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Mineralocorticoid Receptor Blockade Lowers Blood Pressure and Improves Endothelial Function in Obese Patients with Metabolic Syndrome

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Abstract

Introduction: Aldosterone has been implicated in the pathophysiology of both metabolic syndrome (MS) and MS-associated arterial hypertension, despite the use of mineralocorticoid receptor antagonists in these scenarios has been little studied.

Objectives: To assess the effects of mineralocorticoid blockade on blood pressure as well as metabolic and renal parameters in mild hypertensive subjects with MS compared with an active control group.

Methods: 27 individuals with the MS were assessed in a quasi-experimental real life study in which the experimental group (SPIRO) received spironolactone (25 to 50 mg/day) and the control group (AMLO) were in use of amlodipine, at dose of 5-10 mg/day, with the aim to reach a blood pressure target of 130/80 mmHg. After a treatment period that lasted 16 weeks, all clinical and laboratorial parameters were reassessed as well as 24 hour ambulatory blood pressure monitoring (24 h-ABPM) and flow-mediated dilation (FMD).

Results: Sixteen subjects were included in spironolactone group and 11 in amlodipine group (active control). At the end of 16 weeks of treatment there was a significant decrease in both, 24-hour systolic -23.98 mmHg, CI: -34.85 to -13.11, in spironolactone group, and -14.36 mmHg, CI: -25.83 to 2.89, in amlodipine group and diastolic pressure -12.84 mmHg, CI: -9.82 to -5.87, in the spironolactone group and -9.59 mmHg, CI: -16.97 to -2.21, in amlodipine group. No significant changes have been noted in the metabolic profile, as assessed by Homeostasis Model Assessment (HOMA-IR), triglycerides and potassium in both groups. In spironolactone group we detected a significant reduction in albuminuria levels, with no significant changes seen in amlodipine group. In addition, we found a significant reduction in C-reactive protein in spironolactone group and a significant increase in C-reactive protein in amlodipine group. We also found a significant association between the decrease in high-sensitivity C-Reactive Protein and flow-mediated dilation improvement in patients treated with spironolactone.

Conclusion: Spironolactone as monotherapyin hypertensive subjects presenting metabolic syndrome was effective in blood pressure control, had additional benefits on endothelial function, observed from C-reactive protein reduction and flow mediated dilation as well as had a potential renal protective effect through decrease in albuminuria excretion.

Keywords

Metabolic syndrome, Hypertesion treatment, Mineralocorticoid receptor blockade, Flow-mediated vasodilation

Introduction

An epidemic of obesity and metabolic syndrome (MS) has been observed in recent years, a phenomenon closely related to the increasing prevalence of hypertension (HT) [1-5]. Recently published data supports that connection and correlates the presence of abdominal obesity with the risk of hypertension [6]. The increase in blood pressure levels associated with MS involves several mechanisms such as sympathetic hyperactivity, sodium retention, hyperinsulinemia as well as hyperactivity of the renin-angiotensin-aldosterone system (RAAS) [4]. Also, the secretion of mineralocorticoid-releasing factors by adipocytes has implied a role for aldosterone in the pathophysiology of HT in MS regardless of angiotensin II-secondary stimulation [7-9]. In addition, some studies suggest a role of endothelial dysfunction mediated by aldosterone in the rise of blood pressure, mainly in groups such as those diagnosed with primary aldosteronism [10,11]. High aldosterone levels were also independently associated with MS [9] and resistant hypertension [12]. Despite such evidence, current guidelines on hypertension treatment do not recommend a preferred class of antihypertensive drugs for MS subjects.

While additional metabolic benefits are recognized with the use of drugs acting on RAAS [13-15], other antihypertensive drugs such as thiazide diuretics and beta-blockers may have unfavorable metabolic effects [16,17]. Based on these findings, it is important to individualize antihypertensive therapy for subjects with MS, aiming at a reduction in blood pressure levels, an improvement in insulin sensitivity as well as kidney protection.

