Irbesartan and Lipoic Acid Improve Endothelial Function and Reduce Markers of Inflammation in the Metabolic Syndrome: Results of the Irbesartan and Lipoic Acid in Endothelial Dysfunction (ISLAND) Study

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Results of the Irbesartan and Lipoic Acid in Endothelial Dysfunction (ISLAND) Study

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Background—The metabolic syndrome is associated with increased angiotensin II activity, induction of a proinflammatory and oxidative state, and endothelial dysfunction. We evaluated the ability of irbesartan, an angiotensin receptor blocker, and lipoic acid, an antioxidant, to affect endothelial function and inflammation in patients with the metabolic syndrome.

Methods and Results—We randomized 58 subjects with the metabolic syndrome in a double-blinded manner to irbesartan 150 mg/d (n=14), lipoic acid 300 mg/d (n=15), both irbesartan and lipoic acid (n=15), or matching placebo (n=14) for 4 weeks. Endothelium-dependent and -independent flow-mediated vasodilation was determined under standard conditions. Plasma levels of interleukin-6, plasminogen activator-1, and 8-isoprostane were measured. After 4 weeks of therapy, endothelium-dependent flow-mediated vasodilation of the brachial artery was increased by 67%, 44%, and 75% in the irbesartan, lipoic acid, and irbesartan plus lipoic acid groups, respectively, compared with the placebo group. Treatment with irbesartan and/or lipoic acid was associated with statistically significant reductions in plasma levels of interleukin-6 and plasminogen activator-1. In addition, treatment with irbesartan or irbesartan plus lipoic acid decreased 8-isoprostane levels. No significant changes in blood pressure were noted in any of the study groups.

Conclusions—Administration of irbesartan and/or lipoic acid to patients with the metabolic syndrome improves endothelial function and reduces proinflammatory markers, factors that are implicated in the pathogenesis of atherosclerosis. **(*Circulation*. 2005;111:343-348.)**

Key Words: metabolic syndrome ■ endothelium ■ inflammation ■ angiotensin

The metabolic syndrome is a constellation of abnormal glucose and lipid metabolism that has reached epidemic proportions over the past decade.[1] Patients with the metabolic syndrome are at considerable risk for developing atherosclerosis-related diseases, including a 2- to 4-fold increased risk of stroke and a 3- to 4-fold increased risk of myocardial infarction compared with those without the metabolic syndrome.[2]

Recent studies suggest that pro-oxidative and proinflammatory processes play a significant role in the development of endothelial dysfunction and the progression of atherosclerosis.[3,4] In fact, inflammatory markers are predictors of cardiovascular events and progression to type II diabetes in healthy individuals as well as those with the metabolic syndrome, underscoring the link between inflammation, metabolic disorders, and cardiovascular disease.[5,6] Chronic inflammation and an abnormal pro-oxidant state are both found in the metabolic syndrome and may play a role in its pathogenesis.[7,8]

The renin-angiotensin system plays a central role in the pathogenesis of atherosclerosis-related diseases. Angiotensin II, the central molecule in the renin-angiotensin system, has multiple effects on inflammation, endothelial function, and atherosclerotic plaque development.[9–11] In the present study, we wished to determine potential mechanisms by which the administration of the angiotensin receptor blocker (ARB) irbesartan (Avapro, Sanofi-Synthelabo) and lipoic acid, an over-the-counter nutritional supplement with strong antioxidant properties (Jarrow Formulas), regulates mechanisms of inflammation and endothelial function in subjects with the metabolic syndrome.

