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Dietary salt restriction increases plasma lipoprotein and inflammatory marker concentrations in hypertensive patients

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Abstract

Background: Dietary salt restriction has been reported to adversely modify the plasma lipoprotein profile in hypertensive and in normotensive subjects. We investigated the effects of the low sodium intake (LSI) on the plasma lipoprotein profile and on inflammation and thrombosis biomarkers during the fasting and postprandial periods.

Methods: Non-obese, non-treated hypertensive adults ($n = 41$) were fed strictly controlled diets. An initial week on a control diet (CD, Na = 160 mmol/day) was followed by 3 weeks on LSI (Na = 60 mmol/day). At admission and on the last day of each period, the 24-h ambulatory blood pressure was monitored and blood was drawn after an overnight fasting period and after a fat-rich test meal.

Results: The dietary adherence was confirmed by 24-h urinary sodium excretion. Fasting triglyceride (TG), chylomicron-cholesterol, hsC-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) concentrations, renin activity, aldosterone, insulin, and homeostasis model assessment insulin resistance (HOMA-IR) values were higher, but non-esterified fatty acids (NEFA) were lower on LSI than on CD. For LSI, areas under the curve (AUC) of TG, chylomicron-cholesterol, apoB and the cholesterol/apoB ratio were increased, whereas AUC-NEFA was lowered. LSI did not modify body weight, hematocrit, fasting plasma cholesterol, glucose, adiponectin, leptin, fibrinogen and factor VII (FVII), and AUC of lipoprotein lipase and of lipoprotein remnants.

Conclusion: LSI induced alterations in the plasma lipoproteins and in inflammatory markers that are common features of the metabolic syndrome.

Keywords: Sodium diet; Remnant lipoproteins; Postprandial lipoproteins; Arterial hypertension; Inflammatory markers; Metabolic syndrome

1. Introduction

The treatment of arterial hypertension, a major cause of cardiovascular diseases, has long been shown to reduce the incidence of cardiovascular complications. Reduction in salt intake, even modest (78 mmol/day), is recommended to lower blood pressure in normotensive and hypertensive patients [1]. However, according to a meta-analysis, low-

Abbreviations: CD, control diet; LSI, low sodium intake; RLP, remnant-like lipoprotein; CRP, hsC-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; FVII, factor VII.

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salt intake (LSI) significantly increases fasting plasma or serum renin, aldosterone, noradrenaline, cholesterol (5.4%), LDL-C (4.6%) and triglyceride (5.9%), as compared with high sodium intake [2]. The reviewers conclude that the magnitude of the effect in Caucasians with normal blood pressure does not warrant a general recommendation to reduce sodium intake and that additional long-term trials of the effect of this diet on blood pressure, metabolic variables, morbidity and mortality are required to establish whether this is a useful prophylactic or treatment strategy [2]. Similar results were also reported on salt restriction in hypertensive patients [3]. Undesirable metabolic alterations have also been reported in individuals on severely restricted sodium diets, such as increases in renin concentration, aldosterone and noradrenaline and reduced insulin-mediated glucose disposal during euglycemic clamp conditions that were independent from plasma non-esterified fatty acids (NEFA) [4,5]. These data suggest that high aldosterone level may be a link between dyslipidemia, insulin resistance, hypertension and salt intake. In addition, it has been suggested that dietary salt restriction lacks clear beneficial effects on the prevention of coronary heart disease [6,7], and also that an inverse association of sodium to CVD mortality contributes to the cardiovascular disease mortality rate, according to one analysis of the NHANES II investigation [8]. The latter finding raises questions regarding the likelihood of a survival advantage accompanying a lower sodium diet, and highlights the need for further study of the relation of dietary sodium to mortality outcomes. Possible explanations for these undesirable effects of the low sodium diet (LSI) in humans stem from studies in mice and rats where dietary salt restriction increases the plasma lipid concentration [9–11], elicits peripheral insulin resistance [12], as well as hypertriglyceridemia, which was ascribed to an impairment in the plasma removal rate of triglyceride-rich lipoproteins [9]. All these disturbances resulted in lipid accumulation in the aortic root of hypercholesterolemic mice [10,13].

