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Research Paper

Efficacy of different doses of aspirin in decreasing blood levels of inflammatory markers in patients with cardiovascular metabolic syndrome

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Abstract

Objectives Inflammation and platelet aggregation and activation are key processes in the initiation of a cardiovascular event. Patients with metabolic syndrome have a high risk of cardiovascular events. This study determined whether small and medium doses of aspirin have anti-inflammation and antiplatelet aggregation effects in patients with metabolic syndrome.

Methods One hundred and twenty-one consecutive patients with metabolic syndrome were randomized into three groups, receiving 100 mg/day of aspirin, 300 mg/day of aspirin or a placebo, respectively, for 2 weeks. The blood levels of thromboxane B2 (TXB2), a stable product of the platelet aggregation mediator TXA2, 6-keto-prostaglandin F1-α (6-keto-PGF1-α), a stable product of the endogenous cyclooxygenase metabolite prostaglandin I2, and inflammatory mediators including high-sensitivity C-reactive protein (hs-CRP), tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), were determined by ELISA and radioimmunoassay.

Key findings The blood levels of hs-CRP, TNF-α, IL-6 and TXB2 were significantly decreased after 2 weeks of treatment with 300 mg/day of aspirin. Patients who received 100 mg/day of aspirin had decreased blood levels of hs-CRP and TXB2. The blood level of IL-6 in the 300 mg/day aspirin group was significantly lower than that in the other two groups after 2 weeks of therapy. Aspirin at either dose did not affect the blood level of 6-keto-PGF1-α.

Conclusions Aspirin at all doses suppresses the blood levels of inflammatory markers and the platelet aggregation mediator TXA2 in Chinese patients with metabolic syndrome. Since the suppression induced by 300 mg/day of aspirin was greater than that induced by 100 mg/day of aspirin, these data suggest that 300 mg/day of aspirin may be beneficial in decreasing the risk of cardiovascular events in Chinese patients with metabolic syndrome.

Keywords aspirin; cytokines; inflammation; metabolic syndrome

Introduction

The cardio-metabolic syndrome is a cluster of risk factors that predispose an individual to cardiovascular morbidity and mortality. This syndrome not only affects nearly one in four adults in Western countries[1] but also is an increasingly major health problem in young populations.[2,3] Patients with the metabolic syndrome are characterized by obesity, insulin resistance, hypertension, atherogenic dyslipidaemia, hypercoagulability, chronic inflammation (elevated markers of subclinical inflammation or chronic proinflammatory state) and endothelial dysfunction.[4,5] All of these are risk factors for atherosclerosis, cardiovascular disease (CVD) and cerebrovascular events. Epidemiological studies strongly suggest that multiple risk factors raise risk more than the summation of the individual risk factors.[6–8] Thus, effective management of each component of the pathophysiological changes accompanying the metabolic syndrome has been emphasized to reduce the overall risk of CVD.[9–11]

The aetiology of the metabolic syndrome is complex, determined by the interplay of both genetic and environmental factors. Pathways leading to clinical manifestations of the

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metabolic syndrome involve inflammatory mediators, such as proinflammatory adipokine and tumour necrosis factor-α (TNF-α).[12] Since TNF-α expression is increased in the adipose tissue of rodent models of obesity and of obese humans,[13] TNF-α has been considered as a candidate gene for obesity. Consistent with this concept, subsequent studies show an overproduction of TNF-α in human fat cells in patients with obesity and adipocyte insulin resistance.[14,15] Studies have shown that TNF-α plays an important role in the inflammatory reaction that is responsible for the development of atherosclerosis and in plaque stability.[16,17] TNF-α also may participate in the development of insulin resistance and type 2 diabetes mellitus.[18] Interleukin-6 (IL-6) is another proinflammatory cytokine and is involved in the inflammatory reaction, immune activation and regulation of TNF-α production.[19] IL-6 can promote cell apoptosis, thrombus formation and neovascularization.[19] Thus, IL-6 also plays a key role in the pathophysiology of cardiovascular diseases.[20]