Methods

Subjects

Men and women 18 years of age or older with the metabolic syndrome were enrolled in the study. Metabolic syndrome was defined according to the National Cholesterol Education Program III

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TABLE 1. NCEP III Diagnostic Criteria for the Metabolic Syndrome

Factor	Criteria
1	Abdominal girth >102 cm (40 inches) in men or >88 cm (35 inches) in women
2	HDL-C <1.03 mmol/L (40 mg/dL) in men or <1.3 mmol/L (50 mg/dL) in women
3	Fasting triglycerides ≥1.69 mmol/L (150 mg/dL)
4	Blood pressure ≥130/85 mm Hg
5	Fasting glucose ≥6.1 mmol/L (110 mg/dL)

NCEP indicates National Cholesterol Education Program. Three of 5 criteria are required for the diagnosis of the metabolic syndrome.

criteria (Table 1); eligible subjects were required to meet at least 3 of the 5 criteria.[12] Subjects were excluded if they had any of the following: tobacco use <6 months before enrollment; a clinical history of coronary artery disease, congestive heart failure, or stroke; use of an ACE inhibitor, an ARB, or lipoic acid <1 month before enrollment; diabetes requiring treatment with insulin or oral medications; hemoglobin A1C ≥7.0%; serum creatinine ≥2.0 mg/dL; serum AST or ALT ≥2 times the upper limit of normal; rheumatological disorders such as lupus; or active malignancy. Written informed consent was obtained from all subjects.

Study Design

Subjects were randomized in a double-blinded manner to 1 of 4 groups: (1) irbesartan 150 mg/d plus matching placebo; (2) lipoic acid 300 mg/d plus matching placebo; (3) irbesartan 150 mg/d plus lipoic acid 300 mg/d; or (4) matching placebo tablets. Allocation concealment was maintained until the end of the study. Subjects were instructed to take all medications in the morning and were treated for 4 weeks. Pill counts were obtained at the end of the 4-week period to determine compliance. Fasting blood samples were drawn before and at the end of therapy at a similar time of day. The dose of irbesartan was chosen on the basis of the results of previous studies in which we found that the addition of irbesartan 150 mg/d reduced markers of inflammation in subjects with coronary artery disease.[13] The dose of lipoic acid was based on preliminary data demonstrating a reduction in oxidative stress in normal subjects by use of doses of 300 mg/d. The study protocol complies with the Declaration of Helsinki as well as local institutional guidelines and was approved by the institutional review board at the participating institution before its implementation.

Endothelial Function

Evaluation of endothelial function was made noninvasively by use of a technique called brachial artery reactivity testing, which uses ultrasound to evaluate endothelium-dependent flow-mediated vasodilation (FMD) in the brachial artery. We followed the *Guidelines for the Ultrasound Assessment of Endothelium-Dependent Flow-Mediated Vasodilation of the Brachial Artery*, published recently by the International Brachial Artery Reactivity Task Force.[14] Briefly, patients were positioned in the supine position with the arm in a comfortable position for imaging the brachial artery. A blood pressure cuff was placed on the forearm, after which a baseline rest image was acquired. The brachial artery was imaged above the antecubital fossa in the longitudinal plane. A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall was selected for continuous 2D gray-scale imaging. Blood flow velocity was estimated by time-averaging the pulsed Doppler velocity signal obtained from a mid-artery sample volume. The cuff was then inflated to ≥50 mm Hg above systolic blood pressure to occlude arterial flow for 5 minutes. After cuff deflation, the longitudinal image of the artery was recorded continuously from 30 seconds before to 2 minutes after cuff deflation. A mid-artery pulsed Doppler signal was obtained on immediate cuff release and no later than 15 seconds after cuff deflation to assess hyperemic velocity. After 15 minutes, nitroglycerin 0.4 mg was given sublingually, and repeat images were obtained to determine endothelium-independent vasodilation.

The diameter of the brachial artery was measured from longitudinal images in which the lumen-intima interface was visualized on both the near (anterior) and far (posterior) walls. Once the image for analysis was chosen, the boundaries for diameter measurements are identified manually with electronic calipers (Medical Imaging Application Vascular Tools); the average diameter was determined from at least 3 different diameter measurements determined along a segment of the vessel. Brachial artery diameter was measured at the same time in the cardiac cycle by use of ECG gating during image acquisition. FMD was typically measured as the change in post-stimulus diameter as a percentage of the baseline diameter. In accordance with the guidelines, we measured and report baseline diameter, absolute change, and percent change in diameter.