One should also bear in mind that all human studies on the effects of a low-salt diet dealt with plasma analyses carried out in the fasting state and were usually of very short duration. This is particularly relevant since hypertriglyceridemia, an independent risk factor for premature atherosclerosis in humans, is aggravated in the postprandial period due to the accumulation of chylomicrons and VLDL remnants, reduced HDL-C concentration and elevated concentrations of the atherogenic small, dense LDL particles [14]. Therefore, we investigated the potential adverse effects of a LSI on the plasma lipoprotein profile in the fasting as well as in the postprandial periods and related these findings to other metabolic parameters, such as plasma adiponectin, leptin, insulin, glucose, and to inflammatory and thrombogenic related blood markers, such as hsC-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), fibrinogen, and factor VII (FVII).

2. Subjects and methods

2.1. Subjects

This was an open, longitudinal study on the effect of LSI on plasma and lipoprotein metabolism. Non-treated, hypertensive (blood pressure ≥140/90 and ≤179/109 mmHg) adult patients (26 women and 15 men) were recruited at the Hypertension Unit of Hospital das Clínicas of the Faculty of Medical Sciences of University of São Paulo. Exclusion criteria were severe hypertriglyceridemia (TG ≥ 400 mg/dL = 4.5 mmol/L), BMI ≥ 30 kg/m^2, diabetes mellitus, alcohol abuse, secondary causes of hyperlipidemia and use of any drug that could interfere with lipid metabolism. The Ethics Committee of the Institution approved the study protocol and all participants signed the informed written consent.

2.2. Study protocol

All patients were placed on a 4-week placebo treatment for hypertension, immediately followed by 24-h ambulatory blood pressure monitoring (24-h ABPM) (SpaceLabs 90207). All participants (n = 41) were fed two frozen meals/day, commercially prepared, for 4 weeks (Condieta, SP, Brazil), where total calories were distributed as carbohydrates (55%), lipids (30%), and proteins (15%) resembling their regular dietary habits before entering the study protocol. In the first experimental week, the control diet (CD) contained approximately 160 mmol/day of sodium. In the ensuing three weeks, they were fed a low-salt diet (LSI = 60 mmol/day). All participants were weighed weekly, and 24-h urine was collected for sodium and creatinine measurements in order to control their dietary adherence. At the end of the CD and LSI periods, 24-h ABPM was monitored and mean blood pressure (BP), 24-h systolic BP and 24-h diastolic BP were determined. We considered those with a 24-h ABPM (mmHg) above 130 (systolic) or 80 (diastolic) as hypertensive.

2.3. Oral fat overload test

Blood samples were drawn after a 10–12 h fasting period and thereafter every 2 h for 10 h after a single liquid fat-rich meal containing 6% protein, 10% carbohydrate and 9% fat, providing 40 g fat/m^2 of body surface (Pulmocare®, Abbott, Brazil). During the test, the patients rested and only water was allowed *ad libitum*. Plasma was isolated immediately for lipid profile (TC, TG, HDL-C, LDL-C), glucose, serum insulin, non-esterified fatty acids, remnant-like protein (RLP), lipoprotein lipase and lipoprotein separation by ultracentrifugation. Blood samples for plasma aldosterone concentration and renin activity were drawn after a 30-min resting period.

