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Tissue sodium content in patients with type 2 diabetes mellitus

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ABSTRACT

Background: Tissue sodium content by ^{23}Na magnetic resonance imaging (MRI) has been found to be increased in arterial hypertension. We analyzed whether tissue sodium content is increased in patients with type-2 diabetes (T2DM).
Methods: Patients with T2DM were compared to those with primary hypertension. Patients with T2DM were off any antidiabetic and hypertensive patients off any antihypertensive therapy for at least 4 weeks. Skin and muscle sodium content was assessed non-invasively with a 3.0 T clinical MRI system (Magnetom Verio, Siemens Health Care, Erlangen, Germany) in each patient.
Results: In patients with T2DM ($N = 59$) we observed significantly greater muscle sodium content (diabetes: 20.6 ± 3.5 vs hypertension: 16.3 ± 2.5 mmol/l, $p < 0.001$) and skin sodium content (diabetes: 24.5 ± 7.2 vs hypertension: 20.6 ± 5.7 mmol/l, $p = 0.01$) than in those with primary hypertension ($N = 33$). When potential confounders (age, body mass index, gender, systolic and diastolic blood pressure, estimated glomerular filtration rate) were entered in a covariance analysis, both skin sodium content ($p = 0.037$) and muscle sodium content ($p < 0.001$) were still clearly elevated.
Conclusion: Patients with T2DM have greater skin and muscle sodium content. These are the first known data to demonstrate increased tissue sodium content in patients with T2DM, measured by ^{23}Na magnetic resonance imaging. Since tissue sodium content is related to organ damage, therapeutic intervention should aim at reducing tissue sodium content.

1. Introduction

Sodium retention plays a predominant pathogenic role in a variety of cardiovascular and metabolic diseases. Severe structural and functional cardiovascular and renal changes produced by sodium loading independent of blood pressure (BP) have been demonstrated experimentally and clinically.[1,2] The well-controlled epidemiological study (i.e. the Trials of Hypertension Prevention [TOHP] study) revealed that greater sodium intake is significantly associated with higher incidence of cardiovascular end points.[3] Even though several studies support a negative impact of sodium on cardiovascular outcomes and organ damages, suggestion of dietary sodium reduction is controversial.[4]

Patients with type 2- diabetes mellitus (T2DM) are characterized by increased sodium retention.[5] Increased sodium retention in T2DM differentiates diabetic from non-diabetic hypertensive subjects and the underlying mechanisms have been extensively examined.[5] Hyperinsulinemia caused by insulin resistance in T2DM has an antinatriuretic effect by activating the sympathetic nervous system,[6,7] which augments angiotensin II–mediated aldosterone production,[8] and directly promotes renal tubular sodium reabsorption.[9] Vasopressin causes volume expansion[10] and induces expression of sodium transporters in the renal tubular system that leads to sodium retention.[11] Increased sodium retention causes volume-dependent arterial hypertension, which has been described almost 50 years ago.[12]

So far, assessment of salt intake has been performed by measuring 24-hour urinary sodium excretion. However, it has been shown that urinary sodium excretion fluctuates from day to day, even in a controlled environment and standardized diet.[13] New evidence has found that sodium is bound non–osmotically to proteoglycans inside muscles and

Abbreviations: BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; ^{23}Na-MRI, ^{23}Na magnetic resonance imaging; SD, standard deviation; T2DM, type-2 diabetes mellitus; SGLT-2, sodium-glucose inhibitor type 2.

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skin, which is considered to reflect sodium storage.[14] In the last years we and others have developed a tool to measure the quantity of tissue sodium content by magnetic resonance imaging (^{23}Na-MRI).[15–17] The validity of this method has been evaluated in experimental and human studies[16,17] and we have analyzed tissue sodium content in patients with arterial hypertension and renal failure.[18,19] Of note, left ventricular mass known to predict cardiovascular morbidity and mortality has been related with tissue sodium content irrespective of other confounders including 24-hour ambulatory BP.[19]

In a previous study we found that tissue sodium content is elevated in patients with uncontrolled hypertension compared to normotensive control subjects.[18] In face of the evidence that mechanisms and magnitude of sodium retention are different between patients with T2DM[5] and patients with arterial hypertension,[20] we now compared tissue sodium content between these groups. Our hypothesis was that tissue sodium content is higher in patients with T2DM compared to hypertensive patients without T2DM.

