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ORIGINAL ARTICLE

High sodium intake is associated with increased glucocorticoid production, insulin resistance and metabolic syndrome

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Abstract

Objective High sodium (HS) diet is associated with hypertension (HT) and insulin resistance (IR). We evaluated whether HS diet was associated with a dysregulation of cortisol production and metabolic syndrome (MetS).

Patients and measurements We recruited 370 adults (18–85 years, BMI 29·3 ± 4·4 kg/m^2, 70% women, 72% HT, 61% MetS). HS diet (urinary sodium >150 mEq/day) was observed in 70% of subjects. We measured plasma hormones, lipid profile, urinary free cortisol (UFC) and cortisol tetrahydrometabolites (THM).

Results Urinary sodium was correlated with UFC (r = +0·45, P < 0·001), cortisol THM (r = +0·41, P < 0·001) and inversely with adiponectin, HDL and aldosterone, after adjusting by age, gender and BMI. Subjects with high, compared with adequate sodium intake (50–149 mEq/day) had higher UFC (P < 0·001), THM (P < 0·001), HOMA-IR (P = 0·04), HT (81% *vs* 50%, P < 0·001), MetS (69% *vs* 41%, P < 0·001) and lower adiponectin (P = 0·003). A multivariate predictive model adjusted by confounders showed a high discriminative capacity for MetS (ROC curve 0·878) using four clinical variables: HS intake [OR = 5·6 (CI 2·3–15·3)], HOMA-IR [OR 1·7 (1·3–2·2)] cortisol THM [OR 1·2 (1·1–1·4)] and adiponectin [OR = 0·9 (0·8–0·9)], the latter had a protective effect.

Conclusions High sodium diet was associated with increased urinary cortisol and its metabolites. Also, HS diet was associated with HT, insulin resistance, dyslipidaemia and hypoadiponectinaemia, even when adjusting by confounding variables. Further, we observed that high salt intake, IR and higher cortisol metabolites, alone or combined in a clinical simple model, accurately predicted MetS status, suggesting an additive mechanism in obesity-related metabolic disorders.

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Introduction

Central obesity, hypertension, derangement of glucose and lipid metabolism are hallmarks of the metabolic syndrome (MetS), which is highly prevalent worldwide.[1] The mechanisms leading to MetS are not fully understood, but several complementary hypotheses have been proposed including insulin resistance (IR), adipose tissue dysregulation, inadequate aldosterone suppression and increased cortisol production.[2,3]

Populations with liberal salt intake have higher incidences of HT and cardiovascular events, and its related health outcomes are associated with high medical costs.[4] Moreover, high sodium intake has been reported to be an important clinical factor implicated in salt sensitivity in MetS.[5] There is also a reported relationship between increased sodium intake and insulin resistance (IR) and type 2 diabetes mellitus (T2DM).[6] Numerous mechanisms have been postulated to explain why liberal sodium intake contributes to metabolic disorders, with special emphasis in inadequate aldosterone suppression and increased mineralocorticoid receptor (MR) activation by factors other than aldosterone.[7,8]

We and others have shown that obesity and MetS, when correctly excluding subclinical Cushing's syndrome, are associated with increased levels of urinary glucocorticoid (GC) metabolites, but normal plasma values[3,9,10] Moreover, GC metabolites levels are correlated with HT, IR and dyslipidaemia, resembling metabolic abnormalities observed with liberal salt intake.[3] Although the relationship between high sodium diet and GC production has been less studied than aldosterone, it has been described that high sodium diet increases local GC production in a rodent model and that salt loading increases urinary cortisol

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and sodium restriction decreases cortisol excretion in human studies.[11–13]

The aim of the present study was to evaluate a possible dysregulation of cortisol production secondary to liberal sodium intake that could have an essential role in MetS and obesity-related metabolic disorders.

Patients and methods

Participants were selected from a larger data set of our Research Group consisting of Hispanic individuals with and without hypertension (HTN) who were willing to participate in our protocol designed to gather information about adrenal steroids, HT and MetS. Individuals included in this study were adult subjects recruited from low- and middle-income primary care centres in Santiago, Chile. The study was approved by our Institutional Review Board for Human Studies, and all patients provided informed consent according to the guidelines of the Declaration of Helsinki.