In a pilot study in subjects presenting MS conducted by our group, which compared spironolactone (SPIRO) with aplacebo, we found that mineralocorticoid receptor (MR) blockade given as monotherapy reduced office blood pressure, improved flow-mediated dilation (FMD), and showed additional metabolic benefits in this group of subjects [18].

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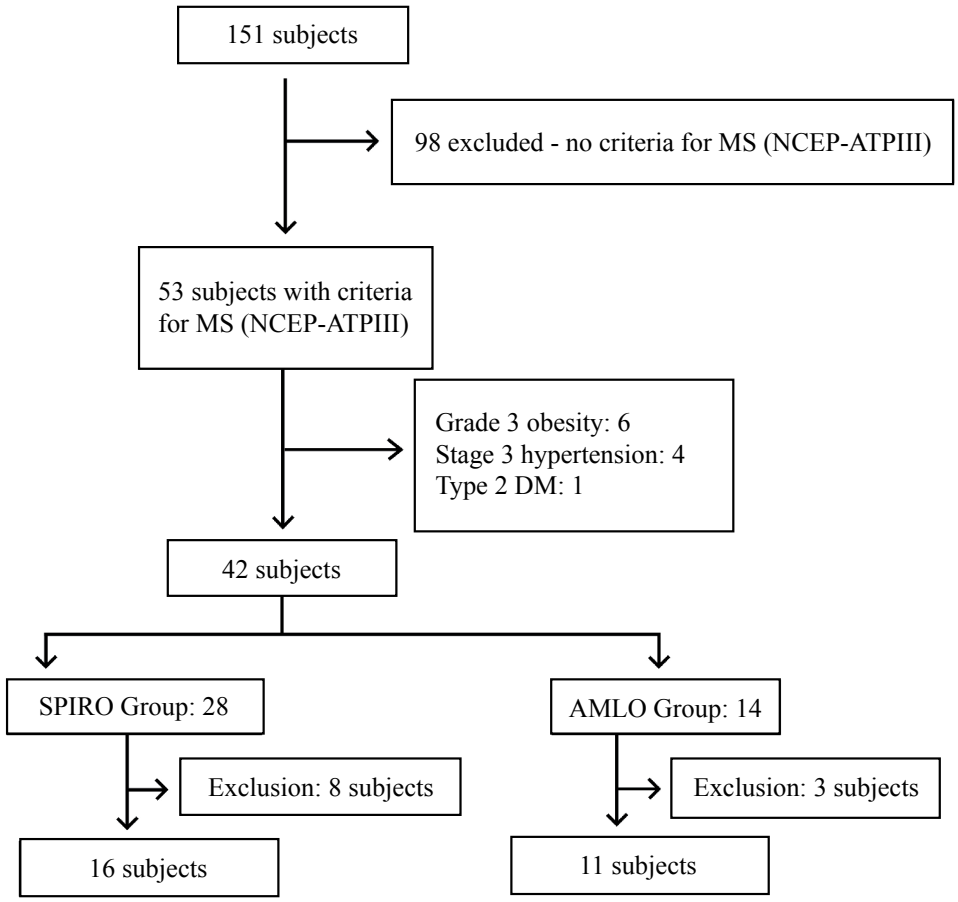

Figure 1: Subject flowchart 53 subjects.

The aim of the present study was to evaluate the effect of MR blockade on blood pressure profile as assessed by 24-h ambulatory blood pressure monitoring (ABPM) and endothelial function as well as metabolic and renal variables in a sample of MS subjects.