2. Methods

2.1. Study design

The study population comprised patients who participated in two observational clinical trials during October 2013 and February 2015. These studies were performed at the Clinical Research Center, Department of Nephrology and Hypertension, University Hospital Erlangen, Germany. Both therapeutic clinical studies were registered at http://www.clinicaltrials.gov (NCT02383238, NCT01870739). These studies were approved by the Ethics Committee of the University Erlangen and performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice guidelines. All patients provided written informed consent prior to inclusion in the studies and fulfilled all inclusion/exclusion criteria. Patients were recruited from the University outpatient clinic, through physician referrals, and through the use of newspaper advertisements. Fifty-nine patients with T2DM (36 out of them diagnosed with hypertension) were compared to 33 patients with primary arterial hypertension. In all subjects measurements of tissue sodium content were performed successfully by ^{23}Na-MRI. The assessment of 24-hour urinary sodium excretion was not done in parallel.

Since antidiabetic and antihypertensive therapy could influence tissue sodium content, a washout period took place (4 weeks washout of anti-diabetic medication for patients with T2DM; 4 weeks washout of antihypertensive medication for hypertensive patients without diabetes) before sodium content in the skin and muscle were measured by ^{23}Na-MRI.

2.2. Study population

Patients with T2DM (defined by fasting plasma glucose [FPG] ≥ 126 mg/dl or HbA1c ≥ 6.5% or on blood glucose lowering medication) (www.clinicaltrials.gov: NCT02383238) were compared to patients with uncomplicated hypertension stage 1 (defined by 140–159 mmHg systolic and/or 90–99 mmHg diastolic BP) and stage 2 (defined by 160–179 mmHg systolic and/or 100–109 mmHg diastolic BP), with a mean sitting office systolic BP ≥140 mmHg and <180 mmHg or treated arterial hypertension (www.clinicaltrials.gov: NCT01870739).

Patients with T2DM were excluded if they had any other form of diabetes mellitus, were treated with insulin or more than one oral antidiabetic agent, had a HbA1c level >10% (86 mmol/mol), had a FPG >240 mg/dl or renal impairment (defined by eGFR<60 ml/min/1.73 m^2). Hypertensive subjects were excluded if they had malignant or severe hypertension (stage 3, defined by ≥180 mmHg systolic and/or ≥110diastolic BP), evidence of secondary hypertension or severe renal impairment (eGFR <30 ml/min/1.73m^2). Patients with any other severe disease or organ dysfunction were excluded in both studies. All subjects had to have no contraindication to perform MRI.

2.3. ^{23}Na-MRI Measurements

3.0T clinical MRI system was used to assess tissue sodium content (Magnetom Verio, Siemens Health Care, Erlangen, Germany). ^{23}Na-MRI measurement was performed with a gradient echo sequence (total acquisition time: 13.7 min, echo time: 2.07 ms, repetition time: 100 ms, flip angle: 90°, 128 averages, resolution: 3 × 3 × 30 mm^3) and a mono-resonant transmit/receive birdcage knee coil (32.6 MHz, Stark-Contrast, Erlangen, Germany). One lower leg was placed in the center of the ^{23}Na knee coil. Saline solutions with sodium concentrations (10, 20, 30, and 40 mmol/l) were used to calibrate relative tissue sodium (Fig. 1). This method has been validated and described previously in detail.[17–19]

2.4. Statistics

Data are presented as means and percentages with standard deviation (SD). Statistical significance of differences between the two groups was determined using unpaired *t*-test. The covariance analysis was performed using univariate linear analysis. Statistical analysis was performed using IBM SPSS Statistics 21.0.0.2, USA. All default parameters were used to generate box plots in SPSS.

3. Results

3.1. Study population

The clinical characteristics of the study population consisted of 59 patients with T2DM and 33 patients with primary hypertension (Table 1). Mean age, mean body weight and gender distribution of the two groups were not different. Mean duration of diabetes was 7 years, with a range of 1 to 296 months. Mean HbA1c of patients with T2DM was 6.7%, with a range of 5.4% to 8.7%. Thirty-six patients with T2DM received on average 1.2 antihypertensive medications. Antihypertensive therapy consisted of angiotensin-converting enzyme inhibitors (N = 12), angiotensin receptor blockers (N = 15), β blockers (N = 12), calcium channel antagonists (N = 16), aldosterone antagonists (N = 2) and diuretics (N = 15). Systolic and diastolic office BP were lower in patients with T2DM than in patients with hypertension, eGFR was greater in the patients with T2DM, but always higher than 60 ml/min per 1.73 m^2 in both groups.

