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Improved insulin sensitivity by the angiotensin II–receptor blocker losartan is not explained by adipokines, inflammatory markers, or whole blood viscosity

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Abstract

We have previously found improved insulin sensitivity after antihypertensive treatment with an angiotensin II–receptor blocker as compared with a calcium channel blocker in hypertensives. In this study, we compare the effect of these 2 principal different vasodilating agents on levels of adipokines, inflammatory variables, and whole blood viscosity in the same hypertensive patients with cardiovascular risk factors. We test whether potential differences in these variables might explain the difference seen in insulin sensitivity. Twenty-one hypertensive patients (11 women, 10 men) with mean age of 58.6 years and blood pressure of 160 ± 3/96 ± 2 mm Hg entered a 4-week run-in period with open-label amlodipine 5 mg. Thereafter, they were randomized double-blindly to additional treatment with amlodipine 5 mg or losartan 100 mg; and after 8 weeks of treatment, all patients underwent laboratory testing. After a 4-week washout phase with open-label treatment, the participants were crossed over to the opposite treatment regimen for 8 weeks before final examination. No significant differences were seen in the blood levels of adiponectin (7814 ± 870 vs 8090 ± 967 ng/mL), leptin (961 ± 122 vs 965 ± 147 pmol/L), resistin (11.7 ± 1.0 vs 11.3 ± 0.7 ng/mL), plasminogen activator inhibitor 1 activity (23.9 ± 2.2 vs 25.1 ± 2.2 U/mL), tumor necrosis factor α (1.35 ± 0.11 vs 1.72 ± 0.28 pg/mL), and high-sensitivity C-reactive protein (3.09 ± 0.84 vs 2.09 ± 0.42 mg/L) between treatment with amlodipine 10 mg or losartan 100 mg + amlodipine 5 mg, respectively. Although no significant differences in whole blood viscosity and blood pressure were observed between the 2 treatment regimens, a consistent trend toward lower viscosity was found at all shear rates as vasodilatory treatment was intensified (baseline to amlodipine 5 mg to amlodipine 10 mg to losartan 100 mg + amlodipine 5 mg). Our data do not support that effects on adipokines, inflammatory markers, and whole blood viscosity could explain improved insulin sensitivity seen on AT1-receptor blockade.

1. Introduction

Reduction in new-onset diabetes and improvements in insulin sensitivity by certain antihypertensive drugs have lately received much attention. To a degree, these may be explained by the vasodilating properties of these drugs. We have previously compared the effects of 2 vasodilating agents, an angiotensin II–receptor blocker (ARB) and a calcium channel blocker (CCB), on peripheral insulin-mediated glucose uptake in hypertensive patients with other cardiovascular risk factors. Insulin sensitivity assessed as glucose disposal rate (GDR) was shown to be significantly higher after treatment with losartan 100 mg + amlodipine 5 mg as compared with treatment with amlodipine 10 mg, despite similar blood pressure (BP)–lowering effects [1]. Thus, angiotensin II AT1-receptor blockade seems to affect glucose metabolism at the cellular level beyond what can be expected by the vasodilatation and BP reduction alone.

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Since 1994 and the discovery of leptin [2], it has been well known that adipose tissue is more than a passive storage of fat and energy. Adipose tissue secretes multiple bioactive molecules with local or systemic effects, called *adipocytokines* or *adipokines*. Dysregulated production of adipokines in obesity and lipodystrophy leads to the development of metabolic syndrome including insulin-resistant diabetes and vascular disease. Adiponectin, leptin, and tumor necrosis factor (TNF) α are among the best characterized of the adipokines and attract attention because of the suggested important role they seem to play in insulin resistance. Restoring the plasma levels of adipokines have been shown to reverse metabolic abnormalities and may be a possible target for prevention of the epidemic of metabolic syndrome. Based on in vitro studies, it has been hypothesized that blockade of the renin-angiotensin system (RAS) promotes the recruitment and differentiation of preadipocytes [3] and thereby delays or prevents the development of insulin resistance or diabetes. Our previous findings may be partly elucidated along these lines.

