Espironolactone Improves Flow-Mediated Vasodilatation in Subjects with the Metabolic Syndrome

Espironolactona Melhora a Vasodilatação Fluxo Mediada em Indivíduos com Síndrome Metabólica

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Abstract

Introduction: The role of aldosterone in the pathophysiology of the metabolic syndrome (MS)-related endothelial dysfunction has been the subject of recent research. **Objective:** To evaluate the effects of aldosterone blockade on flow-mediated vasodilation (FMD) and on renal and metabolic parameters of patients with the MS. **Methods:** 19 MS subjects underwent clinical examination, laboratory work-up (serum lipid profile, glucose and insulin; creatinine clearance; microalbuminuria investigation), ambulatory blood pressure monitoring (ABPM), and FMD analysis before and after 16 weeks of aldosterone blockade with spironolactone. **Results:** After the treatment period, FMD increased from 7.6 ± 5.63 % to 15.0 ± 6.10 % ($p < 0.001$), associated with a non-significant decrease of blood pressure (from 142.2 ± 16.37 mmHg to 138.8 ± 16.67 mmHg, and from 84.3 ± 10.91 mmHg to 82.7 ± 9.90 mmHg, respectively). HDL-cholesterol significantly increased, microalbuminuria showed a decreasing trend and creatinine clearance did not change after treatment. **Conclusion:** Aldosterone blockade in patients with the MS improved FMD without interfering with metabolic and renal parameters.

Keywords: Aldosterone. Endothelium. Vascular Permeability. Metabolic Syndrome X.

Resumo

Introdução: O papel da aldosterona na fisiopatologia da disfunção endotelial relacionada à síndrome metabólica (SM) tem sido objeto de estudos. **Objetivo:** Avaliar o bloqueio da aldosterona sobre a vasodilatação fluxo mediada (VDFM) e sobre parâmetros renais e metabólicos em indivíduos com SM. **Métodos:** Dezenove indivíduos com SM foram submetidos a exame clínico; exames complementares: glicose, insulina, lipidograma, depuração da creatinina, microalbuminúria e a monitorização ambulatorial da pressão arterial (MAPA) e análise da VDFM antes e após 16 semanas do uso de espironolactona. **Resultados:** Após o tratamento, observou-se aumento da VDFM, de 7,6 ± 5,63 % para 15,0 ± 6,10 % ($p < 0,001$), com redução não significante da pressão sistólica e diastólica (142,2 ± 16,37 mmHg para 138,8 ± 16,67 mmHg e 84,3 ± 10,91 mmHg para 82,7 ± 9,90 mmHg, respectivamente). O colesterol HDL (*High-density lipoprotein* – lipoproteína de alta densidade) aumentou de modo significante, a microalbuminúria apresentou tendência à redução, enquanto a depuração da creatinina não variou significativamente com o tratamento. **Conclusão:** O bloqueio da aldosterona em pacientes com SM melhorou a VDFM, sem induzir alterações no perfil metabólico e em parâmetros renais.

Palavras-chave: Aldosterona. Endotélio. Permeabilidade Vascular. Síndrome X Metabólica.

Introduction

The obesity epidemic of the last decades has been accompanied by an increased prevalence of the metabolic syndrome (MS) and its complications, chiefly cardiovascular diseases.[1] Abdominal adipose tissue produces inflammatory mediators which interfere with vascular structure

and function, thus increasing the risk of cardiovascular events.[2,3] It has been demonstrated that obese individuals have activation of the components of the renin-angiotensin-aldosterone system (RAAS).[4,5] Furthermore, dysfunctional adipose tissue can secrete aldosterone independently from renin stimulation.[6] Deleterious effects of aldosterone on human vascular endothelium have been suggested in the past few years.[7] Yet, the impact of aldosterone antagonism on the endothelial function of MS subjects has not been fully assessed.

Methods

We prospectively studied subjects diagnosed with the MS according to the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATPIII) modified criteria.[8] The participants, from both sexes and aged between 18 and 60 years, had stage I hypertension, body mass index (BMI) between 25 kg/m^2 and 40 kg/m^2, and serum potassium levels between 3.5 mEq/L and 5.0 mEq/L. The protocol was approved by the Committee of Research Ethics of the Federal University of Juiz de Fora Hospital (HU/UFJF).

After signing their informed consent, the subjects underwent clinical examination and a laboratory work-up consisting of the following: calculation of the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Homeostasis Model Assessment of Beta-cell function (HOMA-ß) indices; blood levels of lipids, potassium and aldosterone and; plasma renin activity. In addition, duplicate measurements of 24-hour creatinine clearance and microalbuminuria were obtained. Ambulatory blood pressure monitoring (ABPM) and flow-mediated vasodilatation (FMD) were also assessed, according to the American College of Cardiology guidelines.[9] For determination of FMD, a cuff was inflated for 5 minutes, around the non-dominant arm, up to 50 mmHg above the systolic pressure. Following cuff deflation for induction of reactive hyperemia, the caliber of the brachial artery was measured. FMD was the percentage of change in artery caliber between baseline and post-occlusion.