High-sensitivity C-reactive protein (hs-CRP) appears to be one of the best indicators of the presence of a proinflammatory state because it provides an integrated indication of the total level of circulating inflammatory cytokines.[21,22] Data suggest that CRP may play an important role in the progression of atherosclerosis and that it is positively correlated with the risk of atherosclerosis.[21] This effect may be due to its ability to promote the oxidation of low-density lipoprotein (LDL) cholesterol to ox-LDL, to enhance macrophage uptake of ox-LDL to become foam cells, and to increase the expression of adhesion molecules and plasminogen activator inhibitor-1 in endothelial cells.[23,24] For these reasons, hs-CRP has been considered a sensitive indicator for ischaemic heart and brain diseases: blood levels of hs-CRP at <1, 1–3 or >3 mg/l indicate a low, moderate or high risk of future heart attack and stroke.[25] Patients with metabolic syndrome often have an increased level of hs-CRP.[26]

Thromboxane A2 (TXA2) is a product of the oxidative metabolism of arachidonic acids via the cyclooxygenase (COX) pathway.[27] TXA2 is synthesized and released by activated platelets in order to induce platelet aggregation.[27] Another oxidative product of arachidonic acids via the COX pathway is prostaglandin I2 (PGI2), which is synthesized and released by endothelial cells of the blood vessels in response to various stresses to these cells.[27] The biological effects of PGI2 are antagonistic to those of TXA2: PGI2 induces vasodilation and prevents platelet aggregation.[27] The biological half-life of TXA2 is around 30 s. After being released, TXA2 is rapidly converted to TXB2, a chemically stable, but biologically inactive hydration product. The bioactivity of TXA2 has been monitored by measuring TXB2. The biological half-life of PGI2 is also short (2–3 min) and it is rapidly converted into 6-keto-prostaglandin F1-α (6-keto-PGF1-α), a stable hydrolysis product; therefore PGI2 production is typically monitored by measuring the amount of 6-keto-PGF1-α.[28,29]

Aspirin has antiplatelet aggregation and anti-inflammation actions and is recommended for use by patients with a high risk of cardiovascular events (a 10-year risk of 6–10%).[30,31] Since low doses of aspirin (75–162.5 mg/day) are as effective as medium doses (162.5–325 mg/day) and high doses (500–1500 mg/day) in reducing cardiovascular events,[32] a low dose of aspirin is often recommended to reduce significant bleeding complications from aspirin use. However, the effects of aspirin on inflammation and platelet aggregation mediators in patients with the metabolic syndrome, a unique syndrome with high risk of cardiovascular events, and the dose selection of aspirin involved in obtaining those effects are not yet known. This randomized study was therefore designed to determine whether aspirin at low and medium doses inhibits the expression of inflammatory mediators in the metabolic syndrome, a condition that often prompts preventive use of aspirin.

Materials and Methods

Patients

This study was a prospective, single centre, randomized, double-blind and placebo-controlled trial. The protocol of this study was approved by the Institutional Committee on Human Research at the First Affiliated Hospital, Zhong-Shan University. After informed consent was given, 121 consecutive patients (including both outpatients and inpatients) (65 men, 56 women, 52.33 ± 9.40 years old ranging from 32–72 years old) who met the diagnostic criteria for the metabolic syndrome set by the Chinese Diabetes Association (modified for the Chinese population from the criteria of the IDF Epidemiology Task Force Consensus Group)[33,34] and who also did not meet the exclusion criteria were randomly divided into three groups during the period from September 2005 to March 2007. Patients were given aspirin in doses of 300 mg/day (41 patients), 100 mg/day (40 patients) or a placebo (40 patients), for 2 weeks. Aspirin was supplied by Bayer HealthCare (Beijing, China) and was enteric coated at 100 mg per tablet. The appearance of the aspirin and placebo tablets was identical. Doctors instructed patients to take either aspirin or placebo in a double-blind way. None of the patients were receiving aspirin before the study.

Patients with the following diseases or states were excluded: documented coronary arterial disease, congestive heart failure, malignant diseases, infectious or other known inflammatory diseases, injuries, autoimmune diseases, rheumatic heart disease, myocarditis, active peptic ulcer, history of gastrointestinal bleeding, uncontrolled hypertension, asthma, allergy to aspirin, currently receiving steroids or non-steroidal anti-inflammatory drugs (NSAIDs), coronary arterial angioplasty, surgery within the previous 6 months, cerebral vascular diseases, peripheral vascular diseases, impaired renal or liver function, bleeding tendencies and age greater than 75 years.

