DR. RENATA LIBIANTO (Orcid ID : 0000-0002-2015-6550)

Author Manuscript

Article type : Letter to Editor

Relationship between Urinary Sodium-to-Potassium Ratio and Ambulatory Blood Pressure in Patients with Diabetes Mellitus

Authors: Renata LIBIANTO[1], John MORAN[2], Christopher O'CALLAGHAN[3], Sara BAQAR[4], Angela X CHEN[5], Scott T BAKER[4], Michelle CLARKE[4], Richard J MACISAAC[1,6], George JERUMS[1,4], Elif I EKINCI[1,4,7]

Affiliations:

[1]Department of Medicine, The University of Melbourne, Melbourne, VIC, Australia

[2] Intensive Care Unit, Queen Elizabeth Hospital, Adelaide, SA, Australia

[3] Department of Clinical Pharmacology, Austin Health, Melbourne, VIC, Australia

[4] Department of Endocrinology, Austin Health, Melbourne, VIC, Australia

[5] Department of Endocrinology, Flinders Medical Centre, Adelaide, SA, Australia

[6] Department of Endocrinology and Diabetes, St Vincent's Hospital Melbourne, Melbourne, VIC, Australia

[7] Menzies School of Health Research, Darwin, NT, Australia

Short title: Ambulatory BP with uNa/K in diabetes

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1440-1681.12852

This article is protected by copyright. All rights reserved

Corresponding author:
Dr Elif I Ekinci
Department of Endocrinology, Heidelberg Repatriation Hospital
300 Waterdale Rd, Heidelberg West, Victoria, Australia 3081
Phone: 61404488958
Email: elif.ekinci@unimelb.edu.au

Author Manuscript

This article is protected by copyright. All rights reserved

Abstract

Previous studies investigating the relationship between sodium intake and blood pressure have mostly relied on dietary recall and clinic blood pressure measurement. In this cross-sectional study, we aimed to investigate the relationship between 24h urinary sodium and potassium excretion, and their ratio, with 24h ambulatory blood pressure parameters including nocturnal blood pressure dipping in patients with type 1 and 2 diabetes. We report that in 116 patients with diabetes, systolic blood pressure was significantly predicted by the time of day, age, the interaction between dipping status with time, and 24h urinary sodium-to-potassium ratio (R^2=0.83) with a relative contribution of 53%, 21%, 20% and 6%, respectively. However, there was no interaction between urinary sodium-to-potassium ratio and dipping status.

Key words: ambulatory blood pressure; diabetes; potassium; sodium; urinary electrolytes

Hypertension is an important contributing factor to cardiovascular disease [1] and is highly prevalent in people with diabetes mellitus. The Prospective Urban Rural Epidemiology (PURE) [2] and the International Study of Salt and Blood Pressure (INTERSALT) [3] studies reported the association of higher clinic blood pressure (BP) with high urinary sodium excretion (uNa) and low urinary potassium excretion (uK) based on morning spot collection and 24-hour urine collection, respectively. Both studies also reported a relationship between a high urinary sodium-to-potassium (uNa/K) ratio with high BP. Where a relationship was found, uNa/K ratio offered a stronger prediction of BP compared to either uNa or uK alone. However, this relationship has not been studied specifically in people with diabetes or where BP has been assessed by 24h ambulatory monitoring, which is a better predictor of cardiovascular events than clinic BP measurements [4].

In normal healthy subjects, mean systolic and diastolic BP levels decrease (“dip”) during night time sleep, and lack of nocturnal BP dipping has been shown to be an independent predictor of mortality in people with diabetes [5, 6]. The association between uNa, uK, or their ratio with BP dipping status has not been documented in diabetes.

This article is protected by copyright. All rights reserved

Author Manuscript

This cross-sectional study therefore aimed to examine (i) the role of 24 hour uNa/K ratio as a predictor of ambulatory systolic BP in people with type 1 and type 2 diabetes, and (ii) the association between uNa/K ratio with nocturnal dipping profile.

Participants (n=116) were recruited from Austin Health diabetes clinics. They completed 24 hour urine collections and a 24h ambulatory BP monitoring within 12 months either side of collection of clinical and laboratory data. The measurement was conducted with a portable recording system (Spacelabs90207) based on an oscillometric method. Day (between 7am to 10pm) and night (between 10pm and 7am) BP were recorded and night-to-day mean systolic BP ratio of >0.9 was used to classify patients as "non-dippers", while the rest were "dippers".

A linear mixed model analysis was performed with systolic BP as the dependent variable [7]. Between patient variability was modeled as a random effect and the following as fixed effects: age, nocturnal dipping status, time of day of BP measurement (as a 24 hour clock), uNa/K ratio, and interaction between time and dipping status. Time was incorporated into the mixed model as a random slope (unstructured covariance matrix) for each subject. Dominance analysis [8] was used to estimate the importance of each predictor in the mixed model. Colinearity between predictors, especially in the context of fractional polynomials and their interactions, was checked using variance inflation factor (VIF) and condition number (CN); where mean VIF <10 and CN <30 were desirable [9].