Population and Methods

In this real life, quasi-experimental study, a reference group treated with spironolactone was compared to a control group previously treated with amlodipine. At the Obesity outpatient Clinic of the Federal University of Juiz de Fora 151 subjects were evaluated. According to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII) criteria for metabolic syndrome, 53 individuals were considered eligible for the purpose of this study. Subjects with a previous history of type 2 diabetes mellitus, stage 3 hypertension (regardless of antihypertensive treatment), chronic kidney disease, heart diseases and pregnancy were excluded as well as grade 3 obesity. Thus, we selected 42 subjects to take part in this study, figure 1. Subject's age ranged from 18 to 60 years, all had hypertension stage 1, and a body mass index (BMI) ranging from 25 kg/m^2 to 39.9 kg/m^2. Serum potassium levels were within the normal range (3.5-5.0 mEq/L).

The Ethics Committee of the Federal University of Juiz de Fora University Hospital approved the study under number # 023/10 (FR: 316844, CAAE: 0014.0.420.000-10).

Obesity Outpatient Clinic Protocol

At first clinical assessment weight and height were collected to calculate body mass index (BMI) and abdominal circumference was determined. Following laboratorial tests are performed: fasting plasma glucose (FPG) and insulin to estimate Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), estimated glomerular filtration rate (eGFR) using Chronic Kidney Disease Epidemiology Collaboration formulae, lipid profile, potassium, aldosterone, plasma renin activity (APR) and C-Reactive protein-high sensitivity (hs-CRP). In addition, albumin to creatinine ratio was determined in spot urine sample, in duplicate. Further a 24 h-ABPM and endothelial function assessment through flow-mediated dilation (FMD).

From the 42 subjects, twenty-eight were under SPIRO treatment (SPIRO group), the interest group. Aiming to determine whether blood pressure reduction *per se* would be responsible for the reduction in urinary albumin excretion (UAE) as observed in our previous study using SPIRO [18], 14 individuals were used as control group since they were under amlodipine treatment (AMLO group). The AMLO is the regular medication in use at the service, and it is a good comparison given its efficacy in reducing blood pressure levels and due to neutral metabolic profile.The experimental group (SPIRO) received spironolactone at dose of 25-50 mg/day and the control group (AMLO) were in use of amlodipine, at dose of 5-10 mg/day, with the aim to reach a blood pressure target of 130/80 mmHg. After a treatment period that lasted 16 weeks, all clinical and laboratorial parameters were reassessed as well as 24 h-ABPM and FMD.

Since this is a real life study, in order to allow a comparison between groups at the baseline period we adopted the propensity score technique (PS) [19,20]. This technique enables to control heterogeneity bias between groups, making them more homogeneous and improving the level of evidence for results. After applying PS, 27 subjects were selected, 16 in SPIRO group and 11 in AMLO group.

Statistical Plan

Data was analyzed by Stata 13 software and values were expressed as mean and standard deviation (SD). The use of propensity scores (PS) aimed to control heterogeneity bias between groups arising from lack of randomization. PS estimates the probability of a subject belongs to treatment group (SPIRO), due to observed variables that