Laboratory Measurements

Fasting plasma levels of interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), and 8-isoprostane were measured by use of sandwich ELISA (Cayman Chemicals). The interassay and intra-assay variations between the samples were as follows: IL-6, 4.2% and 3.9%; PAI-1, 3.9% and 3.9%; and 8-isoprostane, 5.7% and 5.2%, respectively. We found no interference of irbesartan, lipoic acid, or their metabolites in these assays.

Blood glucose was measured by use of a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. LDL and HDL fractions were separated from fresh serum by combined ultracentrifugation and precipitation. Lipoprotein fraction cholesterol and triglycerides were measured enzymatically.

Study End Points

The primary end point of the study is changes in endothelium-dependent FMD of the brachial artery. The secondary end points included changes in plasma levels of the inflammatory markers IL-6, PAI-1, and 8-isoprostane.

Statistical Analysis

All values are presented as the mean±SD for continuous variables and as the percentage of total patients for categorical variables. The independent sample t test and χ^2 test were used for comparison of continuous and categorical variables, respectively. A probability value of $P<0.05$ was considered statistically significant, and all probability values were 2-sided. Comparisons within the placebo and the irbesartan/lipoic acid groups (irbesartan alone, lipoic acid alone, or both irbesartan and lipoic acid) were determined by use of 2-way ANOVA with a Bonferroni correction. The study was designed to have 80% power ($\beta=0.2$) to detect a 30% improvement in FMD of the brachial artery, ie, an absolute increase of 2%.

Results

Patient Characteristics

We screened 72 subjects for enrollment; of these, 60 subjects (20 men and 40 women) met enrollment criteria and were enrolled in the study. Of the latter group, 2 subjects (1 man and 1 woman) withdrew consent after randomization. Follow-up data are available on 58 subjects, all of whom were followed up for 4 weeks. The 4 experimental groups (irbesartan, lipoic acid, irbesartan plus lipoic acid, and placebo) had similar demographic characteristics at baseline (Table 2). The mean age was 45±12 years; the mean body mass index was 35±11 kg/m^2; and the mean LDL cholesterol, HDL cholesterol, and triglyceride levels were 3.8±0.4 mmol/L (145.7±14 mg/dL), 1.1±0.18 mmol/L (40.3±7.0 mg/dL), and 4.9±0.9 mmol/L (188±36 mg/dL), respectively. Three of the subjects were on a statin (1 in the placebo group; 2 in

TABLE 2. Patient Demographics and Baseline Characteristics

	Irbesartan 150 mg/d (n=14)	Lipoic Acid 300 mg/d (n=15)	Irbesartan 150 mg/d+ Lipoic Acid 300 mg/d (n=15)	Placebo (n=14)	*P*
Age, y	39±8	46±15	48±12	44±13	0.7
Men, %	6 (43)	5 (33)	5 (33)	6 (43)	0.6
Body mass index, kg/m^2	32±7	31±8	34±8	30±4	0.7
Waist circumference, cm	107±25	109±31	114±28	102±33	0.3
Systolic BP, mm Hg	136±10	130±17	135±18	130±14	0.9
Diastolic BP, mm Hg	80±10	80±10	85±10	75±7	0.5
LDL cholesterol, mmol/L	4±0.2	3.9±0.2	3.9±0.3	3.8±0.2	0.6
HDL cholesterol, mmol/L	1±0.2	1.2±0.1	1±0.2	1.1±0.2	0.7
Triglycerides, mmol/L	2±0.4	2.2±0.5	2.1±0.3	2.3±0.5	0.4
Fasting glucose, mmol/L	6.4±0.8	6.3±0.7	6.5±0.8	6.3±0.5	0.9
Hypertension	8	5	6	6	0.5

BP indicates blood pressure.

the irbesartan plus lipoic acid group), and 2 were on aspirin (1 in the lipoic acid group; 1 in the irbesartan plus lipoic acid group). None of the patients were taking calcium channel blockers or diuretics. No statistically significant differences were noted in baseline characteristics between the 4 treatment groups. After 4 weeks of therapy, there was a decrease in systolic blood pressure of 2.2±1 mm Hg and 1.8±3 mm Hg in the irbesartan and the irbesartan plus lipoic acid groups (P=0.9 and P=0.3, respectively), with no significant change in the lipoic acid or placebo groups (data not shown).