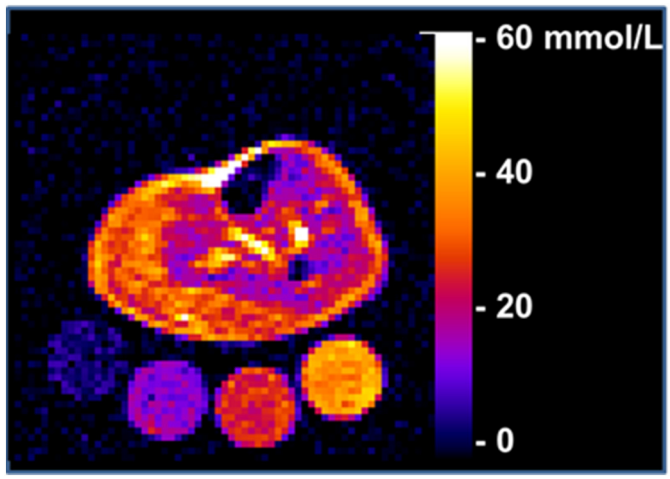

Fig. 1. ^{23}Na magnetic resonance imaging (^{23}Na-MRI) of lower leg showing magnitude of sodium signal intensity. Tubes with solutions containing 10, 20, 30, and 40 mmol/l of NaCl are arranged below the extremity (left to right), thereby allowing us to calibrate tissue sodium.

Table 1
Clinical characteristics of patients.

Parameter	Hypertensive group (N = 33)	Diabetic group (N = 59)	p-Value
	Mean ± SD	Mean ± SD	
Age, years	59.6 ± 10.9	60.3 ± 7.6	0.72
Gender, % male	59	61	0.92
Body weight, kg	85.9 ± 15.3	87.4 ± 13.3	0.62
BMI, kg/m^2	28.4 ± 4.0	29.7 ± 4.4	0.14
office SBP, mmHg	155.5 ± 8.3	130.4 ± 13.6	<0.001
office DBP, mmHg	92.8 ± 8.0	79.1 ± 9.4	<0.001
24-h SBP, mmHg	–	129.2 ± 11.9	–
24-h DBP, mmHg	–	77.3 ± 9.0	–
Serum sodium, mmol/l	140.7 ± 2.3	138.6 ± 2.0	<0.001
Serum potassium, mmol/l	4.5 ± 0,4	4.1 ± 0.4	<0.001
Serum creatinine, mg/dl	0.91 ± 0.2	0.83 ± 0.2	0.03
eGFR, ml/min per 1.73m^2	83.8 ± 14.2	89.9 ± 12.3	0.03
HbA1c, %	–	6.7 ± 0.7	–
LDL, mg/dl	135 ± 29.9	143 ± 32.2	0.22
HDL, mg/dl	60.5 ± 14.4	48.1 ± 10.6	<0.001
Total cholesterol, mg/dl	224.8 ± 33.7	206.9 ± 38.7	0.03
Hematocrit, %	44.4 ± 3.3	40.1 ± 2.7	<0.001
Number of antihypertensive drugs, N	0	1.2 ± 1.2	–

Data are given as mean ± SD, BMI-body mass index, SBP-systolic blood pressure, DBP- diastolic blood pressure, eGFR- estimated glomerular filtration rate, LDL-low density lipids, HDL-high density lipids.

3.2. Tissue sodium content

In patients with T2DM we observed greater muscle sodium content (diabetes: 20.6 ± 3.5 vs hypertension: 16.3 ± 2.5 mmol/l, p < 0.001) and skin sodium content (diabetes: 24.5 ± 7.2 vs hypertension: 20.6 ± 5.7 mmol/l, p = 0.01) than in those with primary hypertension (Fig. 2). When potential confounders like age, body mass index, gender, systolic and diastolic BP and eGFR were entered in the covariance analysis, both muscle sodium content (p < 0.001) and skin sodium content (p = 0.037) were still found to be significantly elevated in patients with T2DM.

3.3. Subgroup analysis

In the two groups we noticed higher skin sodium content in male than in female patients (diabetes: 26.7 ± 6.8 vs 21.1 ± 6.6 mmol/l, p = 0.003; hypertension: 22.9 ± 5.4 vs 17.1 ± 4.5 mmol/l, p = 0.003; Fig. 3A), whereas muscle sodium content was similar in male and female patients (Fig. 3B). In male patients with T2DM (N = 36) skin sodium content was greater (p = 0.037) than in male hypertensive patients (N = 20). Similar trend between the two groups was found for female subjects (p = 0.064) (Fig. 3A). In male and female patients with T2DM muscle sodium content was clearly elevated compared to hypertensive subjects (male: p < 0.001; female: p = 0.002; Fig. 3B).

