6 months of febuxostat treatment and adiponectin increased significantly (Fig. 1 and 2). On the other hand, the enhancing effect of UA on PDMPs was not observed in an *in vitro* experiment using platelet-rich plasma of healthy persons (Fig. 3).

Discussion

UA has been shown to be a predictor and an independent risk factor for

atherothrombotic diseases, such as DM, cerebrovascular disease and acute coronary syndrome [22,23]. In addition, a close association between elevated UA and numerous markers of inflammation has been noticed [24]. These findings suggest that UA is one of the determinants for a vascular event in atherosclerosis. As usual, allopurinol has long been regarded as a first-line drug for the treatment of hyperuricemia. However, this drug has been reported to cause some adverse reactions such as renal dysfunction and hypersensitivity vasculitis [1,15]. Unlike allopurinol, febuxostat is more reliable and it has been reported to have a stronger effect on hyperuricemia than allopurinol [25]. In the present study, UA levels were also significantly lower in patients after treatment with febuxostat.

Activated platelets and PDMPs may cause capillary microembolization secondary to the formation of microaggregates [26]. PDMPs play an important role in the clotting process, so an increase in PDMPs is likely to cause hypercoagulability [6,26]. We previously reported that PDMP levels were significantly increased in atherothrombotic patients [27]. Because PDMPs promote the expression of adhesion molecules by monocytes and endothelial cells [26,28], it seems possible that these microparticles may participate in the development or progression of atherosclerosis [28].

In the present study, febuxostat therapy significantly decreased PDMP levels. Although we did not show any direct changes in platelet function, febuxostat therapy also decreased expression of another platelet activation marker, sP-selectin, in our patients with hyperuricemia. However, we cannot conclude whether the same mechanism caused these changes or not. If anything, different mechanisms are a possibility. UA and IL-6 levels already decreased significantly after 2 months of febuxostat treatment. This result suggests that there is an association between a decrease in UA and inflammation, because IL-6 is a proinflammatory cytokine [29,30]. However, PDMP and sP-selectin decreased significantly after 6 months of febuxostat treatment. This result suggests that the improvement of PDMPs after febuxostat treatment was independent from the decrease of UA. In deed, the UA of various concentrations did not effect on PDMP levels was not observed in an *in vitro* experiment using platelet-rich plasma of healthy persons. We accordingly guess that the effects of febuxostat for PDMPs seen may be the effect on XO, because it is previously reported that XO eventually causes excess ROS formation, leading to tissue damage [17,31]. Therefore, it is possible that febuxostat can prevent XO-dependent tissue dysfunction [19].

The plasma level of adiponectin is decreased in obese individuals [9,26] and is closely related to whole-body insulin sensitivity [12]. A significant decrease

of plasma adiponectin has also been found in patients with type 2 diabetes [12]. Adiponectin has been reported to suppress the attachment of monocytes to endothelial cells [32] and plays a role in protection against vascular injury, so hypoadiponectinemia is associated with endothelial dysfunction [26]. Hypoadiponectinemia also seems to cause platelet activation. The level of NO, which regulates platelet activation, has been shown to be decreased by hypoadiponectinemia because adiponectin stimulates NO production by vascular endothelial cells [13,14,26]. Thus, platelet activation occurs because of low NO concentrations in individuals with hypoadiponectinemia. Therefore, the increase of adiponectin caused by febuxostat may have an antiplatelet effect via promotion of NO production.

We postulate that one possibility for the mechanism underlying adiponectin elevation by febuxostat treatment is the participation of ROS. Oxidative stress plays a pivotal role in the pathogenesis of various diseases [33]. In diabetes, oxidative stress impairs glucose uptake in muscle and fat and decreases insulin secretion from pancreatic β -cells [34,35]. Inflammation is closely linked to the formation of ROS [33,36], and preadipocytes produce ROS [33,36,37]. Finally, ROS cause hypoadiponectinemia [33,37]. Febuxostat may have a possible effect on ROS, as suggested by previous reports demonstrating the anti-inflammatory effect of febuxostat that may relate to

its ability to block the production and/or activity of ROS [31,38]. Therefore, the improvement of hyperuricemia by febuxostat could be due to alteration of the posttranslational modification of adiponectin. However, further studies are necessary to elucidate the effects of febuxostat itself on adiponectin production.