Methods

Clinical history, blood pressure, weight, height and waist circumference were taken in all patients. Blood pressure was taken according to the 2003 WHO/ISH guidelines and recommendations. The weight and height of every patient were measured early in the morning without shoes and overcoats. Waist circumference was measured by placing a measuring tape around the abdomen horizontally at the middle point between the lower border of the 12th rib and the

uppermost border of the iliac crest while the legs were spread apart 5–10 cm. The measurement was recorded with an accuracy of 0.1 cm. Body mass index (BMI) was calculated according to the standard formula:

$$\text{BMI} = \text{weight(kg)}/\text{height}^2(\text{m}^2).$$

To ensure that patients were in compliance with the study drug regimen, patients were told to remain on the drugs that we prescribed and to contact us regarding any discomfort before they considered stopping the drugs. Patients were also told not to take any NSAIDs. Patients were followed up in the clinic or in hospital twice during the study: the first time at 1 week after they had started to take the study medication and the second time after they had finished the 2-week drug therapy. Questions regarding compliance with the drug regimen were asked during these two follow-ups. Drug bottles were returned in the second follow-up and no pills were left in any of the bottles (tablets sufficient for only 2 weeks were distributed to each patient at the beginning of the study).

Laboratory tests

Blood was drawn in the fasting state, early in the morning, just before the beginning of treatment and the following morning after the last dose of aspirin or placebo. Blood samples were assayed for inflammatory markers (hs-CRP, TNF-α and IL-6), basic chemistry panel, liver function panel, lipid profile, TXB2 and 6-keto-PGF1-α. The blood samples were tested for the basic chemistry panel, liver function and lipid profile in the chemistry laboratory in our hospital using an automatic ARCHITECT c8000 (Abbott Laboratories, Abbott park, IL, USA). The 75 g oral glucose tolerance test was performed using the WHO method.[35] The hs-CRP concentration was determined using a particle enhanced immunoturbidimetric assay kit (Orion Diagnostica Oy, Espoo, Finland). Blood samples for measuring TXB2 and 6-keto-PGF1-α were drawn in a syringe filled with 0.2 ml of indometacin-EDTA-Na_2, a cyclooxygenase inhibitor, and shaken well to mix them thoroughly. The samples were then transferred to a test-tube and centrifuged at 3500 rpm at 4ºC for 15 min to isolate plasma, which was then stored at –20ºC. The plasma concentration of TXB2 and 6-keto-PGF1α was determined by radioimmunoassay peformed by the Radio-immunological Institute of the General Hospital of the People's Liberation Army, Beijing, China.

Statistical analysis

Data are expressed as mean ± SD or number of patients (%) as appropriate. Comparison of hs-CRP, IL-6, TNF-α, TXB2 and 6-keto-PGF1α levels, within each patient group, before and after the 2-week aspirin treatment period was performed by paired *t*-test. Comparison of these data among the three groups was performed by one-way ANOVA followed by the Student–Newman–Keuls method for post-hoc comparison. The comparison of data presented as frequencies among the three groups of patients was analyzed by chi-square. $P < 0.05$ (2-tailed) was considered statistically significant.

Results

All patients who were randomized completed the study. The baseline characteristics, including clinical information, laboratory values and drug treatment of these patients, are shown in Table 1. There were no statistical differences in any of the parameters among the three groups.

Blood levels of hs-CRP, TNF-α, IL-6, TXB2 and 6-keto-PGF1-α were not changed in patients who received a placebo for 2 weeks (Table 2). Treatment with 100 mg/day of aspirin for 2 weeks significantly decreased blood levels of hs-CRP and TXB2 compared to pretreatment values. Patients who received aspirin for 2 weeks at 300 mg/day had significantly reduced blood levels of hs-CRP, TNF-α, IL-6 and TXB2 compared to pretreatment levels. The blood level of 6-keto-PGF1-α was not affected by aspirin at either dosage (Table 2).

There were no significant differences in the pretreatment blood levels of hs-CRP, TNF-α, IL-6, TXB2 and 6-keto-PGF1-α among the three groups. However, the post-treatment blood levels of IL-6 and TXB2 in the 300 mg/day aspirin group were significantly lower than those in the placebo group (Table 2).

Six patients had small dermal ecchymoses on their limbs after treatment: three in the 300 mg/day aspirin group, two in the 100 mg/day aspirin group and one in the placebo group. These six patients were all female. Eight patients in the aspirin groups (five in the 300 mg/day aspirin group and three in the 100 mg/day aspirin group) complained of mild abdominal discomfort. No patient had any major gastro-intestinal bleeding or ulcers. All patients completed the course of aspirin treatment.