Obesity has been proposed to be a state of chronic inflammation, and possible differences in inflammatory markers may also be an explanation for the difference seen in insulin sensitivity in our losartan-amlodipine study [1]. We also wanted to investigate fibrinolytic activity in our patients, as reduced fibrinolytic activity has been associated with abdominal obesity and insulin resistance [4,5]. Increased whole blood viscosity has been linked to insulin resistance; and previous studies from our group have found a negative relationship between whole blood viscosity and insulin sensitivity [6,7], rendering important further investigations of the effect on viscosity of our 2 different vasodilating treatment regimens.

In the present study, we examine the effects of the 2 vasodilators on adipokines, inflammatory markers, and viscosity to elucidate the mechanisms behind the difference seen in insulin sensitivity [1]. We hypothesized that additional treatment with an ARB, despite similar changes in BP compared with treatment with CCB alone, would have a positive effect on these variables (eg, increased levels of adiponectin) and that such changes could explain the improvement of insulin sensitivity seen during the hyperinsulinemic isoglycemic glucose clamp.

2. Method

2.1. Study design

This was a 24-week, single-center, double-masked, randomized crossover study. After a 4-week run-in period on open-label amlodipine 5 mg, all hypertensive patients (BP >140/90 mm Hg) were randomized to an addition of either losartan 100 mg or amlodipine 5 mg for 8 weeks. At the end of this 8-week period, patients underwent clinical examinations, laboratory tests, and hyperinsulinemic isoglycemic glucose clamp. The patients then continued open-label 5 mg amlodipine for a 4-week washout period before crossing over to the other treatment regimen for another 8 weeks as in the previous treatment period. Blood samples were collected from the patients after the 2 treatment periods (amlodipine 10 mg and losartan 100 mg + amlodipine 5 mg) and stored for later analyses of adipokines and inflammatory markers altogether. Whole blood viscosity, hemoglobin, and hematocrit were measured at baseline, after treatment with open-label amlodipine 5 mg, and after treatment with the 2 comparing regimens.

2.2. Biochemical methods and calculations

Blood samples were collected after overnight fasting and stored at −70°C before analyses of adipokines and inflammatory markers. Adiponectin and TNF-α were measured in serum and analyzed by a commercial enzyme-linked immunosorbent assay method (R&D Systems Europe, Abingdon, Oxon, United Kingdom) with interassay coefficients of variation (CVs) of 5.2% and 8.5%, respectively. Plasminogen activator inhibitor (PAI) 1 activity (CV, 4.8%) was determined in citrated plasma with a commercially available kit (Spectrolyse/pL, Biopool AB, Umeå, Sweden). Serum values of leptin (CV, 9%-18%) and total ghrelin (CV, 7%-15%) were analyzed by radioimmunoassay kits, and serum resistin (CV, 4%) was measured by an enzyme-linked immunosorbent assay kit (Linco Research, St Charles, MO). High-sensitivity C-reactive protein (hs-CRP) was analyzed on a Hitachi 917 analyzer (Roche, Basel, Switzerland) using a commercial agent by Roche.

Whole blood viscosity was measured in EDTA-anticoagulated blood at a temperature of 37°C using a Bohlin controlled stress 10 rotational double-gap rheometer (Bohlin Instruments, Lund, Sweden). Measurements were performed at many shear rates, but only 2 low (0.5/s and 1.1/s) and 2 high (99/s and 201/s) shear rates are included in this article to reduce the number of analyses. The technique has an interassay CV of less than 7% at all shear rates.

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated in fasting conditions as serum glucose (in millimoles per liter) multiplied by serum insulin (in picomoles per liter) and divided by 135, as described by Matthews and colleagues [8]. A high HOMA-IR denotes low insulin sensitivity or insulin resistance.

2.3. Statistical analyses

The sample size of the study was calculated based on earlier studies of the effect of losartan on glucose metabolism by Moan et al [9], and the calculation was made according to our primary end point of insulin sensitivity (GDR) and not to the secondary end points of adipocytokines, inflammatory markers, and viscosity that are reported in this present investigation.