A standardized survey was administered to all participants, including demographic data, information about comorbid conditions and medications. All free-living subjects maintained their regular dietary habits, including sodium intake before recruitment. The measurement of dietary sodium was estimated using 24-h urinary sodium excretion which is less likely to report biases compared with dietary surveys or abbreviated urine recollection because of diurnal variation of sodium excretion.[14] Most guidelines recommend a daily urinary sodium close to 100 mEq/day (that represents a daily salt intake of roughly 6 g) and consider a high salt diet if urinary sodium is >150 mEq/24 h (roughly 9 g of salt).[15] Moreover, new evidence suggests that the association between estimated sodium excretion and cardiovascular events could be J-shaped and that a sodium excretion of <50 mEq/24 h (3 g per day) is associated with increased risk of mortality and hospitalization.[16] For these reasons, participants were categorized as having a high sodium (HS > 150 mEq/24 h) or adequate sodium intake (AS 50–149 mEq/24 h) according to urinary sodium excretion.

Participants were categorized as having MetS if they met at least three of the following conditions according to the Joint Scientific Statement of the IDF, NHLBI, AHA, World Heart Federation, IAS and IASO[17]:

(a)Waist circumference $\geq$40 inches for males (102 cm), $\geq$35 inches in females (88 cm).

(b)HDL cholesterol $\leq$1·03 mM in males (40 mg/dl), $\leq$1·3 mM in females (50 mg/dl).

(c)Triglycerides $\geq$1·7 mM (150 mg/dl) or taking medication to reduce triglycerides.

(d)Systolic blood pressure (BP) $\geq$130 mmHg, diastolic BP $\geq$85 mmHg or taking antihypertensive medication (same criteria used for categorizing HTN status).

(e)Fasting glucose $\geq$5·6 mM (100 mg/dl) or taking medication for hyperglycaemia.

We excluded from our larger dataset all subjects with recent use of steroid medication, severe organ failure, alcohol abuse and mood disorders as these conditions could modify steroid production and metabolism.

We excluded for this particular study patients with suspected Cushing's syndrome or primary hyperaldosteronism by elevated urinary free cortisol (UFC) or high aldosterone/renin ratio (ARR > 25). We confirmed these cases by dexamethasone suppression test, midnight salivary cortisol or saline suppression test using the cut-off values suggested by the Endocrine Society guidelines.[18,19] We also excluded from this analysis women using estrogens (contraceptive or supplementation) due to the known effects on cortisol binding globulin.

All subjects visited our outpatient clinic after a 12-h fasting period, and blood samples were obtained at 09:00 am. Serum lipid profile and serum fasting glucose concentrations were measured using an automated Roche Hitachi Modular chemistry analyzer (Hitachi, Tokyo, Japan). Total serum adiponectin was analysed by radioimmunoassay (Millipore, Billerica, MA, US), and the intra-assay and interassay coefficients of variation were 6·5% and 8·9%, respectively. Serum leptin was measured by radioimmunoassay (Diasource, Nivelles, Belgium), and the intra-assay and interassay coefficients of variation were 4·6% and 6·2%, respectively. Fasting insulin was measured by radioimmunoassay (Siemens, Deerfield, IL, USA), and the intra-assay and interassay coefficients of variation were 5·7% and 6·7%, respectively. We evaluated insulin resistance (HOMA-IR) and pancreatic β-cell function (HOMA-β) by the Oxford University HOMA Calculator 2·2®.

Cortisol was measured by immunoassay using automated equipment (IMMULITE 2000, Siemens Healthcare Diagnostics Inc., Germany), and cortisone, aldosterone and renin activity was measured by RIA. According to our protocol, in subjects who were taking antihypertensive drugs that could affect the renin angiotensin system measurement (β-blockers, ACE inhibitors, ARB or MR antagonists), a washout for at least 21 days was performed. Subjects were placed on amlodipine or doxazosin for blood pressure control if values were higher than 140/90 mmHg. Aldosterone/renin ratio is expressed in conventional units.

We measured free cortisol levels (UFC) by immunoassay using automated equipment (IMMULITE 2000, Siemens, Germany). We previously showed that in a similar population, this immunoassay for cortisol has a reasonable correlation with HPLC-MS/MS, considered the gold standard, despite the fact that concentrations obtained by HPLC–MS/MS were lower than those obtained by immunoassay.[20] Cortisol tetrahydrometabolites (THM) were measured by gas chromatography–mass spectrometry (GC-MS) using a Hewlett-Packard 7890A gas chromatograph coupled with a Hewlett-Packard 5975C XL quadrupole mass selective detector (Agilent, Avondale, PA, USA). The sum of the following cortisol metabolite levels was recorded as total THM and expressed in conventional units: α-tetrahydrocortisol (α-THF), β-THF, tetrahydrocortisone (THE), cortol, β-cortol, cortolone and β-cortolone. To exclude incomplete collections, urinary creatinine was measured.