Discussion

Aspirin has been shown to reduce cardiovascular events. Small doses of aspirin are recommended for primary and secondary prevention in patients with a high risk of cardiovascular events.[30,31,36] Since all components of the metabolic syndrome are risk factors for cardiovascular events, patients with the metabolic syndrome are often considered to have a high risk of cardiovascular events.[37] In this study, we show that aspirin decreases inflammation, as demonstrated by its causing a decrease in blood levels of inflammatory mediators in metabolic syndrome patients. Chronic inflammation is often present in patients with the metabolic syndrome and is a significant contributor to the development of a cardiovascular event.[10,38] Our results also suggest that aspirin reduces TXA2, a potent promoter of platelet aggregation in patients with the metabolic syndrome.[27] Our study provides initial evidence to suggest that low and medium doses of aspirin can reduce blood levels of proinflammatory cytokines and platelet aggregation mediator in patients with the metabolic syndrome. Consistent with our study, it has been shown that 300 mg/day aspirin reduces plasma levels of CRP, IL-6 and TXB2, and the frequency of myocardial ischaemic episodes in patients with chronic stable angina.[39,40] However, a previous study showed that l00 mg/day or 300 mg/day aspirin did not significantly affect the plasma levels of CRP and IL-6 in patients with type 2 diabetes but who had yet to show any obvious signs of

Table 1 Baseline characteristics of the enrolled subjects

	300 mg aspirin group (n = 41)	100 mg aspirin group (n = 40)	Placebo group (n = 40)	P value
Male	22 (53.7%)	21 (52.5%)	22 (55%)	NS
Female	19 (46.3%)	19 (47.5%)	18 (45%)	NS
Age (years)	51.2 ± 8.3	52.9 ± 8.5	51.1 ± 10.0	NS
Hypertension	34 (82.9%)	31 (77.5%)	32 (80.0%)	NS
Abnormal blood glucose[1]	28 (68.3%)	28 (70.0%)	27 (67.5%)	NS
Abnormal waist[2]	28 (68.3%)	27 (67.5%)	28 (70.0%)	NS
BMI > 25	30 (73.2%)	29 (72.5%)	30 (75%)	NS
Systolic BP (mmHg)	152 ± 12	153 ± 13	152 ± 18	NS
Diastolic BP (mmHg)	89 ± 7	90 ± 8	86 ± 6	NS
Fasting glucose (mmol/l)	6.1 ± 1.3	6.1 ± 1.6	6.0 ± 1.2	NS
Postprandial glucose (mmol/l)	10.0 ± 3.0	9.6 ± 1.5	10.3 ± 3.4	NS
Waist circumference (cm)	90.3 ± 8.0	90.4 ± 6.2	90.3 ± 8.0	NS
BMI	27.1 ± 2.5	26.7 ± 6.2	27.0 ± 3.7	NS
Triglyceride (mmol/l)	2.28 ± 0.74	2.31 ± 1.02	2.26 ± 1.14	NS
Cholesterol (mmol/l)	5.57 ± 1.05	5.66 ± 0.56	5.56 ± 0.61	NS
Height (cm)	165.2 ± 6.3	164.7 ± 9.3	162.5 ± 8.2	NS
Drug:				
Metformin	21 (51.2%)	19 (47.5%)	20 (50.0%)	NS
Statins	25 (60.9%)	25 (62.5%)	24 (60.0%)	NS
ACEI or ARB	30 (73.2%)	28 (70.0%)	29 (72.5%)	NS
HCTZ	15 (36.5%)	13 (32.5%)	12 (30.0%)	NS
CCB	14 (34.1%)	15 (37.5%)	14 (35.0%)	NS
β-blocker	18 (43.9%)	19 (47.5%)	19 (47.5%)	NS
Fenofibrate[3]	4 (9.8%)	3 (7.5%)	3 (7.5%)	NS

[1]Fasting glucose ≥ 6.1 mmol/l and/or postprandial glucose ≥ 7.8 mmol/l. [2]Waist > 90 cm in Asian men, > 85 cm in Asian women. [3]Patients with triglyceride ≥ 5.67 mmol/l (500 mg) were given fenofibrate. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HCTZ, hydrochlorothiazide; CCB, calcium channel blocker. NS, not significant. Data are expressed as mean ± standard deviation (SD) or number of patients with the percentage in brackets.