Table 1
Clinical and laboratory data after the CD and LSI (mean ± S.D., $n = 41$)

	Diet	
	CD	LSI
Body weight (kg)	65.8 ± 10.1	65.5 ± 10.3
Blood pressure (mmHg/24 h)		
Systolic	144 ± 13	136 ± 13[b]
Diastolic	93 ± 8	89 ± 8[b]
Mean	110 ± 9	105 ± 9[a]
NaU (mmol/24 h)	170 ± 53	76 ± 37[b]
Plasma aldosterone (ng/dL) ($n = 32$)	9.8 ± 3.6	12.2 ± 5.8[a]
Plasma renin activity (ng/mL/h) ($n = 12$)	1.7 ± 1.5	2.6 ± 1.6[a]
Hematocrit (%)	48 ± 5	48 ± 4
Fasting glucose (mmol/L)	5.5 ± 0.6	5.5 ± 0.6
Fasting insulin (μU/ml)	13.1 ± 5.4	14.6 ± 5.7[a]
HOMA-IR	1.68 ± 0.71	1.90 ± 0.74[a]

[a] $P < 0.05$; paired Student's t-test.
[b] $P < 0.001$; paired Student's t-test.

2.4. Methods

Plasma and lipoprotein cholesterol and TG (Roche Diagnostics GmbH, Germany), glucose (Labtest Diagnostica, Brazil), NEFA, apoB, free cholesterol and phospholipid (Wako Chemicals USA, Inc.) concentrations were measured by standard enzymatic assays with commercially available kits, in a Cobas Mira autoanalyzer system. HDL-cholesterol was measured after precipitation of apoB containing lipoproteins [15] allowing for the estimate of LDL-C by the Friedewald formula [16]. Serum insulin (Linco Research, USA), aldosterone (TKAL2, DPC, USA) and plasma renin activity (CIS, USA) were determined by radioimmunoassay. Lipoprotein lipase concentration was determined in non-heparinized serum by ELISA (Daiichi Pure Chemicals Co., Ltd., Japan). Additional measurements included the high-sensitivity C-reactive protein by immunonephelometry (Roche Diagnostica, Brazil), IL-6 (Quantikine HS human IL-6, R&D System, USA), TNF-α (Quantikine HS human TNF-α, R&D System, USA), adiponectin and leptin (Linco Research), factor VIIa by ELISA (IMUBIND, American Diagnostica Inc., USA), and fibrinogen by the Clauss clotting technique (Fibrinogen-C Instrumentation Laboratory, USA). Homeostasis model assessment insulin resistance (HOMA-IR) was calculated according to a computer model [17].

Chylomicrons were isolated from the fasting and postprandial plasma samples by ultracentrifugation in a SW 41Ti rotor, at 78,000 × g (30 min, at 4 °C) in a Beckman L80 ultracentrifuge (Beckman Instruments, USA) [18]. VLDL ($d < 1.006$ g/mL), IDL ($d = 1.006$–1.019 g/mL) and LDL ($d = 1.019$–1.063 g/mL) fractions were isolated by discontinuous density gradient ultracentrifugation, in a L80 ultracentrifuge (Beckman Instruments) [19]. Remnant-like lipoprotein fraction was measured using the immune separation technique described by Nakajima et al. [20].