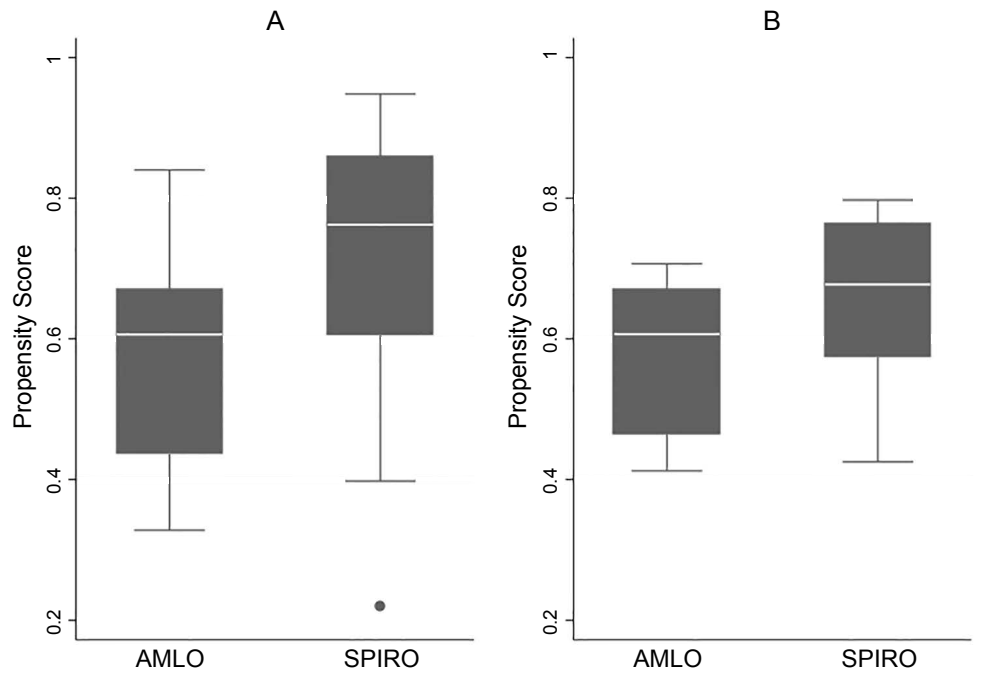

Figure 2: Distribution of studied groups by using propensity scores.

Table 1: Comparison of baseline data (following stratification).

Variable	SPIRO Group (n = 16)		AMLO Group (n = 11)		P-value (t-test)	P-value (k-test)	Effect size
Age (years)	43.8	11.1	45.5	12.6	0.707	0.778	- 0.156
weight (kg)	90.6	10.3	89.1	8.6	0.686	0.544	0.141
BMI (kg/m^2)	35.3	3.3	35.5	2.6	0.885	0.66	- 0.049
Fasting plasma glucose (mg/dL)	87.9	6.8	96.8	11	0.021	0.086	- 1.314
2 h-plasma glucose level OGTT (mg/dL)	106.5	22.3	123.9	41.6	0.202	0.028	- 0.781
HOMA-IR	3.6	2.1	3.2	1.3	0.546	0.9	0.187
Total cholesterol (mg/dL)	209.1	50.6	215.9	47.1	0.717	0.398	- 0.134
HDL-cholesterol (mg/dL)	44.4	8.6	47	7.3	0.388	0.315	- 0.304
Triglycerides (mg/dL)	195	84.8	193.2	115.9	0.964	0.778	0.021
CKD-EPI (ml/min/1.73 m^2)	100.2	19.2	98.4	22	0.921	0.996	0.095
Urinary albumin excretion (mg/g creatinine)	23.2	18.6	40.7	41.5	0.186	0.264	- 0.943
hs-CRP (mg/L)	4.1	2.6-6.3	2.6	2.0-4.5	0.149	0.315	0.381
FMD (%)	10	5.9	13.7	6.4	0.123	0.213	- 0.636
SBP 24 h (mmHg)	146.2	15.1	152.5	20.5	0.38	0.398	- 0.415
DBP 24 h (mmHg)	87.2	11.1	90.9	17.4	0.522	0.778	- 0.336

Values are expressed as mean ± SD. Except for hs-CRP, it is expressed as median (25-75% title).

OGTT: 75-g Oral Glucose Tolerance Test, BMI: Body Mass Index, CPK-EPI: Chronic Kidney Disease-Epidemiology Collaboration, hs-CRP: C Reactive Protein-high sensitivity, DBP: Diastolic Blood Pressure, FMD: Flow Mediated Dilation, HDL: High - Density Lipoprotein, HOMA IR: Homeostasis Model Assessment of Insulin Resistance, SBP: Systolic Blood Pressure, SD: Standard Deviation.

might be potential confounders to estimate the effect of interest [19,20].