Treatment With Irbesartan and Lipoic Acid Improves Endothelial Function in the Metabolic Syndrome

After 4 weeks of therapy, FMD of the brachial artery was increased by 67%, 44%, and 75% in the irbesartan, the lipoic acid, and the irbesartan plus lipoic acid groups, respectively (Table 3), compared with the placebo group (irbesartan, 6.7±0.9%; lipoic acid, 6.2±0.8%; irbesartan plus lipoic acid, 7.2±0.8%; placebo, 4.6±1.1%; P<0.005 for the difference between irbesartan versus placebo, lipoic acid versus placebo; and irbesartan plus lipoic acid versus placebo). In addition, the difference in changes in FMD between the lipoic acid and the irbesartan plus lipoic acid groups was statistically significant (P=0.04). There was no significant relationship between treatment with aspirin or statin use and changes in FMD (P=0.5 and P=0.7, respectively).

Treatment With Irbesartan and Lipoic Acid Reduces Markers of Inflammation and Oxidative Stress in the Metabolic Syndrome

At baseline, there was a statistically significant difference between plasma levels of IL-6 in the irbesartan plus lipoic acid group versus the placebo group (20.9±1.3 versus 17.1±3.3 pg/mL; P=0.03). After 4 weeks of therapy, plasma levels of IL-6 were reduced by 25%, 15%, and 40% in the irbesartan, the lipoic acid, and the irbesartan plus lipoic acid arms, respectively (Figure 1), compared with the placebo group (irbesartan, 14.6±0.5 pg/mL; lipoic acid, 16.7±1.6 pg/mL; irbesartan plus lipoic acid, 12.1±1.8 pg/mL; placebo, 17.7±2.2 pg/mL; P=0.01 for the difference between irbesartan versus placebo and lipoic acid versus placebo; P<0.001 for the difference between irbesartan plus lipoic acid versus placebo). In addition, the difference in the changes in IL-6 levels between the lipoic acid and the irbesartan plus lipoic acid groups was statistically significant (P=0.002).

After 4 weeks of therapy, plasma levels of PAI-1 were reduced by 19%, 14%, and 27% in the irbesartan, the lipoic acid, and the irbesartan plus lipoic acid arms, respectively (Figure 2), compared with the placebo group (irbesartan, 16±2.6 pg/mL; lipoic acid, 17.2±1 pg/mL; irbesartan plus lipoic acid, 15.6±1.5 pg/mL; placebo, 19.6±1 pg/mL; P<0.001 for the difference between irbesartan versus placebo, lipoic acid versus placebo, and irbesartan plus lipoic acid versus placebo).

TABLE 3. Improvements in Endothelial Function With Irbesartan and Lipoic Acid

Variables	Irbesartan 150 mg/d (n=14)	Lipoic Acid 300 mg/d (n=15)	Irbesartan 150 mg/d+ Lipoic Acid 300 mg/d (n=15)	Placebo (n=14)	*P*
FMD % change, baseline	4.0±0.7	4.3±0.6	4.1±0.8	4.4±0.8	NS
FMD % change, 4 weeks	6.7±0.9	6.2±0.8	7.2±0.8	4.6±1.1	< 0.005
FMD absolute change, baseline, mm	0.13	0.16	0.12	0.14	NS
FMD absolute change, 4 weeks, mm	0.27	0.26	0.29	0.19	< 0.005
Endothelium-independent vasodilation, baseline, %	13.7±1.9	15.6±8.8	13.3±7.3	14.7±8.2	NS
Endothelium-independent vasodilation, 4 weeks, %	12.9±3	14.2±5.6	14.9±3.5	15.2±5.3	NS