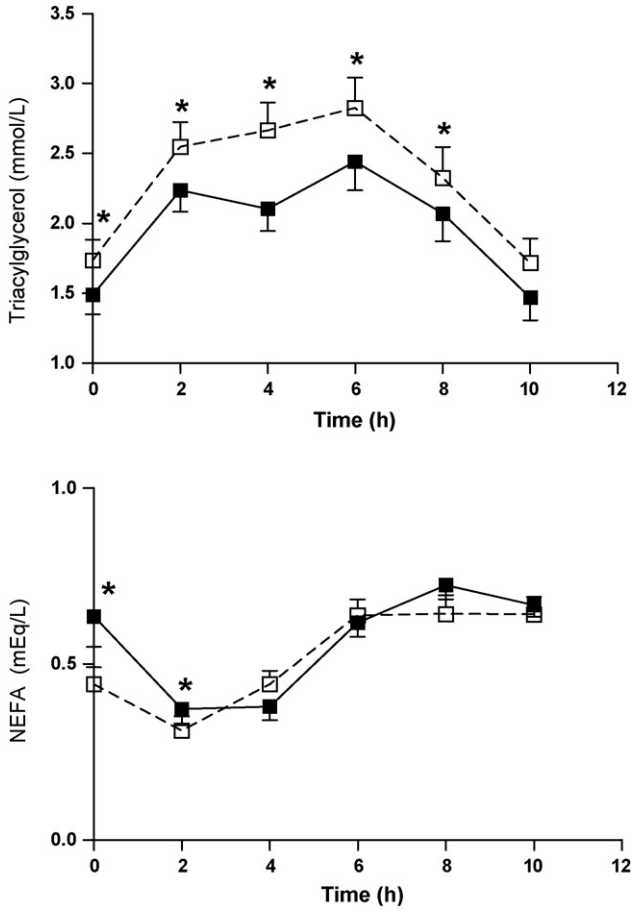

Fig. 1. Plasma concentrations of triglyceride (upper panel) and non-esterified fatty acids (lower panel) measured in the fasting and in the postprandial state on the control (filled squares) and on low-salt intake (open squares). *Significant differences at $P < 0.05$.

3. Statistical analyses

All values are expressed as mean ± standard deviation (S.D.). The integrated area under the curves (AUC) for TC, TG, NEFA, RLP, chylomicrons and lipoprotein lipase were calculated using Graph Pad Prism version 4 (GraphPad Software, Inc., USA). Differences between means on CD and LSI periods were calculated by paired Student's t-test using Graph Pad Prism version 4 (GraphPad Software, Inc.). Statistical significance was reached when $P < 0.05$.

4. Results

Forty-one patients (mean ± S.D.), 53.5 ± 8.5 years of age and with 26.1 ± 2.3 kg/m^2 BMI completed the protocol. Their body weight and hematocrit remained unaltered after 3 weeks on the LSI. The mean difference in the 24-h urinary sodium excretion between the CD and the LSI was approximately 100 mmol/day, and on the LSI increases in plasma renin activity and serum aldosterone concentration were observed, together with the expected reduction in the 24-h monitored

Table 2
Plasma lipids and lipoprotein lipase concentrations and area under the curves in fasting and during oral fat overload test on CD and LSI

	Diet	
	CD	LSI
Fasting		
Cholesterol (mmol/L)	4.7 ± 0.7	4.7 ± 0.7
TG (mmo/L)	1.4 ± 0.8	1.6 ± 0.9[a]
LDL-C (mmol/L)	2.9 ± 0.7	2.8 ± 0.8
HDL-C (mmol/L)	1.2 ± 0.4	1.1 ± 0.4
NEFA (mEq/L), $n=33$	0.65 ± 0.25	0.53 ± 0.24[a]
Lipoprotein lipase (ng/mL), $n=23$	60 ± 17	53 ± 17
Area under the curve		
Cholesterol	46.5 ± 8.2	47.4 ± 7.7
TG	20.7 ± 10.6	24.3 ± 12.0[b]
NEFA ($n=33$)	6.37 ± 1.59	5.75 ± 1.51[a]
Lipoprotein lipase ($n=18$)	550 ± 118	567 ± 163

LDL-C was calculated by the Friedewald formula (mean ± S.D., $n=41$).
[a] $P<0.05$; paired Student's t-test.
[b] $P<0.001$; paired Student's t-test.

Table 3
Composition of the chylomicrons ($n=16$), plasma RLP-C and RLP-TG ($n=28$), concentrations and area under the curves in fasting and during oral fat overload test on CD and LSI (mean ± S.D.)

	Diet	
	CD	LSI
Fasting		
Cholesterol (mg/dL)	7.7 ± 5.4	17.6 ± 20.3[a]
TG (mg/dL)	25.4 ± 20.3	55.3 ± 69.3
ApoB (mg/dL)	5.4 ± 4.8	9.6 ± 10.2
RLP-C (mg/dL)	13.8 ± 13.8	13.9 ± 12.8
RLP-TG (mg/dL)	38.8 ± 64.7	44.9 ± 62.3
Area under the curve		
Cholesterol	97.8 ± 52.1	232 ± 229[a]
TG	714 ± 496	1599 ± 2089
ApoB	61.4 ± 43.6	129 ± 108[a]
Cholesterol/apoB	18.7 ± 14.9	38.0 ± 52.8[a]
TG/apoB	15.4 ± 18.5	30.6 ± 45.4
RLP-C	167 ± 144	174 ± 129
RLP-TG	847 ± 849	983 ± 844

[a] $P<0.05$; paired Student's t-test.

arterial blood pressure (systolic −5%, diastolic −4.3% and mean −4.5%). LSI did not influence the plasma glucose, but increased serum insulin concentration and HOMA-IR index (Table 1).