Conclusion

Febuxostat directly or indirectly increased circulating adiponectin levels in hyperuricemic patients. In addition, febuxostat treatment led to a decrease in PDMPs and sP-selectin related to platelet activation. Febuxostat may be beneficial for the primary prevention of atherothrombosis in hyperuricemic patients. However, validation of this hypothesis will require a large clinical trial.

Acknowledgments

This study was supported in part by a grant from the Japan Foundation of Neuropsychiatry and Hematology Research, the Research Grant for Advanced Medical Care from the Ministry of Health and Welfare of Japan, and a grant (13670760 to S.N.) from the Ministry of Education, Science and Culture of Japan.

Conflict of Interest

None.

References

- 1 Fagugli RM, Gentile G, Ferrara G, Brugnano R. Acute renal and hepatic failure associated with allopurinol treatment. *Clin Nephrol* 2008; **70**: 523-526.
- 2 Kaya EB, Yorguna H, Canpolata U, Hazirolan T, Susman H, Ülgen A, et al. Serum uric acid levels predict the severity and morphology of coronary atherosclerosis detected by multidetector computed tomography. *Atherosclerosis* 2010; **213**: 178-183.
- 3 Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. *Circulation* 2003; **107**: 1991- 1997.
- 4 Park SH, Shin WY, Lee EY, Gil HW, Lee SW, Lee SJ, et al. The impact of hyperuricemia on in-hospital mortality and incidence of acute kidneyinjury in patients undergoing percutaneous coronary intervention. *Cir J* 2011; **75**: 692-697.
- 5 Nomura S, Ozaki Y, Ikeda Y. Function and role of microparticles in various clinical settings. *Thromb Res* 2008; **123**: 8-23.

- 6 Nomura S, Shimizu M. Clinical significance of procoagulant microparticles. *J Intensive Care* 2015; **3**: 2-11.
- 7 Miyazaki Y, Nomura S, Miyake T, Kagawa H, Kitada C, Taniguchi H, et al. High shear stress can initiate both platelet aggregation and shedding of procoagulant containing microparticles. *Blood* 1996; **88**: 3456-3464.
- 8 Sinauritz EI, Kireev DA, Popenko NY, Pichugin AV, Panteleev MA, Krymskaya OV, et al. Platelet microparticle membranes have 50- to 100-fold higher specific procoagulant activity than activated platelets. *Thromb Haemost* 2007; **97**: 425-434.
- 9 Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappa B signaling through a cAMP-dependent pathway. *Circulation* 2000; **102**: 1296-1301.
- 10 Nomura S, Shouzu A, Omoto S, Inami N, Shimazu T, Satoh D, et al. Effects of pitavastatin on monocyte chemoattractant protein-1 in hyperlipidemic patients. *Blood Coagul Fibrinolysis* 2009; **20**: 440-447.
- 11 Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999; **257**: 79-83.
- 12 Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association

- with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 2001; **86**: 1930-1935.
- 13 Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. *J Biol Chem* 2003; **278**: 45021-45026.
- 14 Hattori Y, Suzuki M, Hattori S, Kasai K. Globular adiponectin upregulates nitric oxide production in vascular endothelial cells. *Diabetologia* 2003; **46**: 1543-1549.
- 15 Becker MA, Schumacher HR, Wortmann RL, MacDonald PA, Eustace D, Palo WA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005; **353**: 2450-2461.
- 16 Berry CE, Hare JM. Xanthine oxidoreductase and cardiovascular disease; molecular mechanisms and pathophysiological implications. *J Physiol* 2004; **555**: 589-606.
- 17 Nakai K, Kadiiska MB, Jiang JJ, Stadler K, Mason RP. Free radical production requires both inducible nitric oxide synthase and xanthine oxidase in LPS-treated skin. *Proc Natl Acad Sci USA* 2006; **103**: 4616-4621.
- 18 Nomura J, Busso N, Ives A, Tsujimoto S, Tamura M, So A, et al. Febuxostat, an inhibitor of xanthine oxidase, suppresses lipopolysaccharide-induced MCP-1 production via MAPK phosphatase-