We used SPSS 14.0.1 (SPSS, Chicago, IL) software for data management and statistical analysis. Changes over time

were analyzed using paired-samples *t* test. Variables with a skewed distribution were analyzed after logarithmic transformation and were back-transformed to natural units for presentation in text and tables. A 2-tailed *P* value < .05 was considered the limit of statistical significance. All values are presented as mean ± SEM unless stated otherwise. Carryover effects may appear with the crossover design; and we therefore used a washout period of 4 weeks between the 8-week treatment periods to minimize carryover effects, and possible carryover effects are considered in the results.

To look at the correlation between the "gold standard" of insulin sensitivity measurement, the hyperinsulinemic isoglycemic glucose clamp [10], and other measured variables, we calculated Spearman rank correlation coefficient (r_s) for the patients who completed all analyses satisfactorily for each of the 2 treatment regimens. The correlation coefficients were considered significant at a 2-tailed *P* value < .05.

2.4. Ethics

The study was approved by the National Committees for Research Ethics in Norway and the Norwegian Medicines Agency, and the patients' verbal and written informed consent to participate was obtained from each patient before inclusion into the study.

The first part of the study was partly financed by school grants given to us by Merck (Whitehouse Station, NJ). Merck (MSD Norge) also supplied double-blinded study medications (losartan 100-mg tablets and matching placebos, as well as amlodipine 5 mg and matching placebos) and open-label 5-mg amlodipine capsules.

3. Results

Twenty-one hypertensive patients (11 women and 10 men) with mean age of 58.6 years (range, 46-75 years) accomplished the study period. The study group had a mean body mass index of 29.2 kg/m^2 and BP of 160 ± 3/96 ± 2 mm Hg. Seventeen of the patients also completed 2 satisfactory hyperinsulinemic isoglycemic glucose clamps [1]. Blood pressure was lowered to the same level after both treatment periods (Fig. 1), and there was a nonsignificant small change in mean body weight (amlodipine 10 mg, 86.9 kg; losartan 100 mg + amlodipine 5 mg, 86.2 kg). The GDR was significantly higher after treatment with losartan 100 mg + amlodipine 5 mg as compared with amlodipine 10 mg (4.9 ± 0.4 vs 4.2 ± 0.5 mg/[kg min], *P* = .039); and there was a trend toward lower values of HOMA-IR after losartan treatment (2.8 ± 0.5 vs 3.1 ± 0.6, not significant), indicating improved insulin sensitivity after additional treatment with losartan 100 mg as compared with amlodipine 5 mg as previously presented [1].

No significant difference was observed in adiponectin level between treatment with amlodipine 10 mg and losartan 100 mg + amlodipine 5 mg as shown in Table 1. As women are known to have higher leptin levels, separate analyses for each sex as well as for the patient group as a whole were done. There was no difference in the level of resistin or the gut peptide ghrelin, which was analyzed to see whether there could be differences between appetite-related hormones produced in adipocytes and in other cells in the body. The results of measured inflammatory variables in Table 1 also showed no significant differences between the 2 treatment regimens.