LSI significantly increased the fasting plasma TG (14%) and TG-AUC (Fig. 1), however, it did not modify plasma TC, LDL-C estimated by the Friedewald formula, and HDL-C concentrations in the fasting state or as the area under the curve (Table 2). Interestingly, plasma NEFA-AUC decreased on the LSI, but this was ascribed to the fasting period and to the early phase in the oral fat diet test (fasting and 2-h values) (Fig. 1).

On the LSI, chylomicron particle composition showed an increase in the cholesterol content and in the TC-AUC, with no alteration of TG; additionally, the apoB content and the TC/apoB AUC in these particles increased only in the postprandial periods, but the TG/apoB ratio remained unaltered (Table 3). The AUC of the remnant particles, measured as plasma RLP-C and RLP-TG, were similar on LSI as compared to CD (Table 3). On the LSI, the VLDL composition disclosed an increase in the total cholesterol and lipid/apoB on fasting alone, but the triglyceride content increased during fasting and at the 4th hour of the postprandial phase, whereas phospholipid concentrations increased only in the latter. LSI did not modify the IDL composition, and decreased the LDL-C content in the fasting state, but not postprandially (Table 4).

Fasting CRP, IL-6 and TNF-α concentrations increased on LSI, but no changes were observed postprandially. LSI did not modify adiponectin, leptin, fibrinogen and FVIIa during both fasting and postprandial periods. As compared to the fasting phase, the postprandial values of IL-6 rose and of adiponectin decreased on the CD alone, whereas FVIIa decreased on the LSI (Table 5).

5. Discussion

In hypertensive patients, LSI reduced the 24-h arterial blood pressure, and increased the plasma triglyceride concentration, in the fasting and postprandial periods, consequently to the accumulation of chylomicron-cholesterol content and particles (represented by the apoB concentration), and VLDL lipid components, but not particle number. Fasting and postprandial triglyceride-rich remnant lipoprotein concentrations, measured as RLP-C and RLP-TG, did not vary on LSI.

These data in humans agree to some extent with results in Wistar rats, where LSI elicited hyperlipidemia secondarily to an impairment of the removal rate of TG-containing lipoproteins [9]. However, in contrast to humans, in rats an increase in plasma NEFA occurred and was attributed to a state of insulin resistance [11,12]. Therefore, the combination of low lipoprotein lipase activity and increased NEFA release from the adipose tissue could have contributed to the plasma TG-rich lipoprotein accumulation in animal experiments [9]. However, in our hypertensive patients on the LSI, plasma NEFA concentration was reduced in the fasting period and at the initial postprandial phase, although the non-heparinized serum lipoprotein lipase concentration was not modified. Consequently, a tissue-specific deficiency of this enzymatic activity capable of lowering the fatty acid production derived from TG-rich particles could not be ruled out. In this study, the postprandial concentration of the plasma TG-rich chylomicron remnant may have then resulted from its lower production rate from chylomicrons being balanced out by the remnant visceral removal rate defect. This interpretation is supported by our previous study on hypertensive subjects treated with hydrochlorothiazide, where a defective delipidation rate of the intravenously infused radioactively doubly labeled artificial chylomicron emulsion particles was observed [21].