- 1-mediated inactivation of JNK. *PLoS One* 2013; **8**: e75527.
- 19 Tatu H, Iwao O. A repeated oral administration study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase in patients with impaired renal function in Japan. *J Clin Rheumatol* 2011; **17**: S27-S34.
- 20 Kamatani N, Fujimori S, Hada T, Hosoya T, Kohri K, Nakamura T, et al. Multicenter, open-label study of long-term administration of febuxostat (TMX-67) in Japanese patients with hyperuricemia including gout. *J Clin Rheumatol* 2011; **17**: S50-S56.
- 21 Osumi K, Ozeki Y, Saito S, Nagamura Y, Ito H, Kimura Y, et al. Development and assessment of enzyme immunoassay for platelet-derived microparticles. *Thromb Haemost* 2001; **85**: 326-330.
- 22 Nakanishi N, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, Tatara K. Serum uric acid risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. *Eur J Epidemiol* 2003; **18**: 523-530.
- 23 Alderman MH. Uric acid and cardiovascular risk. *Curr Opin Pharmacol* 2002; **2**: 126-130.
- 24 Ruggiero C, Cherubini A, Ble A, Bos AJ, Maggio M, Dixit VD, Lauretani F, Bandinelli S, Senin U, Ferrucci L. Uric acid and inflammatory markers. *Eur Heart J* 2006; **27**: 1174-1181.

- 25 Sezai A, Soma M, Nakata K, Hada M, Yoshitake I, Wakui S, et al. Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients (NU-FLASH Trial). *Cir J* 2013; **77**: 2043- 2049.
- 26 Shimazu T, Inami N, Satoh D, Kajiura T, Yamada K, Iwasaka T, et al. Effect of acarbose on platelet-derived microparticles, soluble selectins, and adiponectin in diabetic patients. *J Thromb Thrombolysis* 2009; **28**: 429-435.
- 27 Nomura S, Shouzu A, Taomoto K, Togane Y, Goto S, Ozaki Y, et al. Assessment of an ELISA kit for platelet-derived microparticles by joint research at many institutes in Japan. *J Atheroscler Thromb* 2009; **16**: 878-887.
- 28 Nomura S, Tandon NN, Nakamura T, Cone J, Fukuhara S, Kambayashi J. High-shear-stress- induced activation of platelets and microparticles enhances expression of cell adhesion molecules in THP-1 and endothelial cells. *Atherosclerosis* 2001; **158**: 277-287.
- 29 Kerr R, Stirling D, Ludlam CA. Interleukin 6 and haemostasis. *Br J Haematol* 2001; **115**: 3-12.
- 30 Baldwin W, McRae S, Marek G, Wymer D, Pannu V, Baylis C, et al. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. *Diabetes* 2011; **60**: 1258-1269.

- 31 Kushiya A, Okubo H, Sakoda H, Kikuchi T, Fujishiro M, Sato H, et al. Xanthine oxidoreductase is involved in macrophage foam cell formation and atherosclerosis development. *Arterioscler Thromb Vasc Biol* 2012; **32**: 291-298.
- 32 Shimabukuro M, Higa N, Asahi T, Oshiro Y, Takasu N, Tagawa T, et al. Hypoadiponectinemia is closely linked to endothelial dysfunction in man. *J Clin Endocrinol Metab* 2003; **88**: 3236-3240.
- 33 Maddux BA, See W, Lawrence JC Jr, Goldfine AL, Goldfine ID, Evans JL. Protection against oxidative stress-induced insulin resistance in rat L6 muscle cells by micromolar concentrations of α -lipoic acid. *Diabetes* 2001; **50**: 404-410.
- 34 Matsuoka T, Kajimoto Y, Watada H, Kaneko H, Kishimoto M, Umayahara Y, et al. Glycation-dependent, reactive oxygen species-mediated suppression of the insulin gene promoter activity in HIT cells. *J Clin Invest* 1997; **99**: 144-150.
- 35 Rudich A, Tirosh A, Potashnik R, Hemi R, Kanety H, Bashan N. Prolonged oxidative stress impairs insulin-induced GLUT4 translocation in 3T3-L1 adipocytes. *Diabetes* 1998; **47**: 1562-1569.
- 36 Chen B, Lam KS, Wang Y, Wu D, Lam MC, Shen J, et al. Hypoxia dysregulates the production of adiponectin and plasminogen activator inhibitor-1 independent of reactive oxygen species in adipocytes.