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Statistical analysis

A descriptive analysis was performed. Continuous variables are presented as mean ± SD and categorical variables as percentage of the total sample. Normality of the parameters was assessed using normality (Q–Q) plot and the Kolmogorov–Smirnov test. Correlations between normally continuous variables were evaluated using Pearson's test. Participants categorized by sodium intake criteria were analysed by Student's *t*-test and chi-square tests. In case a variable was not normally distributed, a resampling with replacement procedure was applied to further test the robustness of our estimates. 1000 iterations were deemed necessary to confirm the internal validation of the analysis. A floating sample size was the option selected to accommodate small amounts of random missing data, avoiding missing imputation.

To extensively analyse our results, we performed several different statistical procedures as follows: First, ANCOVA analysis comparing high and adequate sodium intake groups and adjusting for confounding variables such as age, gender and BMI was performed. For continuous variables, a linear regression model with explanatory variables adjusted by age, gender and BMI was performed, and results are presented as partial correlation coefficients. Further analysis to check for interactions, normality of residuals and nonlinearity effect modification were performed. Then, a logistic regression model was performed. Crude and adjusted odds ratios for the association of MetS with variables of interest are reported. Postestimation diagnostics were assessed, and goodness of fit determined by the Hosmer–Lemeshow test. A sensitivity analysis for urinary sodium as a categorical variable was carried out with a higher cut-off (200 mEq/day) that has also been proposed as high sodium intake.[13] Finally, a predictive model was developed using a backward stepwise approach in a multivariate logistic regression model. Bonferroni corrections were applied to avoid possible multitesting false-positive results. Discriminative capacity using C-statistic, sensitivity, specificity and total proportion of correctly predicted cases were reported. Differences were considered statistically significant at $P < 0{\cdot}05$ of two sides. All analyses were performed using SPSS 15·0 and STATA 11 statistical packages.

Results

Characteristics of participants

A total of 370 adults were included in our analysis. Our cohort characteristics are the following: age was 50·1 ± 10·4 years (range from 18 to 85 years), BMI was 29·3 ± 4·4 kg/m^2, 70% were female, 72% had HTN, and 61% had three or more criteria of MetS. With respect to sodium intake, 24-h urinary sodium ranges from 51 to 585 mEq/day, with a mean of 195 ± 80·7 mEq/day. High sodium diet, defined by urinary sodium >150 mEq/day, was detected in 255 (70%) of recruited subjects and adequate sodium intake (defined as urinary sodium 51–149 mEq/day) in 115 (30%) of the study participants.

Anthropometric and biochemical characteristics of all participants

When analysing all subjects ($n = 370$), we observed a positive correlation between urinary sodium and UFC ($r = +0{\cdot}45$, $P < 0{\cdot}001$), cortisol THM ($r = +0{\cdot}42$, $P < 0{\cdot}001$) (Fig. 1), glycaemia ($r = +0{\cdot}12$, $P = 0{\cdot}04$) and anthropometric variables such as weight ($r = +0{\cdot}29$, $P < 0{\cdot}001$) and BMI ($r = +0{\cdot}12$, $P = 0{\cdot}02$). An inverse correlation between urinary sodium and adiponectin