Following PS calculation, there are several methods to make groups comparable [21] and the method applied depends on some aspects such as PS distribution between groups and sample size. In the present study, we chose to apply "stratification" by the simplicity and parsimony provided by the method, despite some sample loss. The tests used were *t* test for mean and Kolmogorov-Smirnov test for comparison among variables distribution.

Linear regression models were used to estimate the effects of SPIRO in relation to AMLO, where the dependent variable was the nominal difference between final versus baseline value of biomarkers. Findings on model assumptions, normality and heteroskedasticity were performed on residual model, and, in all cases, deviations from these assumptions were negligible. After stratification, a greater homogeneity was observed between the groups. Although the comparison of fasting plasma glucose, showed a statistically significant difference between groups, glucose levels of 87.9 ± 6.8 mg/dL in SPIRO group *vs* 96.8 ± 11.0 mg/dL in AMLO group are not clinically relevant, since none of the groups reached the cutoff that is indicative of DM. Homogeneity between AMLO and SPIRO groups is well evidenced in figure 2, which shows the distribution of PS before and after stratification, with the exclusion of strata 1 and 4. On the other hand, although it was not observed a significant difference between hs-CRP in groups SPIRO and AMLO, great discrepancies between groups were seen (6.3 ± 7.50 mg/L in the SPIRO group and 3.2 ± 2.0 mg/L, in AMLO group) (Table 1). Furthermore, compared to baseline an increase of 1.94 mg/L was observed inhs-CRP values in AMLO group ($p < 0.01$) while in the SPIRO group, a decrease of 1.0 mg/L was observed ($p = 0.03$), suggesting a significant reduction in inflammatory status after mineralocorticoid receptor blockade. In view of these findings and aiming to adjust the estimates of outcomes differences between the groups, hs-CRP levels were also used in the regression models, with a cutoff value of 3.0 mg/L which is used in clinical practice as an indicator of inflammation. Also, in all models, in addition to the variable that accounted for treatment and inflammation variable, the model was adjusted to baseline biomarker value, as a way to control the well-known problem of regression to the mean [22,23] in which, in general, the greatest differences occur

in subjects with more extreme values at baseline. In all cases, we also checked for an interaction between the drug and this value at baseline.

After adjustment of final models, the differences were estimated: final finding-baseline finding, for study drug selected subjects. Despite being adjusted mean differences for the other parameters studied in the model, the interpretation is a simple difference and should be interpreted in the original unit of measurement of analyzed parameters.

As a result of variable analysis intended for comparison and the use of stratification procedure, we obtained four strata. Strata 1 and 4 were excluded as they represented PS outliers, where the greatest differences probably had occurred. Therefore, only subjects from strata 2 and 3 were used in the final analysis, totaling 27 subjects: 11 in control group (AMLO) and 16 in treatment group (SPIRO).

Results

The mean age was 43.8 ± 11.1 and 45.5 ± 12.6 years for SPIRO and AMLO groups, respectively. Mean BMI was 35.3 ± 3.3 kg/m^2 and 35.5 ± 2.6 kg/m^2 for SPIRO and AMLO groups, respectively (p = 0.707). Demography and baseline values for other variables obtained after stratification and exclusion of strata 1 and 4 are shown in table 1.

Following stratification, we noted higher homogeneity between groups at baseline. In addition to comparisons presented at table 1, homogeneity between groups was evidenced in figure 2 that shows PS distribution before and after stratification, excluding strata 1 and 4.

Even after stratification, at baseline, hs-CRP showed a mean value two times greater in the treated group compared with the control group, despite p-values higher than 0.10. Since it is a potentially confounding variable and aiming to control a potential bias of this biomarker in the result, hs-CRP values were used in the regression models for groups comparison with a cut-off point of 3.0 mg/L which, in clinical practice suggest inflammation [24].