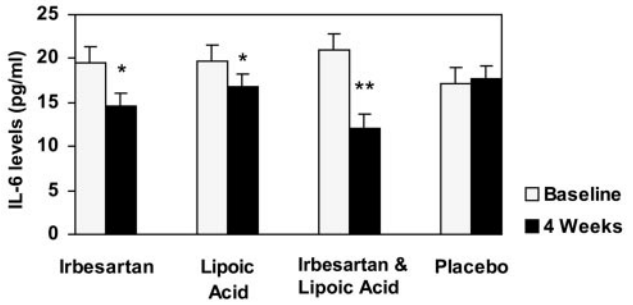

Figure 1. Reduction of IL-6 levels by irbesartan and lipoic acid. After 4 weeks of therapy, serum levels of IL-6 were reduced by 25%, 15%, and 40% in irbesartan, lipoic acid, and irbesartan plus lipoic acid arms, respectively, compared with placebo. *$P<0.01$; **$P<0.001$.

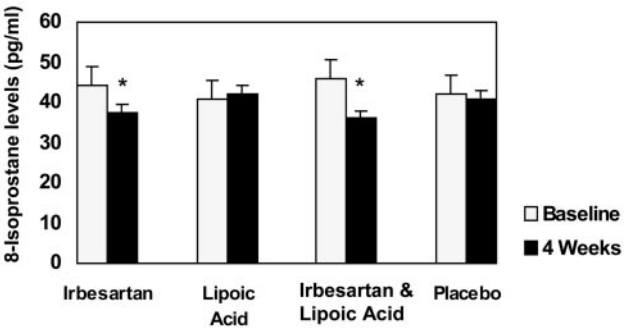

Figure 3. Reduction of 8-isoprostane levels by irbesartan. After 4 weeks of therapy, serum levels of isoprostane were reduced by 15% and 22% in irbesartan and irbesartan plus lipoic acid arms, respectively, compared with placebo. *$P<0.01$.

After 4 weeks of therapy, plasma levels of 8-isoprostane were reduced by 15% and 22% in the irbesartan and the irbesartan plus lipoic acid arms, respectively (Figure 3), compared with the placebo group (irbesartan, 37.6±4.5 pg/mL; lipoic acid, 42.0±5.0 pg/mL; irbesartan plus lipoic acid, 36.0±5.3 pg/mL; placebo, 41.0±4.8 pg/mL; $P=0.01$ for the difference between irbesartan versus placebo and irbesartan plus lipoic acid versus placebo; $P=0.28$ for the difference between lipoic acid versus placebo). There was no significant relationship between treatment with aspirin or statin use and any of the markers used in this study.

Discussion

We found that short-term treatment with the ARB irbesartan and the antioxidant drug lipoic acid resulted in significant improvements in endothelial function, including a 67% and a 44% increase, respectively, in endothelium-dependent FMD of the brachial artery when these agents were taken alone and a 75% increase in endothelium-dependent FMD when used in combination compared with placebo. In addition, treatment with these agents led to the reduction of IL-6 and PAI-1, markers of inflammation that are implicated in the pathogenesis of atherosclerosis. Irbesartan was also associated with a reduction in plasma levels of 8-isoprostane, a marker of oxidative stress. Furthermore, these effects were noted with nonsignificant changes in blood pressure, although the patients in our study were not particularly hypertensive to begin with (mean systolic and diastolic blood pressures of 133±15 and 80±9 mm Hg, respectively).