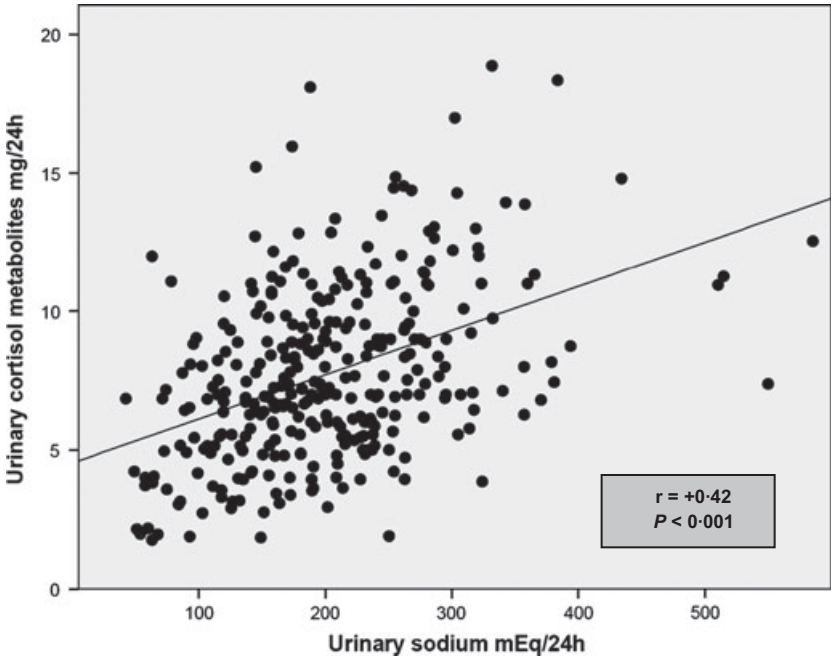

Fig. 1 Pearson's correlation between urinary sodium and urinary cortisol metabolites.

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($r = -0{\cdot}17$, $P = 0{\cdot}004$) and HDL cholesterol ($r = -0{\cdot}15$, $P = 0{\cdot}007$) was observed, as well as the expected inverse correlation regarding urinary sodium with aldosterone ($r = -0{\cdot}16$, $P = 0{\cdot}002$) and PRA ($r = -0{\cdot}13$, $P = 0{\cdot}01$). Age, LDL, triglycerides, high sensitive CRP, plasma cortisol, plasma cortisone and leptin had no significant correlation with sodium intake (data not shown). The determined association of urinary sodium with UFC and THM remain significantly correlated when adjusted by urinary creatinine.

In a linear regression model with cortisol THM as the response variable, urinary sodium remained significantly associated with THM values even when adjusting by age, gender and BMI. (partial correlation coefficient = +0·32, $P < 0{\cdot}001$). Similarly, when analysing UFC, urinary sodium as the explanatory variable remained significant associated when adjusted by covariates (partial correlation coefficient = +0·41, $P < 0{\cdot}001$). On the contrary, adiponectin levels lost statistical significance with urinary sodium when adjusted (partial correlation coefficient = −0·11, $P = 0{\cdot}12$) (Table 1). Further, in a second model with adiponectin as a response variable, we observed that adjusted urinary cortisol THM, but not urinary sodium was inversely associated to adiponectin levels (partial correlation coefficient = −0·61, $P = 0{\cdot}03$) with no significant interaction between urinary sodium and cortisol THM.

Table 1. Unadjusted and adjusted correlations between sodium intake and biochemical parameters

Parameter	Urinary sodium (mEq/24 h)	Urinary sodium adjusted by age, gender and BMI
Urinary free cortisol (nmol/24 h)	$r^* = +0{\cdot}45$, $P < 0{\cdot}001$	$r^\dagger = +0{\cdot}41$, $P < 0{\cdot}001$
Cortisol metabolites (umol/24 h)	$r^* = +0{\cdot}42$, $P < 0{\cdot}001$	$r^\dagger = +0{\cdot}32$, $P < 0{\cdot}001$
Adiponectin (ug/ml)	$r^* = -0{\cdot}18$, $P = 0{\cdot}004$	$r^\dagger = -0{\cdot}11, P = 0{\cdot}12$

*Pearson's coefficient.
†Partial correlation coefficient after adjusting by covariates.

Clinical and biochemical characteristics categorized by sodium intake

High sodium intake group, compared to adequate sodium intake group, had no statistical differences in age, and BMI, but had a higher percentage of subjects with HT, MetS and male gender as described in Table 2. As expected, subjects with high salt intake had lower aldosterone levels ($P = 0{\cdot}01$) and a trend to lower PRA levels ($P = 0{\cdot}09$). Further, subjects on a high sodium intake had significantly higher UFC levels, cortisol THM, triglycerides, insulin and HOMA-IR (all $P < 0{\cdot}01$). High sodium intake group showed lower adiponectin levels, HOMA -β and HDL cholesterol (all $P < 0{\cdot}01$). We observed no differences in other biochemical parameters including LDL and total cholesterol, plasma cortisol, plasma cortisone or leptin (Table 2). We also compared urinary αTHF/ βTHF and (αTHF + βTHF/ THE) ratios, which showed no differences by sodium intake.