Table 4
Composition of the VLDL, IDL and LDL, separated by ultracentrifugation, in subjects on the CD and LSI during fasting and at the 4th hour of the postprandial period (mean mg/dL ± S.D., $n = 16$)

	Fasting		4th hour postprandial	
	CD	LSI	CD	LSI
VLDL				
Total cholesterol	8.1 ± 6.2	12.0 ± 7.5[a]	12.0 ± 6.2	15.1 ± 6.8
TG	37.8 ± 36.0	56.6 ± 42.0[a]	68.6 ± 45.6	93.2 ± 46.4[a]
Phospholipids	18.2 ± 12.2	24.5 ± 15.5	32 ± 14	42.3 ± 15.2[a]
ApoB	3.4 ± 1.3	4.2 ± 1.6	5.0 ± 2.3	4.7 ± 1.5
Lipids[b]/apoB	17.5 ± 10.4	22.6 ± 13.7[a]	24.7 ± 10.2	31.6 ± 12.4[a]
IDL				
Total cholesterol	8.0 ± 4.1	9.2 ± 9.5	5.7 ± 2.8	7.0 ± 3.4
TG	12.0 ± 10.6	12.6 ± 7.7	9.3 ± 7.6	11.0 ± 7.8
Phospholipids	12.6 ± 5.7	12.0 ± 5.6	8.6 ± 3.0	12.0 ± 6.0
ApoB	5.2 ± 1.5	5.6 ± 1.7	4.5 ± 0.7	5.2 ± 1.5
Lipids[b]/apoB	6.6 ± 2.2	7.0 ± 5.2	5.3 ± 2.6	6.6 ± 3.6
LDL				
Total cholesterol	111 ± 37	99 ± 37[a]	103 ± 28	101 ± 44
TG	24 ± 8	23 ± 8	23 ± 9	24 ± 9
Phospholipids	79 ± 21	71 ± 16	73 ± 19	77 ± 16
ApoB	58 ± 12	51 ± 11	53 ± 11	52 ± 12
Lipids[b]/apoB	3.7 ± 0.6	3.8 ± 0.9	3.7 ± 0.5	3.8 ± 0.6

[a] $P < 0.05$, CD *vs.* LSI; paired Student's *t*-test.
[b] Lipids = total cholesterol + triglycerides + phospholipids.

Similarly to the animal experiments [11,12], a reduction in insulin sensitivity developed on the LSI could explain the abnormal plasma lipoprotein metabolism. Insulin resistance is known to be associated with increased plasma angiotensin II concentrations [22], and LSI activates the renin–angiotensin system, leading to increased plasma renin and aldosterone [3–5]. In noninsulin-dependent diabetes mellitus patients, dietary sodium restriction was related to a reduction in insulin sensitivity mediated by elevated angiotensin II [23]. Our interpretation is only partially supported by previous studies, as a reduction in insulin sensitivity was found in hypertensive volunteers [24] and in noninsulin-dependent diabetic patients [23], but no alterations [25], and even increased insulin sensitivity [26] have been reported in hypertensive patients. In spite of these controversies, an impairment of insulin sensitivity induced by LSI has been related to an increased sympathetic nervous activity in hypertension [4,27].

In the present study in humans, the lowering of plasma NEFA does not seem to conform to an increased insulin

Table 5
Fasting CRP, fasting and postprandial IL-6, TNF-α, adiponectin, leptin, fibrinogen, and factor VII concentrations in subjects on the CD and LSI (mean ± S.D.)

	n		CD	LSI
CRP (mg/L)	32	Fasting	1.61 ± 1.57	2.44 ± 2.54[a]
IL-6 (pg/mL)	24	Fasting	1.48 ± 0.66	1.84 ± 1.21[a]
		Postprandial	1.97 ± 1.45[c]	1.91 ± 1.50
TNF-α (pg/mL)	26	Fasting	0.99 ± 0.42	1.18 ± 0.56[b]
		Postprandial	1.00 ± 0.43	1.09 ± 0.47
Adiponectin (ng/mL)	23	Fasting	7.55 ± 3.23	7.13 ± 2.84
		Postprandial	6.93 ± 2.85[d]	7.29 ± 2.95
Leptin (ng/mL)	20	Fasting	9.76 ± 6.26	10.45 ± 7.78
		Postprandial	8.81 ± 6.67	10.08 ± 8.97
Fibrinogen (mg/dL)	25	Fasting	318 ± 53	338 ± 62
		Postprandial	314 ± 50	323 ± 59
Factor VIIa (ng/mL)	27	Fasting	5.21 ± 1.60	5.72 ± 2.61
		Postprandial	4.81 ± 1.63	5.54 ± 1.51[d]