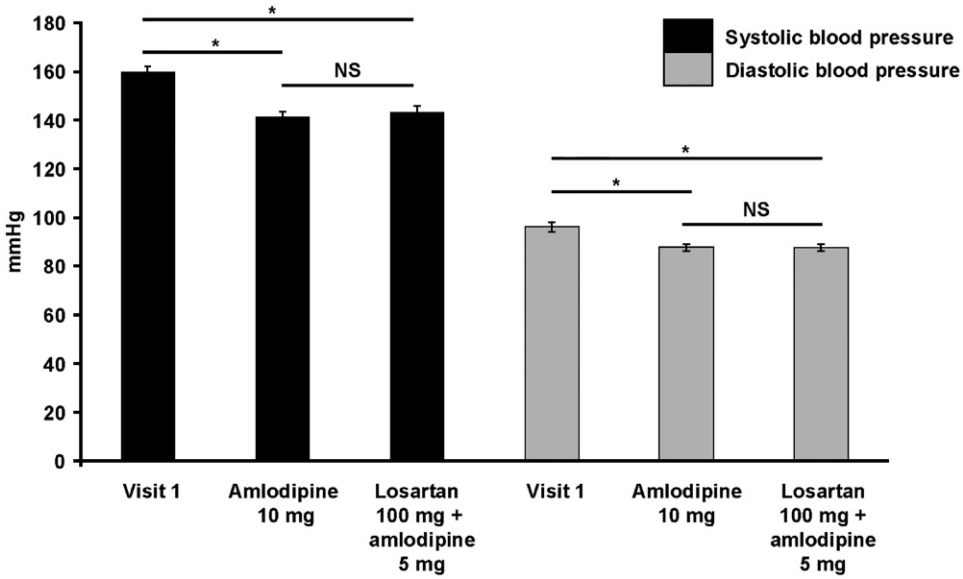

Fig. 1. Systolic and diastolic BPs at baseline (visit 1) and after treatment with amlodipine 10 mg and losartan 100 mg + amlodipine 5 mg. *P < .001. NS indicates not significant.

Table 1
Adipokines and inflammatory markers after treatment with amlodipine 10 mg and losartan 100 mg + amlodipine 5 mg in 21 patients

	Amlodipine 10 mg	Losartan 100 mg + amlodipine 5 mg	P
Adiponectin (ng/mL)	7814 ± 870	8090 ± 967	NS
Ghrelin (pg/mL)	1401 ± 158	1356 ± 176	NS
hs-CRP[a] (mg/L)	3.09 ± 0.84	2.09 ± 0.42	NS
Leptin (pmol/L)	961 ± 122	965 ± 147	NS
	♂ 625 ± 70	♂ 668 ± 84	
	♀ 1267 ± 183	♀ 1235 ± 247	
PAI-1 activity (U/mL)	23.9 ± 2.2	25.1 ± 2.1	NS
Resistin (ng/ml)	11.7 ± 1.0	11.3 ± 0.7	NS
TNF-α (pg/mL)	1.35 ± 0.11	1.72 ± 0.28	NS

Data are presented as mean ± SEM. NS indicates not significant.
[a] High-sensitivity CRP values >20 mg/L are not included in analyses; n = 20 patients.

When looking at the correlations between insulin sensitivity measured by the hyperinsulinemic isoglycemic glucose clamp and the investigated variables (Table 2), significant correlations were found between insulin sensitivity and adiponectin levels for both treatment regimens (Fig. 2).

There was no significant difference in viscosity between treatment with amlodipine 10 mg and treatment with losartan 100 mg + amlodipine 5 mg when looking at both high and low shear rates as seen in Table 3. However, there was a highly significant reduction from baseline to treatment with both amlodipine 10 mg and losartan 100 mg + amlodipine 5 mg ($P < .001$ for all shear rates). A significant reduction was also found from treatment with amlodipine 5 mg to treatment with both amlodipine 10 mg ($P < .01$) and losartan 100 mg + amlodipine 5 mg ($P < .001$) for all shear rates. There was also a significant reduction from baseline to treatment with open-label amlodipine 5 mg ($P < .05$ for all shear rates).

There was no significant difference in hemoglobin and hematocrit level between treatment with amlodipine 10 mg and with losartan 100 mg + amlodipine 5 mg as shown in Table 2. However, there were significant differences ($P < .05$) in both hemoglobin and hematocrit between baseline and amlodipine 5 mg, amlodipine 10 mg and losartan 100 mg + amlodipine 5 mg, as well as amlodipine 5 mg and amlodipine 10 mg and losartan 100 mg + amlodipine 5 mg.

4. Discussion

There have been fewer cases of diabetes development observed in patients treated with blockers of RAS (angiotensin-converting enzyme inhibitors and ARBs) compared with CCB in large hypertension trials [11-13]. The VALUE trial, which was the first trial to formally compare the effects of any inhibitor of RAS with a CCB on the development of new-onset diabetes, showed a 23% relative risk reduction in new-onset diabetes on valsartan (ARB) treatment compared with amlodipine (CCB) treatment [13,14]. Calcium channel blockers are considered to be neutral in their effects on glucose homeostasis [15], indicating a possible preventive effect of the RAS blockade. In accordance with this, we found significantly improved insulin sensitivity as assessed by the hyperinsulinemic isoglycemic glucose clamp technique after treatment with losartan 100 mg + amlodipine 5 mg compared with treatment with amlodipine 10 mg, despite similar BP reduction. To further investigate this difference in insulin sensitivity, we analyzed different adipokines and markers of inflammation and fibrinolysis in these patients.