After treatment with spironolactone or amlodipine for 16 weeks, no significant differences were observed in BMI and abdominal circumference in relation to baseline values in both groups. In SPIRO group there was a significant reduction in 24 h-systolic blood pressure (24 h-SBP) of 15.2 ± 5.3 mmHg (p = 0.001; CI: 16.8-5.0) and in 24-hour diastolic blood pressure (24 h-DBP) 8.1 ± 2.5 mmHg (p = 0.004, CI: -13.4 to -2.90). In AMLO group we found a non-significant

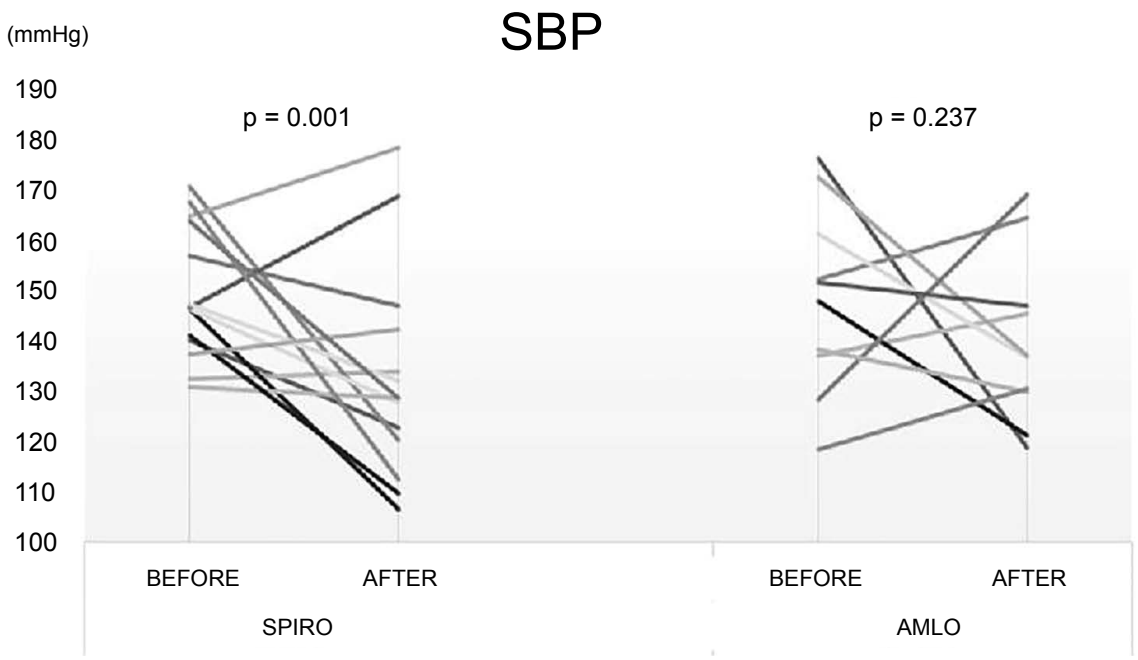

Figure 3: Systolic blood pressure by ABPM before and after treatment.

Table 2: Differences before and after treatment between SPIRO and AMLO groups.

Variable	SPIRO diff. (CI 95%)	AMLO diff. (CI 95%)	Effect	P-value
FPG (mg/dL)	0.8 (-2.53:4.13)	5.5 (1.37:9.57)	-4.7 (-10.25:0.90)	0.096
HOMA -IR	0.2 (-0.60:0.92)	0.8 (-0.17:1.75)	-0.6 (-1.86:0.61)	0.306
Potassium (mEq/L)	0.1	0.1	0.0	0.907
	(-0.03:0.33)	(-0.08:0.35)		
HDL-cholesterol (mg/dL)	4.6	1.8	2.7	0.202
	(1.88:7.32)	(-1.44:5.15)	(-1.6:7.07)	
Triglycerides (mg/dL)	-14.1	-22.7	7.9	0.639
	(-35.90:7.67)	(-48.36:4.33)	(-26.52:42.33)	
hs-CRP (mg/L)	-1.0	1.9	-2.9	0.000
	(-1.93:-0.69)	(0.81:3.06)	(-4.42:-1.45)	
Plasma aldosterone (ng/dL)	9.15	0.83	8.3	0.007
	(5.7:12.5)	(-3.75: 5.41)	(2.53:14.11)	
Urinary albumin excretion (mg/g creatinine)	-10.9	-0.19	-10.7	0.152
	(-19.79:-1.99)	(-11.62:11.23)	(-25.63:4.24)	
FMD (%)	4.9	-3.9	8.8	0.000
	(2.18:7.70)	(-7.25:-0.54)	(4.39:13.28)	