The ANCOVA analysis adjusted by age, gender and BMI showed that HS intake had higher UFC ($P < 0{\cdot}001$), cortisol THM levels ($P < 0{\cdot}001$), increased levels of HOMA-IR ($P = 0{\cdot}01$) and triglycerides ($P = 0{\cdot}01$) when compared to adequate sodium intake. Also, the HS intake group remains significantly associated with lower adiponectin levels ($P = 0{\cdot}01$) and HDL ($P < 0{\cdot}05$).

As the results related to IR, triglycerides, HDL or adiponectin could be related to secondary changes in UFC or cortisol THM by sodium intake, we performed linear regression models with these three variables (urinary sodium > 150 mEq, UFC and

Table 2. Characteristics and biochemical parameters of recruited subjects categorized by sodium intake

$n = 370$	High salt intake (> 150 mEq/24 h) (70%)	Adequate salt intake (51–149 mEq/24 h) (30%)	*P* value
Age (years)	49·7 ± 10·2	50·6 ± 11·2	NS
Female (%)	63	88	**<0·001**
Body Mass Index (kg/m2)	29·4 ± 4·2	29·0 ± 4·6	NS
Hypertension (%)	81	50	**<0·001**
HDL cholesterol (mM)	1·22 ± 0·44	1·38 ± 0·39	**0·01**
Triglycerides (mM)	1·75 ± 0·91	1·43 ± 0·77	**0·005**
Metabolic syndrome (%)	69	41	**<0·001**
HOMA-IR*	3·6 ± 2·4	2·7 ± 1·9	**0·004**
Plasma aldosterone (pM)	170·1 ± 80·1	210·9 ± 140·2	**0·01**†
Plasma renin activity (ng/ml*h)	1·2 ± 1·1	1·7 ± 1·6	NS†
Plasma cortisol (nM)	303·6 ± 115·9	317·4 ± 115·8	NS
Urinary free cortisol (nmol/24 h)	132·2 ± 52·1	85·0 ± 38·1	**<0·001**
Cortisol metabolites (mg/24 h)	8·4 ± 3·2	6·1 ± 2·7	**<0·001**
Leptin (ng/ml)	15·6 ± 11·2	18·0 ± 11·1	NS†
Adiponectin (ug/ml)	11·0 ± 5·4	15·6 ± 5·2	**0·007**

Bold values denote statistical significance.
NS, not significant.
*HOMA-IR: homoeostasis model assessment of insulin resistance index.
†*P* value obtained by 1000 iteration bootstrapped *t*-test.

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THM) adjusted by age, gender and BMI. We observed that HS intake (>150 mEq/day), but not UFC or THM, remained statistically associated with HOMA-IR (partial correlation coefficient = +0·24, $P = 0·003$) and triglycerides (partial correlation coefficient = +0·22, $P = 0·007$). Regarding HDL, the model showed that HS diet (partial correlation coefficient = −0·16, $P = 0·04$) and cortisol THM levels remained inversely associated (partial correlation coefficient = −0·37, $P < 0·001$). We again observed that changes in adiponectin remained inversely related to cortisol THM (partial correlation coefficient = −0·24, $P = 0·005$) but not HS intake or UFC.

Association between hypertension and sodium intake

An association between HS intake and HT was confirmed by logistic regression analysis [OR = 4·79 (95% CI: 2·9–7·9)]. Moreover, adjusted logistic model by age, gender and BMI remained highly significant assessing HT status in relation to HS intake [OR = 5·0 (95% CI: 2·9–8·6)].

Association between metabolic syndrome and sodium intake

A linear regression model showed that increase urinary sodium (as a continuous variable) was associated with increasing number of variables of MetS (p for the trend <0·001). The same result was observed when adjusted by age, gender and BMI.

When analysing HS intake categorized by urinary sodium >150 mEq/day, the unadjusted analysis showed that was highly associated with MetS [OR = 3·26 (95% CI: 1·91–5·55)]. Cortisol THM and UFC were associated with MetS and adiponectin had a protective effect in unadjusted analysis (Table 3). HS intake and MetS remained highly significant in a logistic regression model adjusted the confounding variables age, gender and BMI [OR = 3·98 (95% CI: 2·15–7·36)]. The adjusted model also showed a significant odds ratio for cortisol THM and UFC in relation to MetS as well as a protective effect of adiponectin (Table 3). Also, the reported OR for MetS (crude or adjusted) where similar if you categorized HS intake defined by urinary sodium > 200 mEq/day (data not shown).