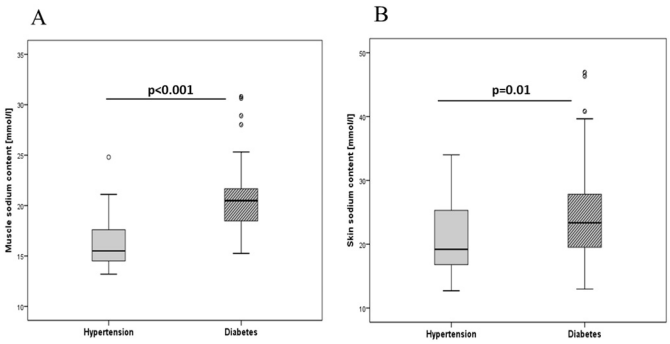

Fig. 2. Sodium content of the muscle (A) and skin (B) in patients with hypertension and patients with T2DM.

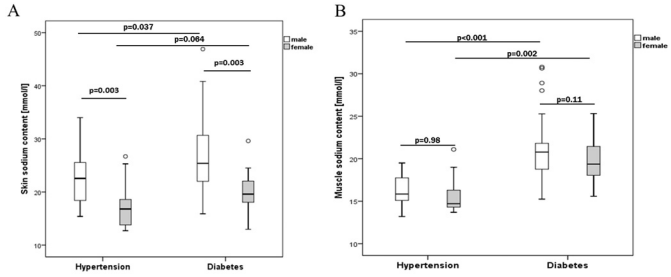

Fig. 3. A: Sodium content of the skin in the two groups, separated in male and female subjects. B: Sodium content of the muscle in the two groups, separated in male and female subjects.

Fifteen patients with T2DM were taking a thiazide diuretic as part of their antihypertensive treatment. The analysis of these patients showed higher skin sodium content compared to those not taking diuretics (27.7 ± 8.0 vs 23.4 ± 6.7 mmol/l, p = 0.044). No difference in patients with diuretics was observed with respect to muscle sodium content.

Finally, we analyzed whether skin and muscle sodium content were related to HbA1c, diabetes duration, age and 24-hour ambulatory BP in patients with T2DM. No correlations were found between tissue sodium content and HbA1c (muscle: r = −0.163, p = 0.216, Fig. 4B; skin: r = −0.147, p = 0.266) and diabetes duration (muscle: r = 0.134, p = 0.313, Fig. 4A; skin: r = 0.002, p = 0.991). A correlation was found between skin sodium content and age (r = 0.285, p = 0.029), and between muscle sodium content and 24-hour ambulatory diastolic (but not systolic) BP (r = 0.292, p = 0.025, Fig. 4C). The correlation between muscle sodium content and 24-hour ambulatory diastolic BP remained significant after partial adjustment for age (r = 0.304, p = 0.020). No correlation existed between skin sodium content and 24-hour ambulatory systolic and diastolic BP.

4. Discussion

The principle finding of our current analysis is that both muscle and skin sodium content are increased in patients with T2DM compared to patients with primary hypertension. We have chosen patients with arterial hypertension as a control group, since we wanted to dissect the effect of diabetes disease from the one of arterial hypertension on tissue sodium content. In our previous studies we found that hypertension is

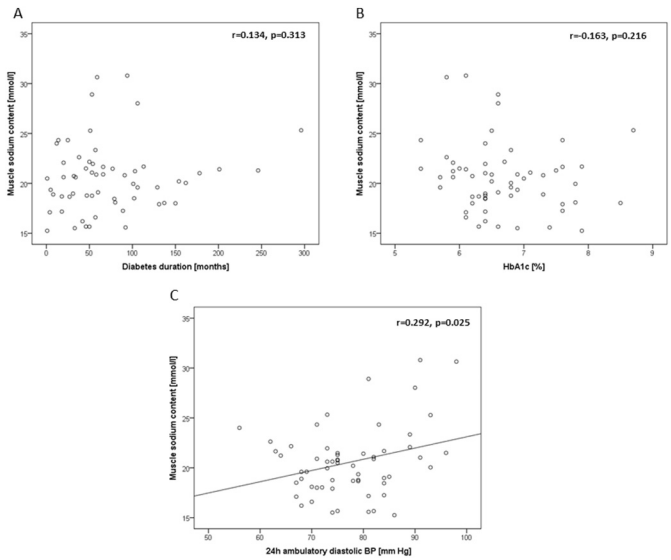

Fig. 4. Correlation between muscle sodium content and diabetes duration (4A) and HbA1c (4B) and 24 h ambulatory diastolic BP (4C) in patients with T2DM.