Table 2 Blood levels of inflammatory mediators, TXB2 and 6-keto-PGF1-α

	hs-CRP (mg/l)	TNF-α (ng/ml)	IL-6 (pg/ml)	TXB2 (pg/ml)	6-keto-PGF1-α (pg/ml)
300 mg aspirin group					
Pretreatment	4.40 ± 3.18	3.54 ± 1.26	127 ± 38	65.6 ± 22.2	234 ± 74
Post-treatment	3.34 ± 2.84	3.11 ± 1.00	107 ± 38[a,b]	57.6 ± 22.2[a]	237 ± 56
P value	0.0009	0.0005	0.0267	0.0012	0.7606
100 mg aspirin group					
Pretreatment	4.31 ± 3.15	3.65 ± 1.64	133 ± 41	66.1 ± 20.1	230 ± 57
Post-treatment	4.08 ± 2.89	3.56 ± 1.66	131 ± 35	60.8 ± 18.2	233 ± 53
P value	0.0201	0.1452	0.3945	0.0001	0.6411
Placebo group					
Pretreatment	4.36 ± 3.11	3.51 ± 2.04	125 ± 48	63.8 ± 15.5	231 ± 49
Post-treatment	4.38 ± 3.29	3.44 ± 1.49	125 ± 44	68.2 ± 15.5	232 ± 56
P value	0.9104	0.7026	0.9869	0.1156	0.8900

hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; 6-keto-PGF1-α, 6-keto-prostaglandin F1-α; TNF-α, tumour necrosis factor-α; TXB2, thromboxane A2. Results are means ± SD. [a]$P < 0.05$ compared to post-treatment values in the placebo group. [b]$P < 0.05$ compared to post-treatment values in the 100 mg/day aspirin group.

cardiovascular disease.[41] These results contrast with our result, namely that 300 mg/day of aspirin significantly reduced the blood levels of CRP and IL-6 in patients with the metabolic syndrome.

A cardiovascular or cerebrovascular event is almost always caused by the development of thrombus on a ruptured atherosclerotic plaque.[42,43] Fatal coronary thrombi often result from a rupture of the plaque's fibrous cap. This rupture allows platelets to come into contact with, and be activated by, the lipid-rich core, leading to platelet aggregation, thrombus formation and, ultimately, an acute ischaemic event.[44] Many inflammatory mediators, such as TNF-α, IL-6 and hs-CRP, participate in the various stages of thrombus formation.[45] The release of soluble platelet factors, such as thrombin, serotonin and TXA2, which can cause platelet aggregation, arterial constriction and

subsequent reduction in the arterial blood flow, facilitates the thrombus formation and organ ischaemia.[27,46]

Although platelets from many patients may be resistant to aspirin because platelets can aggregate in response to activators such as ADP and thrombin, one of the major mechanisms for aspirin's antiplatelet aggregation property has been proposed to be the irreversible inhibition of COX-1, reducing TXA2 production.[37] Consistent with this idea, our results show that aspirin decreases blood levels of TXB2. Since COX in platelets is sensitive to aspirin, aspirin at 100 mg/day or 300 mg/day effectively decreases TXB2 blood level. Small doses of aspirin have been recommended for clinical use to induce beneficial effects, such as the inhibition of TXA2 production, in order to limit bleeding complications and to avoid inhibition of the production of the beneficial factor, PGI2, from endothelial cells. Our results suggest that aspirin at 100 mg/day or 300 mg/day for 2 weeks does not affect the production of PGI2, supporting the clinical observation that aspirin in a broad range of doses from 75 mg to 1500 mg daily is beneficial in reducing the risk of cardiovascular events.[32,36,37] The mechanisms for the differential effects of aspirin on COX in the platelets and endothelial cells are not entirely clear. Aspirin, especially at low doses, may preferentially inhibit COX in the platelets in the presystemic vascular bed, while first-pass metabolism deactivates aspirin by metabolizing it to salicylic acid, which cannot inhibit COX in the endothelial cells in the majority of blood vessels.[47] In addition, endothelial cells can synthesize new COX proteins, whereas protein synthesis may be very limited in the platelets.