Obesity and type 2 diabetes mellitus are associated with low plasma levels of the adipokine adiponectin in different ethnic groups, and it has been shown that circulating adiponectin levels correlate better with insulin resistance and hyperinsulinemia than adiposity and glucose intolerance [16]. We also found that adiponectin concentrations in our patients correlated well with insulin sensitivity as measured with the hyperinsulinemic isoglycemic glucose clamp (Fig. 2). This was the only investigated variable with a significant correlation after both treatment periods (Table 2). However, no significant difference was found between the 2 treatment regimens. This is in accordance with 2 recently published studies where treatment with the ARBs olmesartan and telmisartan had a significant effect on insulin sensitivity assessed by the HOMA index, but no effect on adipokines [17,18]. On the other hand, other investigations have shown that blockade of RAS increased adiponectin concentrations and suggested that it thereby may improve insulin sensitivity [19-22]. There are different hypotheses on how RAS blockade may increase adiponectin levels, for example, by suppressed TNF-α synthesis [23] or by prevention of oxidative stress [24]. Based on the hypothesis of Sharma et al [3], RAS blockade may promote an increased adipogenesis and adipocyte differentiation that may result in a greater capacity for lipid storage and adiponectin production. The effects may also be at the gene expression level because a positive effect of thiazolidinediones is seen [25,26] and at least one ARB, telmisartan, has been shown to act as a peroxisome proliferator–activated receptor (PPAR) γ agonist like the thiazolidinediones [27]. One experimental study has concluded that ARB-induced

Table 2
Correlation coefficients for investigated variables and insulin sensitivity in 17 hypertensive patients (only 17 patients completed 2 clamp procedures) treated with amlodipine 10 mg or losartan 100 mg + amlodipine 5 mg

	Amlodipine 10 mg		Losartan 100 mg + amlodipine 5 mg	
	r_s	P	r_s	P
HOMA-IR	−0.309	NS	−0.691	.002
Adiponectin	0.728	.001	0.600	.011
Ghrelin	0.282	NS	0.218	NS
hs-CRP	−0.063	NS	−0.289	NS
Leptin	−0.049	NS	−0.527	.030
PAI-1 activity	−0.225	NS	−0.458	NS
Resistin	0.064	NS	0.313	NS
TNF-α	−0.542	.025	−0.286	NS

r_s indicates Spearman correlation coefficient.

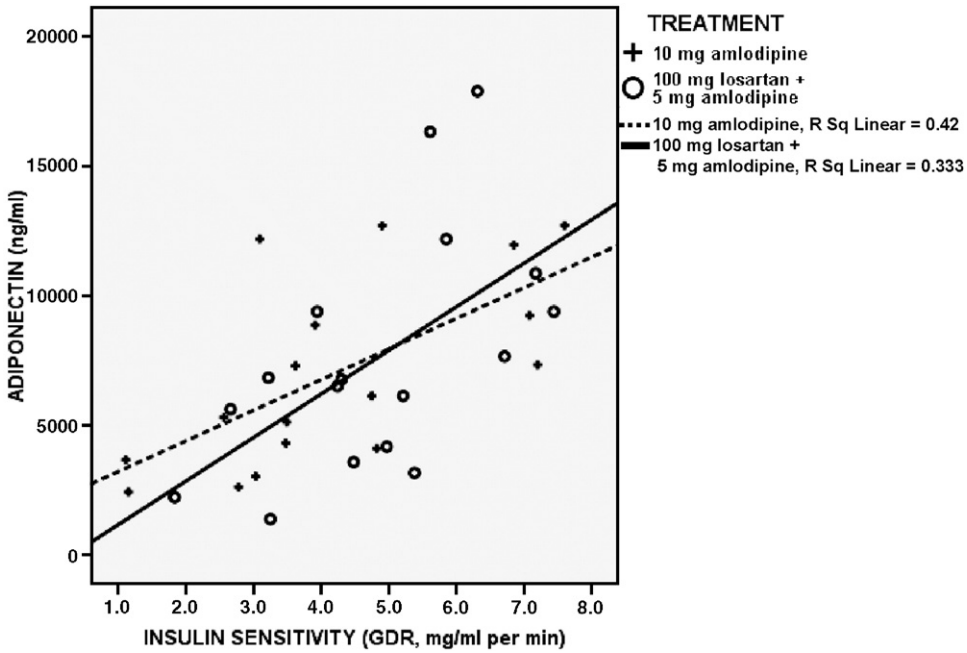

Fig. 2. Correlation between insulin sensitivity and adiponectin levels in 17 hypertensive patients (only 17 completed 2 clamp procedures satisfactorily), measured after 8 weeks of treatment with amlodipine 10 mg (+) and losartan 100 mg + amlodipine 5 mg (○).