Biochem Biophys Res Commun 2006; **341**: 549- 556.

37 Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest* 2004; **114**: 1752-1761.

38 Tausche AK, Christoph M, Forkmann M, Richter U, Kopprasch S, Bielitz C, et al. As compared to allopurinol, urate-lowering therapy with febuxostat has superior effects on oxidative stress and pulse wave velocity in patients with severe chronic tophaceous gout. *Rheumatol Int* 2014; **34**: 101-109.

Table and Figure Legends

Table 1 Clinical characteristics and various factors of the hyperuricemic patients and normouricemic controls

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; UA, uricemic acid; DM, diabetes mellitus; HT, hypertension; HC, hypercholesterolemia; P-CAD, previous history of coronary artery disease; PDMP, platelet-derived microparticle; interleukin-6; sP-selectin, soluble P-selectin; sE-selectin, soluble E-selectin; sVCAM-1, soluble vascular cell adhesion molecule; MCP-1, monocyte chemotactant protein-1

Data are shown as mean \pm SD.

P value, hyperuricemic patients vs normouricemic controls

Table 2 Multiregression analysis on UA in hyperuricemic patients

Abbreviations: see to Table 1

β standardized regression coefficients * : statistical significant

Figure 1 Changes in the plasma levels of UA, IL-6, PDMP and sP-selectin before and after febuxostat treatment in hyperuricemic patients

Abbreviations: see to Table 1

Data are shown as mean \pm SD. P value, 0 vs. 2 or 6 months

N.S., not significant

Figure 2 Changes in the plasma levels of MCP-1, adiponectin, sE-selectin and sVCAM-1 before and after febuxostat treatment in hyperuricemic patients

Abbreviations: see to Table 1

Data are shown as mean \pm SD. P value, 0 vs. 2 or 6 months

N.S., not significant

Figure 3 Effect of UA for PDMPs in normal platelet-rich plasma

Abbreviations: see to Table 1

Data are shown as mean \pm SD. N.S., not significant

Table 1

	Normouricemic Controls	Hyperuricemic Patients	p value
n	51	62	
Men/women (no.)	29 / 22	38 / 24	
Age (years)	56 ± 13	73 ± 10	< 0.01
BMI (kg/m²)	24.1 ± 3.6	25.9 ± 3.9	N.S.
HbA1c (%)	6.1 ± 2.4	7.6 ± 2.8	< 0.05
UA (mg/dL)	4.23 ± 0.83	8.29 ± 1.21	< 0.001
DM (%)	46.8	68.7	< 0.05
HT (%)	55.2	66.9	N.S.
HC (%)	23.2	35.5	N.S.
Smoking (%)	33.4	41.8	N.S.
P-CAD (%)	6.5	17.8	< 0.05
PDMP (U/ml)	12.7 ± 7.3	23.9 ± 8.1	< 0.001
IL-6 (pg/ml)	3.1 ± 1.4	4.7 ± 2.2	< 0.05
sP-selectin (ng/ml)	198 ± 52	251 ± 72	< 0.05
sE-selectin (ng/ml)	75.9 ± 11.3	92.6 ± 14.1	< 0.01
sVCAM-1 (ng/ml)	587 ± 138	902 ± 216	< 0.001
MCP-1 (ng/ml)	262 ± 74	421 ± 101	< 0.01
Adiponectin (µg/ml)	5.17 ± 1.61	3.78 ± 1.53	< 0.01