Our results clearly show that aspirin inhibits blood levels of inflammatory markers in patients with the metabolic syndrome. Inflammation plays a critical role in the development of atherosclerosis, and inflammatory mediators participate in various stages of thrombosis and subsequent ischaemic organ injury.[38] Our results show that 100 mg/day of aspirin decreases blood levels of hs-CRP and 300 mg/day of aspirin decreases blood levels of hs-CRP, TNF-α and IL-6. Blood levels of IL-6 in patients receiving 300 mg/day of aspirin were significantly lower than those in patients treated with 100 mg/day of aspirin. These results suggest that 300 mg/day of aspirin has a better anti-inflammatory effect than 100 mg/day in Chinese patients with the metabolic syndrome. As discussed in the introduction, hs-CRP, IL-6 and TNF-α are important inflammatory mediators and may contribute to clinical presentations of the metabolic syndrome.

According to Framingham's score, virtually all patients with the metabolic syndrome have a 10-year risk of a first clinical cardiovascular event of more than 10%.[37] These patients may have far more cardiovascular events than those matched by age, gender, heredity and race. Aspirin has been consistently shown to decrease the risks for cardiovascular and cerebrovascular events.[32,48,49] The usual recommended dose is 75–150 mg daily and the first dose is 300 mg.[32] Based on the results reported here, 300 mg/day of aspirin may be used for better anti-inflammatory effects in patients with the metabolic syndrome provided there is no counter-indication.

Our study has limitations. Our patient sample size is relatively small. However, the decrease in blood levels of inflammatory mediators and platelet aggregation regulators measured in this study was statistically significant, except for 6-keto-PGF1-α, where aspirin caused no change in levels at 100 mg/day or 300 mg/day. Furthermore, all of our patients are Chinese. It is not known whether our findings are applicable to other populations of patients. Finally, we collected blood samples the morning following the last dose of the drug therapy. It is not known whether the drug effects that we observed here represent the maximal effects of the drug regimen.

Conclusions

We have shown that aspirin at 100 or 300 mg/day suppresses blood levels of inflammatory markers and the production of the platelet aggregation mediator TXA2 in patients with the metabolic syndrome. The suppression achieved by the higher dose (300 mg/day) of aspirin was greater than that caused by the lower dose (100 mg/day). These data suggest that 300 mg/day of aspirin may be beneficial in decreasing the risk of cardiovascular events in patients with the metabolic syndrome.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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References

1. Ford ES *et al*. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002; 287: 356–359.
2. Porto PI *et al*. Clinical features of the metabolic syndrome in adolescents: minor role of the Trp64Arg beta3-adrenergic receptor gene variant. *Pediatr Res* 2004; 55: 836–841.
3. Weiss R *et al*. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004; 350: 2362–2374.
4. Avogaro A. [Diabetes and multimetabolic syndrome]. *Ital Heart J* 2003; 47: 13S–21S.
5. Isomaa B. A major health hazard: the metabolic syndrome. *Life Sci* 2003; 73: 2395–2411.
6. Ferrucci L *et al*. Treatment of isolated systolic hypertension is most effective in older patients with high-risk profile. *Circulation* 2001; 104: 1923–1926.
7. Kahn R *et al*. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005; 28: 2289–2304.
8. Kannel WB. Importance of hypertension as a major risk factor in cardiovascular disease. In: Genest J *et al.* eds. *Physiology and Treatment*. New York: McGraw-Hill, 1977: 888–910.
9. Goldstein LB *et al*. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group;

Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2006; 113: e873–e923.
10. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. *J Clin Endocrinol Metab* 2007; 92: 399–404.
11. Liberopoulos EN *et al*. Diagnosis and management of the metabolic syndrome in obesity. *Obes Rev* 2005; 6: 283–296.
12. Sonnenberg GE *et al*. A novel pathway to the manifestations of metabolic syndrome. *Obes Res* 2004; 12: 180–186.
13. Hotamisligil GS *et al*. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 1993; 259: 87–91.
14. Hotamisligil GS *et al*. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest* 1995; 95: 2409–2415.
15. Porter MH *et al*. Effects of TNF-alpha on glucose metabolism and lipolysis in adipose tissue and isolated fat-cell preparations. *J Lab Clin Med* 2002; 139: 140–146.
16. Hansson GK. Immune and inflammatory mechanisms in the development of atherosclerosis. *Br Heart J* 1993; 69: S38–S41.
17. Odeh M. Tumor necrosis factor-alpha as a myocardial depressant substance. *Int J Cardiol* 1993; 42: 231–238.
18. Hotamisligil GS. The role of TNFalpha and TNF receptors in obesity and insulin resistance. *J Intern Med* 1999; 245: 621–625.
19. McCarty MF. Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, smoking, diabetes, and visceral obesity: down-regulation with essential fatty acids, ethanol and pentoxifylline. *Med Hypotheses* 1999; 52: 465–477.
20. Ridker PM *et al*. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 2000; 101: 1767–1772.
21. Pearson TA *et al*. Markers of inflammation and cardiovascular disease: application to clinical and public health practice. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; 107: 499–511.
22. Ridker PM *et al*. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14719 initially healthy American women. *Circulation* 2003; 107: 391–397.
23. Devaraj S *et al*. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: implications for the metabolic syndrome and atherothrombosis. *Circulation* 2003; 107: 398–404.
24. Zwaka TP *et al*. C-reactive protein-mediated low density lipoprotein uptake by macrophages: implications for atherosclerosis. *Circulation* 2001; 103: 1194–1197.
25. Ridker PM. Cardiology Patient Page. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation* 2003; 108: e81–e85.
26. Adam FM *et al*. Fasting insulin, adiponectin, hs-CRP levels, and the components of metabolic syndrome. *Acta Med Indones* 2006; 38: 179–184.
27. Willerson JT *et al*. Pathophysiology and clinical recognition. In: Willerson JT, Cohen LS, eds. *Cardiovascular Medicine*. New York: Churchill Livingstone, 1995.
28. Chapman MJ. From pathophysiology to targeted therapy for atherothrombosis: a role for the combination of statin and aspirin in secondary prevention. *Pharmacol Ther* 2007; 113: 184–196.
29. Ridker PM *et al*. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336: 973–979.
30. Hayden M *et al*. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the US Preventive Services Task Force. *Ann Intern Med* 2002; 136: 161–172.
31. Pearson TA *et al*. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 2002; 106: 388–391.
32. Collaboration AT. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324: 71–86.
33. Alberti KG *et al*. The metabolic syndrome – a new worldwide definition. *Lancet* 2005; 366: 1059–1062.
34. Metabolic Syndrome Trialists' Collaboration of Chinese Diabetes Association. The suggestion of metabolic syndrome of Diabetes Branch Association in Chinese Medical Association. *Clinical Journal of Diabetes* 2004; 12: 156–161.
35. Gabir MM *et al*. The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. *Diabetes Care* 2000; 23: 1108–1112.
36. Hennekens CH *et al*. Aspirin as a therapeutic agent in cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1997; 96: 2751–2753.
37. Shields TM, Hennekens CH. Management of metabolic syndrome: aspirin. *Endocrinol Metab Clin North Am* 2004; 33: 577–593, vii.
38. Willerson JT. Inflammation as a cardiovascular risk factor. *Circulation* 2004; 109: II2–I10.
39. Ikonomidis I *et al*. Reduction of daily life ischaemia by aspirin in patients with angina: underlying link between thromboxane A2 and macrophage colony stimulating factor. *Heart* 2004; 90: 389–393.
40. Ikonomidis I *et al*. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation* 1999; 100: 793–798.
41. Hovens MM *et al*. Effects of aspirin on serum C-reactive protein and interleukin-6 levels in patients with type 2 diabetes without cardiovascular disease: a randomized placebo-controlled crossover trial. *Diabetes Obes Metab* 2008; 10: 668–674.
42. Davies MJ. The pathophysiology of acute coronary syndromes. *Heart* 2000; 83: 361–366.
43. Fuster V *et al*. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). *N Engl J Med* 1992; 326: 242–250.
44. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation* 2005; 111: 3481–3488.
45. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; 340: 115–126.
46. Altman R. Acute coronary disease athero-inflammation: therapeutic approach. *Thromb J* 2003; 1: 2.
47. Schafer A *et al*. Antiplatelet agents. In: Braunwald E, *et al.* eds. *Hemostasis, Thrombosis, Fibrinolysis, and Cardiovascular Disease*. Philadelphia: WB Saunders, 2001: 2113–2115.
48. Antiplatelet collaborative overview of randomised trials of antiplatelet therapy – I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994; 308: 81–106.
49. Eidelman RS *et al*. An update on aspirin in the primary prevention of cardiovascular disease. *Arch Intern Med* 2003; 163: 2006–2010.