adiponectin stimulation is most likely to be mediated via PPAR-γ activation involving a posttranscriptional mechanism [28], but this does not explain the positive effect seen in other RAS blockers with less known PPAR-γ effect [29]. The reason why no significant difference was found between the 2 treatment regimens in our study may of course be due to the limited number of patients included in our study and a possible type II error indicated by the positive correlation between insulin sensitivity and the adiponectin level (Fig. 2). On the other hand, we compared 2 active treatment regimens in our study, in contrast to other placebo-controlled studies [19-21]; and this may have diminished a possible positive effect of RAS blockade in our study. To our knowledge, the effect on adipocytokines between CCB and ARBs has not previously been investigated in a crossover design.

The primary biological role of leptin seems to be adaptation to low energy intake rather than inhibition of overconsumption and obesity [26]. Leptin is considered to play a key role in the elevation of sympathetic activity commonly found in obese hypertensive patients [30-32]. And because treatment with amlodipine has shown increased sympathetic activity in previous studies [33], we could speculate that our 2 treatment regimens could have different effects on the sympathetic-parasympathetic balance. However, no significant difference in leptin levels was found between the treatment regimens.

The adipokine resistin was discovered in 2001 by screening for genes that were induced during adipocyte differentiation and down-regulated in mature adipocytes treated with thiazolidinediones, and it got its name because of the thinking of this being the linkage between obesity and diabetes (*RESIST*ance to *IN*sulin) [34]. In mice studies, high levels of resistin have been shown to correlate with insulin-resistant states [34]; but there are differences in protein

Table 3
Hemoglobin, hematocrit, and viscosity at baseline and after treatment with open-label amlodipine 5 mg for 4 weeks and amlodipine 10 mg and losartan 100 mg + amlodipine 5 mg for 8 weeks in 21 hypertensive patients with other cardiovascular risk factors

	Baseline	Amlodipine 5 mg	Amlodipine 10 mg	Losartan 100 mg + amlodipine 5 mg	P [a]
Hemoglobin (g/dL)	15.1 ± 0.2	14.7 ± 0.3	13.7 ± 0.2	13.7 ± 0.2	.930
Hematocrit (fraction)	0.444 ± 0.007	0.433 ± 0.007	0.402 ± 0.006	0.403 ± 0.006	.834
Viscosity					
Shear rate 201/s	4.6 ± 0.1	4.4 ± 0.1	4.1 ± 0.1	4.0 ± 0.1	.216
Shear rate 99/s	5.1 ± 0.1	4.9 ± 0.1	4.5 ± 0.1	4.4 ± 0.1	.171
Shear rate 1.1/s	21.2 ± 1.1	19.1 ± 1.0	15.8 ± 0.9 [b]	14.7 ± 0.9 [c]	.059 [c]
Shear rate 0.5/s	29.0 ± 1.2	26.0 ± 1.3	21.0 ± 1.1	19.7 ± 1.0	.144

Data are presented as mean ± SEM.

[a] P value for difference between treatment with amlodipine 10 mg and losartan 100 mg + amlodipine 5 mg.

[b] Twenty-one patients (if 20 patients, 16.0 ± 1.0).

[c] Twenty patients.

structure between mice and human resistin, and the link between obesity and diabetes in humans has been shown to be complicated.

Several proteins of the hemostasis and fibrinolytic system are secreted by adipocytes including PAI-1. Plasminogen activator inhibitor 1 has been to linked to a variety of biological processes, is elevated in obesity and insulin resistance, is positively correlated with features of the metabolic syndrome, and predicts future risk of type 2 diabetes mellitus and cardiovascular disease [35]. Weight loss and improvement in insulin sensitivity due to treatment with antidiabetic drugs have shown significant reduction in circulating PAI-1 levels [35], but different effects of antihypertensive treatment with ARBs and CCBs have to our knowledge not been shown.