Table 2

Analysis	Univariate		Multivariate	
	β	p value	β	p value
Age (years)	0.6216	<0.00001*	0.5049	0.00487*
Sex (men)	- 0.0359	0.25231		
BMI (kg/m ²)	0.2241	0.06773		
HbA1c (%)	0.3175	0.04315*	0.2415	0.10234
DM (%)	0.3971	0.01397*	0.2851	0.08951
HT (%)	0.1346	0.08791		
HC (%)	- 0.0657	0.23169		
P-CAD (%)	- 0.0392	0.32861		
PDMP (U/ml)	0.6506	<0.00001*	0.4156	0.00562*
IL-6 (pg/ml)	0.1766	0.21778		
sP-selectin (ng/ml)	0.4586	0.00141*	0.3378	0.02316*
sE-selectin (ng/ml)	0.3917	0.00749*	0.2791	0.08846
sVCAM-1 (ng/ml)	0.4325	0.00164*	0.3171	0.06625
MCP-1 (pg/ml)	0.5784	0.00008*	0.4019	0.00892*
adiponectin (μ g/ml)	0.6393	<0.00001*	- 0.5175	0.00212*

Fig. 1

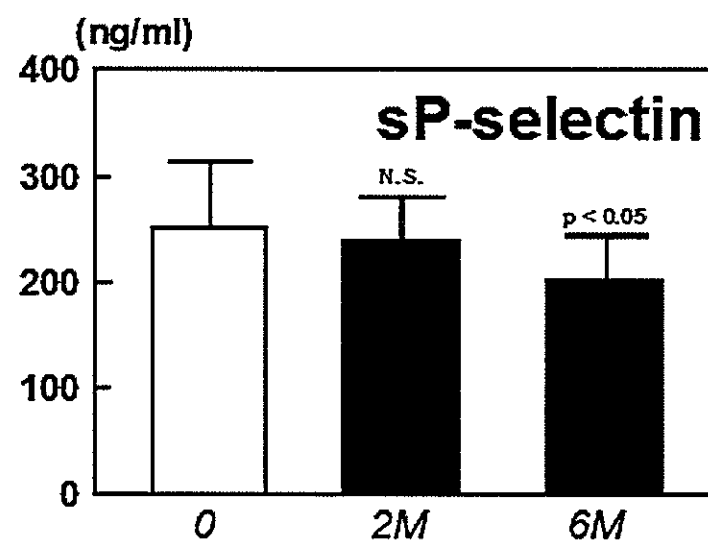
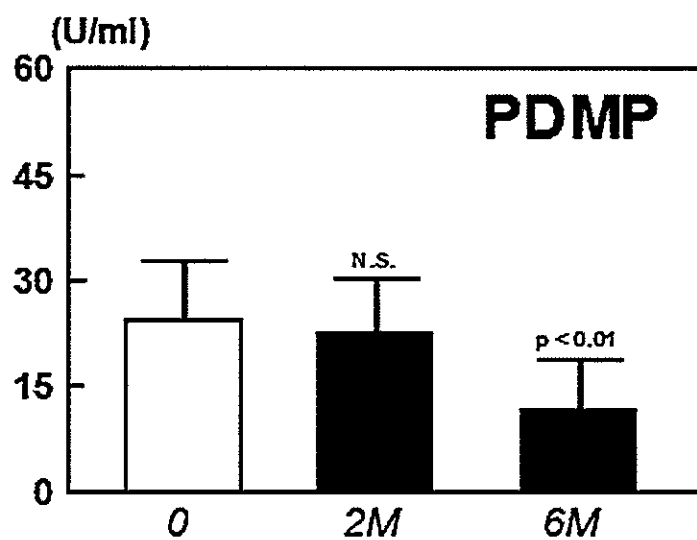
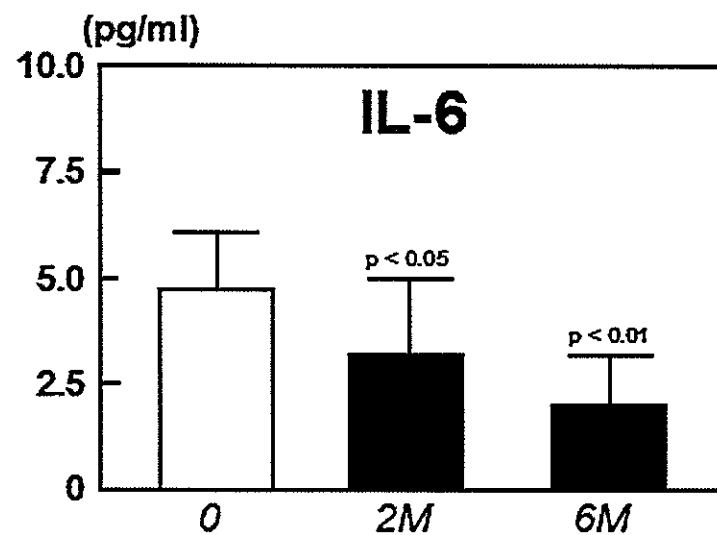
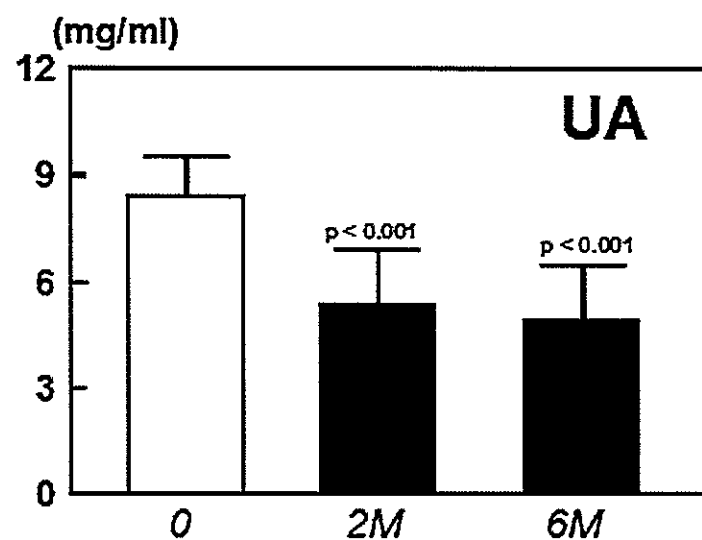