hs-CRP: C Reactive Protein-high sensitivity, Diff: Difference after-before treatment, Effect: Differences between differences in each group, FMD: Flow Mediated Dilation, FPG: Fasting Plasma Glucose, HDL: High Density Lipoprotein, HOMA IR: Homeostasis Model Assessment of Insulin Resistance.

reduction in 24 h-SBP of 5.9 ± 5.3 mmHg (p = 0.273; CI: -16.85 to 5.01) and in 24-hour DBP of 4.9 ± 3.2 mmHg (p = 0.141; CI: -11.5 to 1.7). However, the effect on SBP and DBP between SPIRO and AMLO group was similar (differences between differences in each group) was 9.24 mmHg (IC: -23.26-4.76), p = 0.185 and -3.2 mmHg (CI: -11.72-5.23), p = 0.435, respectively.

Mean value for individual 24 h-SBP values of both groups are shown in figure 3. The differences found in several variables, that is, final result minus baseline result for each group of subjects selected, based on treatment given can be seen in table 2.

Discussion

In the present study, we found that MR blockade with spironolactone as monotherapy was associated with a reduction in 24-h blood pressure values, in addition to an improvement in FMD and a decrease in hs-CRP in hypertensive subjects with MS. Such effects were not found in the control group treated with amlodipine.

In recent years, aldosterone has been related to the genesis of high blood pressure associated with MS. In the Framingham Offspring Study that evaluated inflammatory markers, neurohormonal activity and endothelial dysfunction in a cohort of newborns, aldosterone plasma levels were related to a higher incidence of MS during the follow-up of these individuals. In this study, a direct association was found between serum aldosterone and systolic blood pressure levels and an inverse relationship with HDL-cholesterol [25].

These findings were recently supported by a prospective longitudinal study which assessed 1674 individuals over 45 years of age and evidenced an association of plasma aldosterone levels in the upper tertiles of the normal range with hypertension, central obesity and higher risk of cardiovascular mortality. These data suggest that aldosterone, even within the normal range, may be a biomarker of cardio renal and metabolic disease [26]. The role of aldosterone in obesity-associated hypertension was previously demonstrated in an experimental model of obesity, where the MR blockade was effective in preventing obesity-induced increases in blood pressure, glomerular hyperfiltration, and sodium retention [27]. Similarly, in an open-label study, in which the investigators added spironolactone to the regimen in patients with resistant hypertension, 24 h-ABPM was significantly lower during spironolactone treatment. In this study, abdominal obesity was an independent predictor of good response to MR blockade [28].

Furthermore, in a pilot study performed in obese patients with MS, the administration of spironolactone as monotherapy compared with placebo led to a decrease in office blood pressure, improved FMD and increased plasma levels of HDL-cholesterol, signaling that MR blockade would be a therapeutic option in the treatment of hypertensive patients with MS [18].

In the present study, both drugs (SPIRO and AMLO) were effective in lowering blood pressure when assessed by 24 h-ABPM. However, in the control group (AMLO group) there was a less significant blood pressure decrease, which was not associated with an improvement in FMD. Similar findings have been described in a previous study, where amlodipine treatment did not result in improved FMD in comparison totelmisartan [29]. Other randomized clinical trials also did not show a significant improvement of FMD as a result of amlodipine use when compared to other agents with action on RAAS, such as perindopril and valsartan [29,30].