Tumor necrosis factor α is a proinflammatory cytokine and has been suggested to play a key role in insulin resistance in obesity [36,37]. It is thought to impair insulin signaling and inhibit tyrosine kinase activity at the insulin receptor [38], which is important for the biological activities of insulin. It has also been shown to increase the release of free fatty acids by adipocytes and reduce adiponectin synthesis [39]. Ersoy et al [40] evaluated the effect of amlodipine 5 to 10 mg for 12 weeks in obese hypertensive patients with type 2 diabetes mellitus and found that BP, fasting glucose, HOMA-IR, and TNF-α decreased significantly after treatment but that there was no correlation between percentage change in TNF-α and HOMA-IR. Other studies have also shown reduction in TNF-α with ARB treatment [41], but no differences were found in our study comparing CCB-based and ARB-based regimens. One explanation may be that both regimens may reduce TNF-α at the same level, but the reduction is not in any way related to the difference seen in insulin sensitivity. The inflammatory marker hs-CRP is a known biomarker of cardiovascular disease, and a relationship between CRP and insulin resistance has been shown [42]. The mean and median values of hs-CRP in our patients were at the level of average risk (1.0-3.0 mg/L) of developing a cardiovascular disease [43]. Measurement of hs-CRP should ideally be repeated within 2 weeks; but in our study, that was not possible because of the study design, and the results are therefore more vulnerable to variations. Previous studies have shown mixed results [44-46], but no significant difference was found between our 2 treatment regimens.

The rheological properties of blood in patients with essential hypertension are known to be altered compared with healthy subjects, and whole blood viscosity is directly correlated to the BP levels [47]. Previous studies from our group have also shown that whole blood viscosity is negatively related to insulin sensitivity [6,7]. In our study, 2 different vasodilating principles were used; but the BP effect was the same. We observed a consistent trend toward lower viscosity as vasodilatory treatment was intensified (baseline to amlodipine 5 mg to amlodipine 10 mg to losartan 100 mg + amlodipine 5 mg), but no significant difference in whole blood viscosity was found between the 2 treatment regimens. A significant difference was found from baseline and open-label amlodipine 5 mg treatment to treatment with both amlodipine 10 mg and losartan 100 mg + amlodipine 5 mg for whole blood viscosity, which probably is related to the differences in BP. However, a significant reduction in hemoglobin level was also found from baseline and open-label treatment to the treatment regimen with losartan; and this may also explain the reduced viscosity. The reduced hemoglobin concentration may be related to a possible antierythropoietic effect of losartan or the blood volume expansion secondary to the vasoconstriction [48].

There are some limitations in our study. The sample size of 22 patients was made on calculations of expected difference in insulin sensitivity between the 2 treatment regimens and not on the secondary end points of adipokines and inflammatory markers. This has implications for power; but as there were consistent results with no difference, except for adiponectin that showed a positive correlation with insulin sensitivity, we conclude that there is no significant difference in these variables between our 2 treatment regimens. The sample size in our trial was also comparable to previous placebo-controlled studies. The patients in our study were all hypertensives in need of antihypertensive treatment, so placebo was not an option. This may complicate the study design and the interpretation; but by using another vasodilating agent as a comparator, we were able to study the metabolic effect of ARB beyond the vasodilating effect of a CCB. Because our aim was to do a direct comparison of the 2 different vasodilating principles and the patients were on different treatments at baseline, the results at baseline are difficult to interpret; so the emphasis must be on the comparison between the 2 study regimens. Possible different results in tissue levels of adipokines have not been investigated in our study.

5. Conclusion

Because no significant differences in adipokines, viscosity, and inflammatory and fibrinolytic markers were found in patients treated with amlodipine 10 mg or losartan 100 mg + amlodipine 5 mg, the present investigation does not support that these variables explain the improved insulin sensitivity seen on angiotensin II AT1-receptor blockade. The difference in insulin sensitivity between treatment with ARB and CCB is most likely caused by other mechanisms.

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