Fig. 2

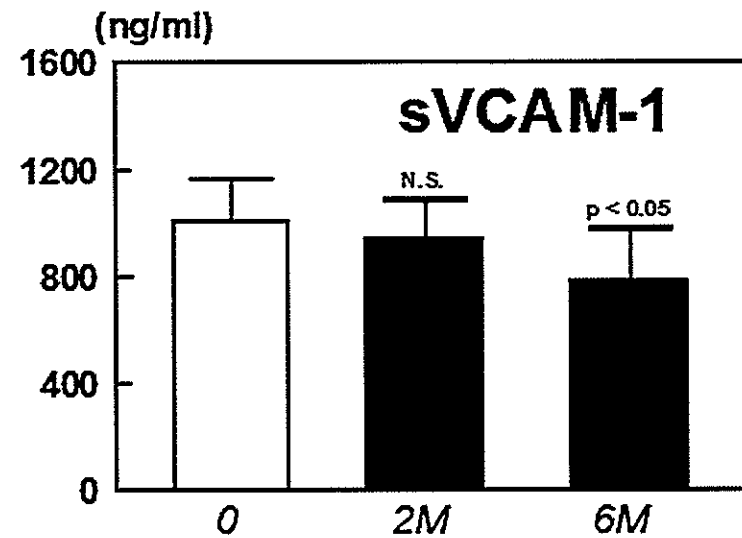
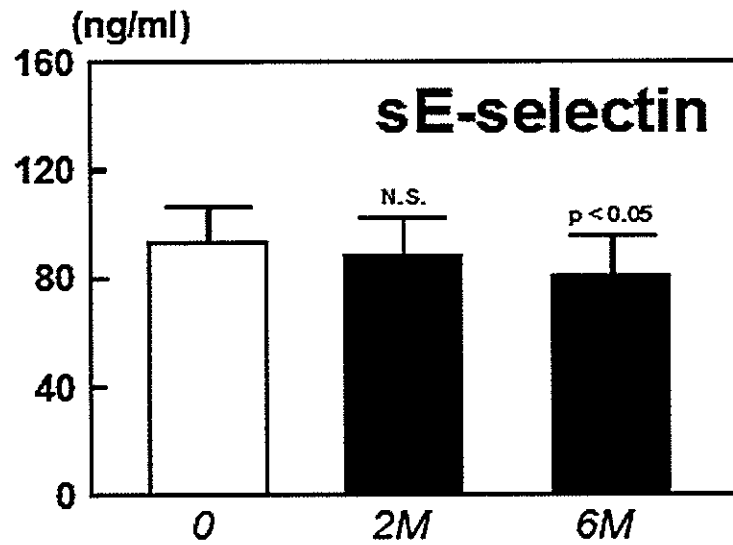
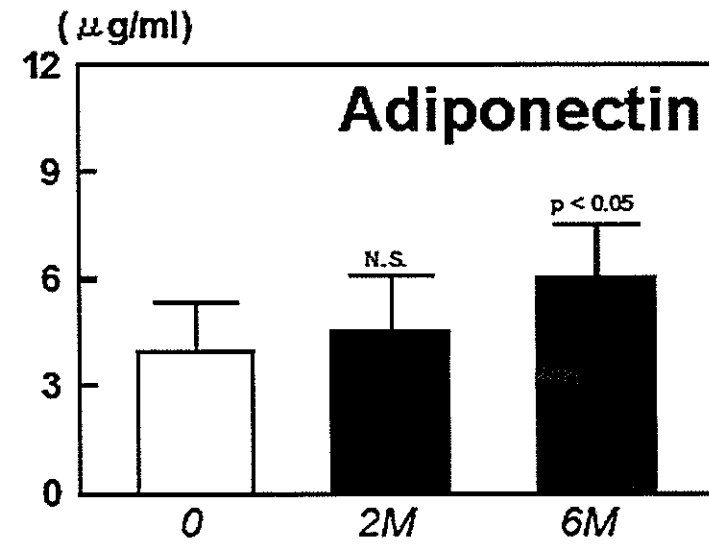
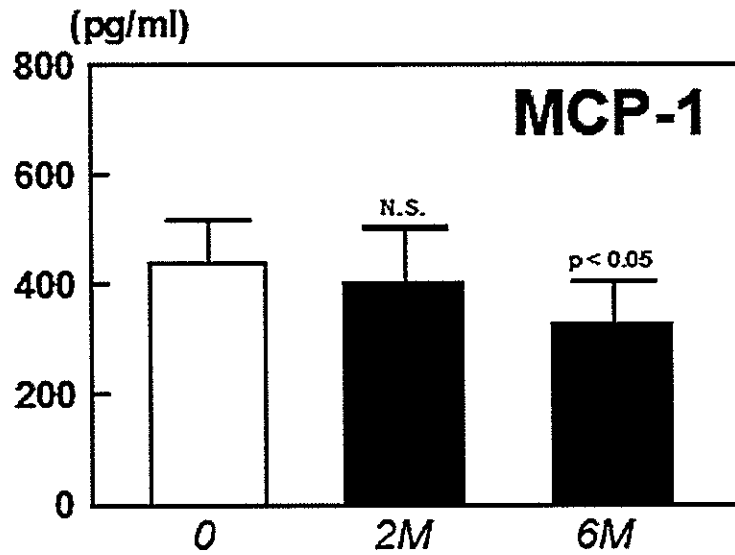


Fig. 3