[a] $P < 0.05$.
[b] $P < 0.001$, CD *vs.* LSI, paired Student's *t*-test.
[c] $P < 0.05$.
[d] $P < 0.01$, fasting *vs.* postprandial, paired Student's *t*-test.

resistance state, however our result agrees with another report where plasma fatty acid did not vary on the LSI in humans [4]. Whereas LSI markedly raised the plasma NEFA concentrations in rats and mice, rats on the LSI develop organ-specific insulin resistance in the liver and in the skeletal muscle, attributed to the impairment of insulin signaling, a decreased PI3-K/Akt pathway, and activation of the JNK and IRS-1 (ser307) phosphorylation. In contrast, the PI3-K/Akt pathway increases in the adipose tissue, demonstrating that tissue-specific insulin resistance facilitates greater adiposity in rats [28]. It is noteworthy that inhibitors of angiotensin-converting enzyme (ACE) or the angiotensin II receptor blocker improve insulin sensitivity [29] and protect against the development of atherosclerosis in animal models [30] and coronary artery disease in humans [31].

Angiotensin II plays an important role in the regulation of the vascular inflammatory response by modulating the expression of adhesion molecules, chemokines and cytokines, including TNF-α and IL-6. These effects of angiotensin II may be mediated in part by the vascular action of the CRP, via increased AT1-receptor expression [32]. In clinical studies, CRP has been reported as an independent predictor of risk of atherosclerosis, cardiovascular events [33] and hypertension [34], and as promoting arterial endothelium activation and macrophage recruitment [35]. Dietary sodium restriction could be linked to vascular pro-inflammatory factors for increasing CRP, IL-6 and TNF-α in the fasting period consequent to the activation of the renin–angiotensin–aldosterone system [36].

LSI did not alter adiponectin and leptin levels. In hypertensive patients, AT1-receptor blocker and angiotensin I-converting enzyme inhibitor increase adiponectin concentrations and improve the insulin sensitivity [37], but angiotensin II infusion reduces the plasma adiponectin level via the AT1-receptor in rats [38]. In addition, angiotensin II infusion in rats does not affect the plasma leptin level [38] in spite of the fact that angiotensin II increases the adipocyte gene expression and secretion of leptin [39].

LSI did not alter plasma fibrinogen and factor VII concentrations, but their roles in atherosclerosis remain controversial. There have been studies denying the importance of factors VII and XIIa, as well as IL-6 and CRP in the prediction of coronary artery disease [40]; other authors have not found any association between SBP or DBP and fibrinogen, factor VII, or von Willebrand factor [41]. Other studies have claimed that fibrinogen is significantly higher in patients with carotid atherosclerotic lesions [42], and hypertensive offspring have been shown to present higher plasma levels of plasminogen activator inhibitor-1 antigen, fibrinogen, fibrin degradation products, protein S antigen and factor XII activity [43]. Furthermore, coagulation factors VIIIc, fibrin monomer and factor VII were present in males with hypertension and hyperlipidemia [44], and plasma factor VII and PAI-1 levels increased in men with hypertension [45]. In addition, the hypertensive status associated with unfavorable lipid and haemostatic profiles was shown to improve in middle-aged men following treatment with beta blockers and ACE inhibitors [46].

Although we have shown, herein, that the importance of the LSI in atherogenesis seems mitigated by lack of unfavorable effects on blood coagulation, the inflammatory and metabolic disturbances elicited by LSI could overcome the benefit of the arterial blood pressure reduction in the development of atherosclerosis in humans [8], and in mice [10,13]. This is a relevant view, since abnormalities elicited by the low-salt diet have been described in the metabolic syndrome [47,48].

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