Model selection was guided by information criteria (Akaike and Bayesian information criteria [10]). Non-linear covariate effect was explored via multivariate fractional polynomials (FP) using a closed-test algorithm. The final covariate form was determined by the plausible clinical effect of the FP, that is subject to knowledge, and overall model fit [11]. A global Wald test was used to test the significance (or otherwise) of sets of parameters; for example, main effect and interaction(s). Stata™ version 14 (2015) was used to perform the statistical analyses.

Author Manuscript

This article is protected by copyright. All rights reserved

Baseline characteristics of the participants are demonstrated in Table 1a. In the mixed model, the time of day of BP measurement (expressed as a 24 hour clock), age, nocturnal dipping status and its interaction with time, and uNa/K ratio were independent predictors of systolic BP (Table 1b). In a multivariate model, dipping status as a categorical variable was not demonstrated to be a significant covariate. However, on an hourly basis, we demonstrated an interaction between dipping status with time, such that between the hours of 23:00 and 08:00 there was a difference on systolic blood pressure of up to 20mmHg between dippers and non-dippers as modeled by a non-linear function. The Wald test for joint significance of dipping status, time (as a fractional polynomial) and their interaction was highly significant, p=0.0001. The model was well specified with normality of random effects and no marked residual heteroscedasticity; the R^2 was 0.83. Multi-colinearity between predictors was not evident (VIF=9.25, CN=13.7).

Using dominance analysis to determine the contribution of each independent variable in predicting systolic BP, 53% of the variability in systolic BP was explained by time of day, 21% by age, 20% by dipping status and the interaction between dipping status with time, and 6% by the urinary sodium-to-potassium ratio. 24h uNa and uK did not individually predict 24h systolic BP. Furthermore, in the multivariate model, no other variables such as diabetes type, use of antihypertensives, use of diuretics or body mass index were significant predictors of systolic BP. There was also no significant interaction between dipping status and uNa/K ratio (modeled as a fractional polynomial).

The mean observed and model-predicted systolic BP over 24 hours for the whole cohort are illustrated in Figure 1a as a “radar” plot. There was approximately a 10mmHg drop in observed systolic BP between midnight and 4am, consistent with the ~10% nocturnal BP reduction expected in dippers who made up the majority of the study population. Between 8am and 11am, the observed BP reading was higher than the predicted BP, reflecting morning BP surge.

Figure 1b illustrates the predicted BP across 24 hours in dippers and non-dippers based on our model. We predicted systolic blood pressure to remain relatively constant in non-dippers,

This article is protected by copyright. All rights reserved

Author Manuscript

while the dippers were predicted to have significant drop in blood pressure at night, up to 20mmHg lower than during the day. This is consistent with current knowledge regarding nocturnal BP dipping, and gave further support to our model's ability in predicting BP based on uNa/K and other covariates.

In comparison to most previous studies which explored the influence of sodium and potassium intake on BP in the general population, the current cross-sectional study comprised a cohort with multiple comorbidities with the majority taking antihypertensive medications. In this cohort, 24h uNa/K ratio contributed 6% of the variation in ambulatory BP. The relatively small contribution may be a reflection of the fact that it is difficult to detect the effects of dietary sodium and potassium intake on BP in the context of different medication use and long standing diabetes with other comorbidities which may have greater influence on BP than their sodium or potassium intake per se. These are the characteristics of patients frequently encountered in specialist diabetes clinics, and therefore the findings from the current study are clinically relevant to this group of patients.

In the current study, 24h uNa and uK individually did not predict ambulatory BP. Furthermore, there was no association demonstrated between nocturnal dipping status with 24h uNa, uK, or uNa/K ratio. A possible factor was the increased sample size requirement for establishment of interactions [12].

Our study also demonstrated the large impact that time of day has on BP readings. Time of day accounted for 53% of the BP prediction in our model – a contribution that is larger than that given by either age or urinary electrolytes. Relying simply on clinic BP readings may result in bias, and we believe that wherever possible, future large outcome studies should take timing of BP reading into consideration. Recording the time of day that study participants take their antihypertensive may also provide further insight into the determinants of ambulatory BP and the dipping pattern.

This article is protected by copyright. All rights reserved

Author Manuscript

Strengths of the current study include the use of 24h ambulatory BP measurement which reflected actual BP better than clinic measurements [13], and 24h urinary collection which provided a more accurate estimate of sodium and potassium intake compared with dietary recall [14]. A previous study demonstrated that despite the administration of a diuretic, there was no change in urinary sodium excretion after 2 weeks [15]. Therefore, even though 47% of our patients were taking diuretics, 24h uNa is still likely to reflect their dietary sodium intake. At the time this study was conducted, SGLT2-inhibitors were not yet available in Australia and therefore none of the participants were taking this medication.

Because we only had data from a single 24h urine collection, we could not account for within person variability in urinary electrolyte excretion across different days. Despite this, we have previously shown that a single 24h urine collection is a useful predictor of sodium intake [15], with intra-individual coefficient of variation of 21%. Another limitation is the fact that we only had one ambulatory BP recording. However, a previous study has shown that the intra-subject variability in nocturnal dipping status is relatively low in patients with diabetes, compared to non-diabetic patients [16].