In our study, the improvement of FMD in SPIRO group was associated with a significant reduction in hs-CRP compared to the control group (AMLO group). The improvement in endothelial dysfunction following the MR blockade could be related to toxic effects of aldosterone on endothelium [31]. Experimental studies from Rocha, et al. demonstrated that aldosterone has an essential role in vascular inflammation, evidenced by the presence of arterial-wall fibrinoid necrosis, perivascular inflammation and focal infarction in the myocardium of hypertensive rats. In this study, animals treated with eplerenone or those that underwent adrenalectomy presented a reduction in myocardial injury associated with a decrease in cyclooxigenase-2 (COX-2) and osteopontin expression, mediators known to be involved in the genesis of vascular damage [32]. Similarly, studies evaluating the role of aldosterone in salt-sensitive hypertension has demonstrated that a high-sodium diet caused perivascular injury, podocyte injury and diastolic dysfunction in obese rats. These changes were mitigated by MR blockade [33]. Accordingly, clinical studies that have evaluated patients with primary hyperaldosteronism demonstrated a significant improvement of FMD following surgical treatment [11].

Such additional effects secondary to MR blockade are probably related to aldosterone non-genomic actions. It is believed that this mineralocorticoid hormone, through its elusive linkage with receptors located on plasma cell membranes of blood vessels and organs such as heart and kidneys,would lead to a chronic inflammatory state, oxidative stress and endothelial damage. In the present study, it was noted that MR blockade in humans was able to reduce inflammation, as expressed by a reduction in hs-CRP levels. A previous experimental study in obese rats demonstrated that MR blockade reduced the expression of pro-inflammatory and pro-thrombotic factors and increased the expression of adiponectin, a peptide produced by the adipocyte with relevant anti-inflammatory properties that leverage the action of insulin and inhibits some steps in the inflammatory process [34]. In our study, however, we did not observe improvement in HOMA-IR, a marker of insulin resistance, or a decrease in glucose levels following MR blockade. This lack of association between aldosterone levels and fasting blood glucose was also not obtained in a classical study that assessed a potential association among aldosterone levels and several other components of the MS. Therefore, the role of MR blockade on glucose homeostasis remains controversial [9].

Another interesting finding was the reduction in urinary albumin excretion in SPIRO group compared to AMLO group (10.9 vs 0.19 mg/g creatinine, respectively). Although it did not reach statistical significance, these data suggest a potential protective effect of SPIRO on endothelial function, possibly associated with the blockade of non-genomic actions of aldosterone.

In addition to lowered blood pressure and improvementof endothelial function, subjects treated with SPIRO showed a trend towards an increase in HDL-cholesterol, supporting previous data from randomized, placebo-controlled clinical studies performed by our group [18]. A potential role of the mineralocorticoid receptor blockade on *cholesteryl ester transferprotein* (CETP) action and its action on the transfer of cholesterol esters to lipoproteins such as LDL-cholesterol, resulting in increased HDL cholesterol levels, could explain these findings. However, further studies are needed to understand the mechanisms involved and the possible outcomes related to this effect.

We are aware about this study limitations, mainly regarding the lack of a proper experimental protocol, as regular randomized clinical trial. However, having data in hand from real life clinical records, it is important to highlight and consider that a proper methodological approach for observational study were applied. Although the rigor used in the selection process led to a small number of subjects it also resulted in homogeneouscomparison groups, that enhances findings reliability.

In summary, the administration of spironolactone in subjects with MS was effective in reducing blood pressure, improving endothelial function and reducing inflammation, without interfering significantly with metabolic parameters.

The study did not allow to recommend the use of spironolactone to treat hypertension for all patitnets with MS worldwide. Therefore, if this data is confirmed in randomized controlled studies, the use of MR blockade can be suggested as an alternative therapy for hypertension associated with MS.

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