associated with increased tissue sodium content, and in light of the fact that T2DM often coexists with hypertension, patients with hypertension but without diabetes appeared to be the ideal control group. Our data are the first known data to demonstrate increased tissue sodium content in patients with T2DM, measured by 23Na MRI. This observation is in line with our previous findings in normotensive, non-diabetic subjects (lower tissue sodium content) and hypertensive non-diabetic patients (similar level of tissue sodium content to our hypertensive group of this study).[18] This finding is also in accordance with previous studies that assessed sodium-retention by analyzing the exchangeable total body sodium content.[5,21] Exchangeable sodium content was found to be increased in diabetic patients, in contrast to non-diabetic hypertensive subjects.[21]

In comparison to patients with CKD, skin sodium content in our patients with T2DM was similarly increased.[19] Of note, in patients with CKD high tissue sodium content was related to higher prevalence of T2DM.[19] Similarly, in a recent study higher tissue sodium deposition in hemodialysis patients with T2DM was observed compared to hemodialysis patients without T2DM.[22] In contrast, in acute kidney failure and acute heart failure tissue sodium content was clearly increased compared to our two patient groups that were in clinically stable conditions.[23,24]

Renal function of our patients may have influenced the results. Any potential influence of eGFR, found to be higher in patients with T2DM than in hypertensive patients were taken into account by using covariance analyses. Apart from that, Schneider et al. found a trend that with decreasing eGFR tissue sodium content is increased.[19]

According to previous results age and gender impact tissue sodium content.[17,18] Previously we reported a striking increase of tissue sodium content with aging in normotensive and hypertensive subjects.[18] We found a similar association between age and skin sodium content in our examined patients with T2DM. With respect of gender, we found higher skin sodium content in male than in female subjects in the both (diabetic and hypertensive) groups, whereas muscle sodium content was not significantly different between males and female subjects. A similar gender-specific difference has been observed in normotensive and hypertensive patients and in patients with CKD.[18,19]

Treatment in patients with diuretics may be a potential confounder of our results. One might expect that patients on diuretics have lower tissue sodium content. In contrast to this assumption we found higher tissue sodium content in our patients with T2DM taking diuretics. We believe that diuretic therapy has been given to those patients with advanced stage of diabetic disease, and thereby serves as an indicator of severity of disease.[23,24]

The question arises if the measurements of tissue sodium content by ^{23}Na-MRI are biased by concomitant changes of volume status of the patients. Our patients were in clinical stable condition without any sign of volume expansion (no signs of pitting edema, pulmonary edema, or recent weight changes). However, one limitation is that our method does not allow distinguishing interstitial sodium content from intracellular sodium content. Another limitation of our study is that 24-hour urinary sodium excretion, which is considered to be the gold standard of assessing dietary salt intake, was not measured in parallel. Previous studies indicate that there is a high fluctuation in urinary sodium excretion from day to day, even under strictly standardized diet in a controlled environment, such as the MARS experiment.[13] These data also showed that a single 24-hour urinary sodium excretion measurement does not provide a very reliable estimate of dietary salt intake, and that several daily measurements are required to reflect the “true” daily salt intake. We preferred to use mmol/l instead of arbitrary units to present our measurements of tissue sodium content. The limitation of that approach is that “true” tissue sodium content may be underestimated. Furthermore, our data are only valid for T2DM in the early stage of the disease (mean duration 7 years) and cannot be extrapolated to advanced stages of T2DM or type-1 diabetes.

In conclusion, T2DM known to be a sodium retention state[5] is characterized by increased skin and muscle sodium content irrespective of age, BP, eGFR and gender. Since tissue sodium content is related to organ damage,[19] therapeutic intervention should aim at reducing tissue sodium content. SGLT-2-inhibitors that excrete glucose and sodium in parallel emerged as an attractive option and are currently under investigation.

Ethics approval and consent to participate

Written informed consent was obtained from each patient before study inclusion. The study protocol of each trial was approved by the Local Ethics Committee (University of Erlangen-Nürnberg), and the studies were conducted in accordance with the Declaration of Helsinki and the principles of good clinical practice guidelines.

Consent for publication

All authors gave full consent for publication.

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No funding received.

Author contributions

DK analyzed data, contributed to discussion and wrote manuscript
MVK analyzed data, contributed to discussion, reviewed manuscript
AB analyzed data, contributed to discussion, reviewed manuscript
CO contributed to discussion, reviewed/edited manuscript
PL contributed to discussion
AMN contributed to discussion
MU contributed to discussion
RES designed the study, analyzed data, contributed to discussion and reviewed/edited manuscript

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