After baseline assessment, the subjects were started on spironolactone, 50 mg/day, for a 16-week treatment period, after which all clinical and laboratory investigations were repeated.

The SPSS 15.0 for Windows program was used for data analysis, the values being expressed as means and standard deviations. For comparisons of the variables before and after spironolactone treatment we used the parametric Student`s paired t test and the non-parametric Wilcoxon`s test, a p value < 0.05 being considered significant.

Results

We studied 19 subjects, aged 46.3 ± 9.80 years. Mean BMI was 33.9 ± 3.79 kg/m^2 and mean abdominal circumference was 109.0 ± 8.73 cm, values which remained unchanged after treatment. After spironolactone, FMD increased from 7.7 ± 5.63% (range: 2.3 – 23.0%) to 15.0 ± 6.10% (range: 8.0 – 30.8%), with a small, non-significant reduction of systolic and diastolic blood pressures (BP). Taking a FMD >/10% as a normal value, 14 of the 19 individuals (74%) had endothelial dysfunction at baseline, while only 3 of the 19 (16%) remained with below-normal values after spironolactone treatment. Whereas HDL-cholesterol levels increased, blood glucose, HOMA-IR, HOMA-β and creatinine clearance did not significantly change. Urinary albumin excretion tended to decrease after spironolactone treatment (Table 1).

Discussion

Acknowledgement of aldosterone role in the MS and of the possible participation of dysfunctional adipose tissue in the stimulation of aldosterone production in overweight patients has contributed to the understanding of the pathophysiology of MS-related vascular injury.[10] Likewise, mineralocorticoid blockade has been associated with enhanced endothelium-dependent vasodilation, with reduction of atherosclerotic disease progression in populations at high risk of cardiovascular disease.[11]

In this study of MS individuals, spironolactone was associated with significantly improved FMD, with a trend towards decreased urinary albumin excretion, in spite of a slight reduction of the BP. These findings are in accordance with previous studies which showed that aldosterone induces endothelial dysfunction and causes a specific vasculopathy.[11] Indeed, patients who had been surgically treated for primary hyperaldosteronism had significant improvement of their FMD.[7] Besides the improved endothelial function we observed, the significantly increased HDL-cholesterol levels, along with the improvement, albeit non-significant, of the HOMA-IR index, point to the favorable metabolic profile of spironolactone.

These finding corroborated a previous study we conducted, which demonstrated for the first time that

Table 1 Clinical and laboratory parameters of the study population

Parameters	Baseline	Post-spironolactone	p
24-hour SBP (mmHg)	142.2 ± 16.37	138.8 ± 16.67	0.530
24-hour DBP (mmHg)	84.3 ± 10.91	82.7 ± 9.90	0.660
Total Cholesterol (mg/dL)	202.2 ± 37.02	208.2 ± 43.51	0.259
HDL-Cholesterol (mg/dL)	41.5 ± 10.46	46.3 ± 6.87	0.010
Triglycerides (mg/dL)	163.8 ± 78.64	188.2 ± 102.41	0.040
Potassium (mg/dL)	4.2 ± 0.30	4.3 ± 0.35	0.256
Fasting glucose (mg/dL)	92.1 ± 8.19	93.4 ± 9.31	0.460
HOMA-IR	4.52 ± 6.85	3.6 ± 2.25	0.580
HOMA-β	266.2 ± 377.23	212.4 ± 177.33	0.450
Plasma renin activity (ng/mL/h)	1.1 ± 1.23	3.9 ± 2.18	< 0.001
Aldosterone (ng/dL)	6.6 ± 4.31	25.7 ± 13.19	< 0.001
Creatinine clearance (mL/min/1.73 m^2)	124.9 ± 33.16	118.4 ± 27.82	0.370
Microalbuminuria (mg/24 hours)	28.1 ± 45.67	18.7 ± 34.23	0.050
Flow-mediated vasodilation (%)	7.7 ± 5.63	15.0 ± 6.10	< 0.001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HDL: High-Density Lipoprotein; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance index; HOMA-β: Homeostasis Model Assessment of Beta-Cell Function index.

aldosterone blockade in MS patients improved FMD and reduced BP, suggesting an association between aldosterone and endothelial dysfunction in the MS.[12] Our findings of reduced urinary albumin excretion associated with improved FMD, in the absence of significant BP reduction, suggest a role for aldosterone in endothelial dysfunction, one which is independent from BP reduction. Further studies with larger samples may contribute to greater understanding of the mechanisms underlying vascular injury in the MS.

Conclusion

Aldosterone blockade in MS patients was associated with increased FMD and reduced microalbuminuria, suggesting improved endothelial function.

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