Further, a multivariate predictive model for MetS was performed including age, gender and BMI as covariates. The discriminative capacity showed a C-statistic of 0·88, with a sensitivity of 92%, specificity of 67% and correctly classifying 93% of true cases of MetS in our cohort. The combination of variables that more accurately predicted MetS were the following: sodium intake >150 mEq/24 h (fivefold increased odd), HOMA-IR (twofold increased odd), cortisol THM (increased odd) and adiponectin (decreased odd), as described in Table 4.

Table 3. Crude and adjusted odds ratios for metabolic syndrome

	Metabolic Syndrome	
Parameters	Crude OR (95% CI)	Adjusted OR by age, gender and BMI (95% CI)
Salt intake >150 mEq/24 h	3·26 (1·92–5·56)	3·98 (2·15–7·37)
Cortisol metabolites	1·24 (1·11–1·39)	1·28 (1·12–1·46)
Urinary free cortisol	1·01 (1·00–1·03)	1·02 (1·01–1·04)
Adiponectin	0·91 (0·88–0·96)	0·88 (0·83–0·93)

Table 4. Variables that maintained simultaneous significance in a multivariate predictive model for metabolic syndrome adjusted by age, gender and body mass index

	Metabolic Syndrome	
Parameters	Odds ratio	95% CI
Salt intake >150 mEq/24 h	5·58	(2·30–15·25)
HOMA-IR	1·66	(1·24–2·16)
Cortisol metabolites	1·22	(1·03–1·45)
Adiponectin	0·92	(0·84–0·99)

Discussion

We report that HS intake is associated with increased urine excretion of cortisol metabolites and UFC, suggesting an increase in overall daily production. Also, increased salt intake was associated with HT, IR, dyslipidaemia and hypoadiponectinaemia, even after adjusting for confounding variables. Further, we showed by logistic regression models that high sodium intake, IR and higher levels of cortisol metabolites are highly associated with MetS, alone or in a combined predictive model.

In the present study, we show that HS intake is associated with increased urinary cortisol metabolites, considered a valid estimation of GC production.[9,10] When analysing all recruited subjects, salt intake explained roughly 20% of cortisol THM variability, being a better predictor of changes in cortisol metabolites levels than other known factors that modify its production such as age, male gender, BMI or waist circumference. Also, HS intake was associated with higher UFC. A similar finding was reported previously by Chamarti *et al.*, showing that a liberal salt diet compared to a low sodium diet increased UFC, roughly by fifty per cent in the hypertensive subjects and sixty per cent in normotensive subjects.[13] Conversely, low sodium intake decrease urinary cortisol suggesting that salt intake can indirectly modulate adrenal cortisol secretion, although the mechanisms remain to be elucidated.[12] In addition, Usukura et al demonstrated in a rodent model that long-term liberal sodium diet increases adipose tissue GC production by 11β-HSD1 enzyme (which converts cortisone to cortisol), suggesting an increase in local GC production by HS diet.[11] It is well known that obese subjects have increased cortisol production, mainly by adrenal secretion secondary to hypothalamic-pituitary-axis dysregulation but also to a lesser extent by an increase in local cortisol activation.[21] Moreover, a recent study corroborated the importance of cortisol in obesity-related metabolic disorders by showing that long-term weight loss was followed by reduced GC production

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and also downregulation of 11β-HSD1[22]The urinary cortisol metabolites represent a more accurate reflection of overall daily GC production because subtle or transitory increases in cortisol secretion can be counterbalanced by the increased activity and/or overexpression of liver reductases that metabolize cortisol.[3,9,10,23] Therefore it should be expected that, if sodium intake increases adrenal cortisol secretion and/or local conversion of cortisol by 11β-HSD1, cortisol dysregulation should be detected more accurately by cortisol tetrahydrometabolites rather than UFC or plasma cortisol, as observed in the present study. However, our methodology cannot elucidate whether the observed changes indicate greater tissue exposure to cortisol or simply increased overall production of cortisol subsequently metabolized. Because we and others have shown that cortisol metabolites are associated with several metabolic disorders resembling Cushing's syndrome it is unlikely from a clinical perspective that increase production of cortisol is only a secondary compensation for an increase in GC metabolism, but this valid question remained to be confirmed.[3,9,10,22,23]

We also observed in our cohort that high sodium intake was associated with HT, a higher HOMA-IR and hypertriglyceridaemia. Several studies also have shown an association between IR and salt loading.[24] In addition, we observed that HS intake is associated with lower HDL and adiponectin levels. We and others have previously shown that higher levels of cortisol production are related with lower HDL and adiponectin levels,[3,25] supported in our study by regression models showing that higher cortisol metabolites levels, driven by HS intake, are associated with HDL and adiponectin modifications.