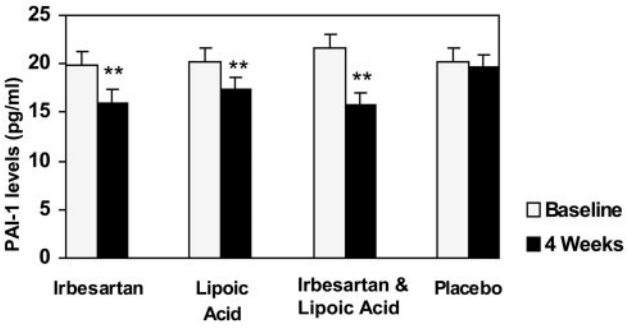

Figure 2. Reduction of PAI-1 levels by irbesartan and lipoic acid. After 4 weeks of therapy, serum PAI-1 levels were reduced by 19%, 14%, and 27% in irbesartan, lipoic acid, and irbesartan plus lipoic acid arms, respectively, compared with placebo. **$P<0.001$.

The renin-angiotensin system plays an important role in mediating the early stages of endothelial dysfunction and inflammation.[15] Experimental evidence derived primarily from animal and in vitro studies associates angiotensin II, the major vasoactive component of the renin-angiotensin system, with several steps of atherosclerosis, including arterial lipid deposition, reactive oxygen species production, activation of monocytes, increasing adhesion of monocytes to endothelial cells, direct modification of LDL molecules, increased oxidized LDL uptake into monocytes, and reduced endothelial NO synthesis.[16–18] Vascular ACE and vascular smooth muscle cell AT_1 receptor expression are upregulated in atherosclerotic lesions, potentially serving as a source for local production of angiotensin II.[19–21] Furthermore, the inhibitory effects of ARBs on the progression of atherogenic changes in rabbits and nonhuman primates fed a high-cholesterol diet and in apolipoprotein E–deficient mice suggest that angiotensin II plays a key role in the initiation and progression of atherosclerosis.[22,23]

In animal models, blockade of AT_1 receptors within atherosclerotic plaques normalizes NADPH oxidase activity, reduces plaque area and macrophage infiltration, and simultaneously improves endothelial function.[15] Unlike ACE inhibitors, however, ARBs may offer an additional advantage by activating the AT_2 receptor, which promotes antiproliferation, differentiation, and vasodilatation.[24,25] ARBs are also potent modulators of NADH/NADPH oxidase, which help normalize superoxide production in vessels, thereby yielding an antioxidant-like effect. A recent study by our laboratory demonstrated significant decreases in plasma levels of soluble vascular cell adhesion molecule-1, soluble tumor necrosis factor-α, and superoxide in normotensive patients with coronary artery disease treated with the ARB irbesartan.[26] The present study extends these anti-inflammatory and antioxidant findings to patients with the metabolic syndrome and also demonstrates that irbesartan improves endothelial function in these patients.

Lipoic acid, also known as α-lipoic acid, is an endogenously produced compound thought to have strong antioxidant activity. Available as an over-the-counter nutritional

supplement, it is commonly marketed as an adjunct in the treatment of diabetic neuropathy. Lipoic acid is readily converted in various tissues to its reduced form, dihydrolipoic acid, which increases intracellular levels of coenzyme Q10, NADPH, and NADH via increased glutathione availability.[27,28] Lipoic acid also acts as a scavenger of several free radicals, including hydroxyl radicals, hypochlorous acid, and singlet oxygen.[29] Surprisingly, we found no significant antioxidant effects of lipoic acid in our study, as determined by plasma levels of 8-isoprostane. This may reflect an inadequate dose of lipoic acid, because higher doses may be needed to demonstrate an effect on 8-isoprostane levels. Conversely, this may be because of the sandwich ELISA method that was used to measure plasma 8-isoprostane, although this is less likely, because this method has been validated previously by comparison with gas chromatography/mass spectrometry.[30] Nevertheless, our data demonstrated a 44% increase in endothelium-dependent FMD of the brachial artery in subjects treated with lipoic acid 300 mg/d for 4 weeks, as well as reductions in plasma levels of IL-6 and PAI-1, suggesting that mechanisms other than antioxidant effects may be involved in this particular patient population.