We must highlight that previous reports on the effect of salt intake on IR and triglycerides had contradictory findings.[26] The mechanisms involved in these discrepant results have not been elucidated but changes in metabolic parameters seem to be dependent on the quantity of dietary sodium restriction.[27] Most of the unfavourable effects relating IR and low sodium diet are mainly on a short-term highly restricted salt intake (<20 mEq/day) resulting in a sevenfold increase in aldosterone levels.[28] In our study we compared chronic HS intake (>150 mEq/day) with adequate salt intake (50–149 mEq/day) observing only a mild increase in aldosterone levels. Moreover, it has been described that other factors could play a role in activation of the MR on a HS diet even if aldosterone levels are appropriately suppressed. Recent reports postulate that Rac1 or LSD1 can crosstalk or modulate MR activation in a liberal salt diet leading to HT, IR and metabolic disorders.[29,30] Consistently, low sodium intake resembles an MR antagonist effect and decreases the expression of MR.[31,32] Although our methodology cannot address the downstream mechanisms of the protective effects of restricted sodium intake, a decreased MR activation in the adequate salt intake group could explain, at least in part, the observed metabolic benefits. Future studies need to address if MR and/or GR could mediate the metabolic disorders associated with increased GC production in the context of liberal sodium intake observed in this study because in tissues lacking the protective effect of 11β-HSD2, that inactivate GC to cortisone, cortisol may act as the predominant ligand.

In relation to MetS, we observed by logistic regression that a HS diet increased the estimated odds of having MetS roughly by threefold, in concordance with another similar observational study.[33] Moreover, the estimated probability of developing MetS was also independently associated with cortisol THM excretion, increasing roughly 30% for every unit of THM. In addition, IR increased the risk while adiponectin had a protective effect regarding MetS, which has been widely described in other populations as well.[34,35] As MetS is a multifactorial disorder, we developed a predictive model that could accurately predict MetS status by the simultaneous combination of four simple clinical parameters not included in MetS criteria: high sodium intake (fivefold increased in odds of having MetS), HOMA-IR (twofold increased odds), cortisol THM (20% increased odds) and adiponectin (10% decreased odds). These additive effects are observed even when adjusting for classic risk factors for MetS such as male gender or BMI, suggesting that inadequate secretion of cortisol and insulin secondary to a high sodium diet may contribute to the metabolic abnormalities clustered in the MetS.

Our study has limitations. As an observational study we can only show associations and we cannot demonstrate causality nor rule out that having MetS could increase your sodium intake. Another limitation for interpreting our results is that UFC was not measured by the gold standard methodology (HPLC/MS-MS). The observed correlation between UFC and sodium intake must be confirmed in future studies as we assessed UFC by an immunoassay that can be inaccurate and overestimate true UFC by measuring cortisol metabolites. We could not perform an intervention in dietary sodium, so we adjust our analysis by well established confounders and performed multivariate regressions to address bias. Also, we measured 24-h urinary sodium on one occasion while subjects maintained their regular dietary habit. Our predictive model, although internally valid, may lack generalizability to other populations; thus, these results should be validated in prospective studies and other ethnicities. Also, future studies are warranted to explore if other dietary factors different than high sodium may explain at least part of the effects observed in this study.

In conclusion, we observed that high sodium intake is associated with increased urinary cortisol metabolites, IR, dyslipidaemia and lower adiponectin levels. Our results suggest that a subtle increase in the overall GC production may partially explain the metabolic disturbances observed with a liberal salt diet in addition to the well-documented risk of HTN. Further, we show that MetS is highly associated with increased sodium intake, IR and higher levels of cortisol metabolites, either alone or combined in a simple clinical predictive model, suggesting an additive mechanism in the pathophysiology of obesity-related metabolic disorders.

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Disclosure statement

The authors have nothing to declare.

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