Endothelial dysfunction is common in patients with the metabolic syndrome and reflects the metabolic and vascular derangements present in this condition. Indeed, the subjects in our study had an average percent change in endothelium-dependent FMD of the brachial artery at baseline of only 4.2%, less than half that of a normal, healthy individual. Lower percent changes in FMD are indicative of poor endothelial function, and such patients have an increased incidence of atherosclerosis-related disease, including coronary artery disease and stroke.[31] Several human studies have found that treatment that improves endothelial function is also associated with reductions in cardiovascular morbidity and mortality.[32] Although our study was not designed to look at clinical end points, the results suggest that irbesartan and lipoic acid may have a role in the prevention of atherosclerosis in subjects with the metabolic syndrome.

Obesity is a major underlying cause of the metabolic syndrome. The mechanisms through which obesity elicits or exacerbates metabolic risk factors are not fully understood, although several recent studies suggest that adipose tissue itself plays an important role. Excess adipose tissue releases increased amounts of IL-6 and PAI-1, the latter of which contributes to a prothrombotic state. PAI-1 is a key regulator of fibrinolysis by inhibiting tissue plasminogen activator, and elevated PAI-1 levels are a marker of impaired fibrinolysis and atherothrombosis.[33,34] Decreased fibrinolysis, primarily attributable to increased PAI-1 activity, has been demonstrated in patients with the metabolic syndrome as well as in those with coronary artery disease, and higher PAI-1 levels are associated with worse outcomes in patients with coronary artery disease.[35,36]

Finally, obesity is often accompanied by high plasma levels of nonesterified fatty acids that cause insulin resistance in skeletal muscle and overload the liver with lipids, producing fatty liver and atherogenic dyslipidemia.[37] Fat accumulation in the liver may also stimulate hepatic cytokine production, leading to further increased levels of IL-6 and PAI-1.[38] Taken together, the abnormal proinflammatory and prothrombotic state that is prevalent in the metabolic syndrome leads to a worsening of metabolic control, abnormal function of the vascular endothelium, and eventually atherosclerosis and its associated diseases.

Limitations of the Present Study

Our study has several limitations that must be noted. Our investigation was a short-term study (4 weeks) involving a modest study population (n=58) to determine potential mechanisms by which irbesartan and lipoic acid may be effective in the metabolic syndrome. First, it is possible that further differences might have been noted had the study been extended for a longer duration or, conversely, that some of the effects may have been attenuated over time. Second, it is possible that the response to therapy with irbesartan or lipoic acid might have been more pronounced if a higher dose of these agents had been used. Third, 67% of the subjects in our study were premenopausal women. During the course of a 4-week study, hormonal status may change, altering endothelial function and PAI-1 levels, among others. Although no changes in these parameters were noted in either the placebo group or between men and women in the different groups, the effects of hormonal factors on study results cannot be excluded. Finally, it is important to recognize that few of our subjects were on statins and/or aspirin, because the concomitant use of these agents might alter the effects of irbesartan and/or lipoic acid on study outcomes.

Conclusions

Treatment of the metabolic syndrome consists of blood pressure reduction with standard antihypertensive drugs as well as diet, exercise, and weight loss. Despite these measures, however, an increasing numbers of patients with metabolic syndrome are being diagnosed with atherosclerosis-related diseases. Pro-oxidative and proinflammatory mechanisms are implicated in endothelial dysfunction and are important in the pathogenesis of atherosclerosis in such patients. The present study suggests, in part, the mechanisms by which the ARB irbesartan and the antioxidant agent lipoic acid may be beneficial in the prevention of atherosclerosis-related diseases. These findings also reinforce the growing evidence of inflammatory and oxidative mechanisms in the pathogenesis of atherosclerosis. Clinical outcome studies should be considered to determine the usefulness of these agents in the primary prevention of atherosclerosis-related diseases in subjects with the metabolic syndrome.

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