In conclusion, 24h uNa/K ratio played a small role in predicting 24h ambulatory BP in patients seen in tertiary referral diabetes clinic. Furthermore, there was no association between uNa/K ratio with nocturnal dipping profile.

Conflicting interests

The Authors declare that there is no conflict of interest

Funding

Dr Ekinci was supported by an NHMRC Early Career Fellowship, a Viertel Clinical Investigatorship, RACP Fellowship and Sir Edward Weary Dunlop Medical Research Foundation research grant.

This article is protected by copyright. All rights reserved

Author Manuscript

Acknowledgements

We would like to thank the Departments of Clinical Pharmacology and Pathology at the Austin Hospital for their help in collecting data.

References

1. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ; Comparative Risk Assessment Collaborating Group., *Selected major risk factors and global and regional burden of disease.* Lancet. 2002 Nov 2;360(9343):1347-60.
2. Mente A, O'Donnell MJ, Rangarajan S, McQueen MJ, Poirier P, Wielgosz A, Morrison H, Li W, Wang X, Di C, Mony P, Devanath A, Rosengren A, Oguz A, Zatonska K, Yusufali AH, Lopez-Jaramillo P, Avezum A, Ismail N, Lanas F, Puoane T, Diaz R, Kelishadi R, Iqbal R, Yusuf R, Chifamba J, Khatib R, Teo K, Yusuf S; PURE Investigators., *Association of Urinary Sodium and Potassium Excretion with Blood Pressure.* N Engl J Med. 2014 Aug 14;371(7):601-11.
3. *Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group.* BMJ. 1988 Jul 30;297(6644):319-28.
4. Eguchi K, Pickering TG, Hoshide S, Ishikawa J, Ishikawa S, Schwartz JE, Shimada K, Kario K., *Ambulatory blood pressure is a better marker than clinic blood pressure in predicting cardiovascular events in patients with/without type 2 diabetes.* Am J Hypertens. 2008 Apr;21(4):443-50. .
5. Astrup AS, Nielsen FS, Rossing P, Ali S, Kastrup J, Smidt UM, Parving HH., *Predictors of mortality in patients with type 2 diabetes with or without diabetic nephropathy: a follow-up study.* J Hypertens. 2007 Dec;25(12):2479-85.
6. Sturrock ND, George E, Pound N, Stevenson J, Peck GM, Sowter H., *Non-dipping circadian blood pressure and renal impairment are associated with increased mortality in diabetes mellitus.* Diabet Med. 2000 May;17(5):360-4.
7. Rabe-Hesketh S, Skrondal A, *Multilevel and Longitudinal Modeling using Stata.* . 3rd edn ed. Vol. Volume 1: Continuous Responses. 2012, College Station, TX: Stata Press.

This article is protected by copyright. All rights reserved

Author Manuscript

8. Luchman JN. *DOMIN: Stata module to conduct dominance analysis.* [cited 2014 23 March]; Available from: http://econpapers.repec.org/scripts/search/search.asp?ft=domin.2014.
9. Belsley DA, *Conditioning diagnostics, collinearity and weak data in regression.* 1991: New York: John Wiley & Sons.
10. Kuha J, *AIC and BIC: Comparisons of Assumptions and Performance.* Sociological Methods Research 33 (2):188-229, 2004.
11. Royston P, Sauerbrei W *Multivariable modelling with cubic regression splines: A principled approach.* Stata Journal 7 (1):45-70, 2008.
12. Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey SG, *Subgroup analyses in randomised controlled trials: Quantifying the risks of false-positives and false-negatives.* Health Technology Assessment. 2001, 5(33):1-56.
13. Head GA, McGrath BP, Mihailidou AS, Nelson MR, Schlaich MP, Stowasser M, Mangoni AA, Cowley D, Brown MA, Ruta LA, Wilson A., *Ambulatory blood pressure monitoring in Australia: 2011 consensus position statement.* J Hypertens. 2012 Feb;30(2):253-66.
14. Leiba A, Vald A, Peleg E, Shamiss A, Grossman E, *Does dietary recall adequately assess sodium, potassium, and calcium intake in hypertensive patients?* Nutrition 2005;21:462–466.
15. Ekinci EI, Thomas G, MacIsaac RJ, Johnson C, Houlihan C, Panagiotopoulos S, Premaratne E, Hao H, Finch S, O'Callaghan C, Jerums G., *Salt supplementation blunts the blood pressure response to telmisartan with or without hydrochlorothiazide in hypertensive patients with type 2 diabetes.* . Diabetologia. 2010 Jul;53(7):1295-303.
16. Cuspidi C, Meani S, Lonati L, Fusi V, Valerio C, Sala C, Magnaghi G, Maisaidi M, Zanchetti A., *Short-term reproducibility of a non-dipping pattern in type 2 diabetic hypertensive patients.* J Hypertens. 2006 Apr;24(4):647-53.

Author Manuscript

FIGURE LEGENDS

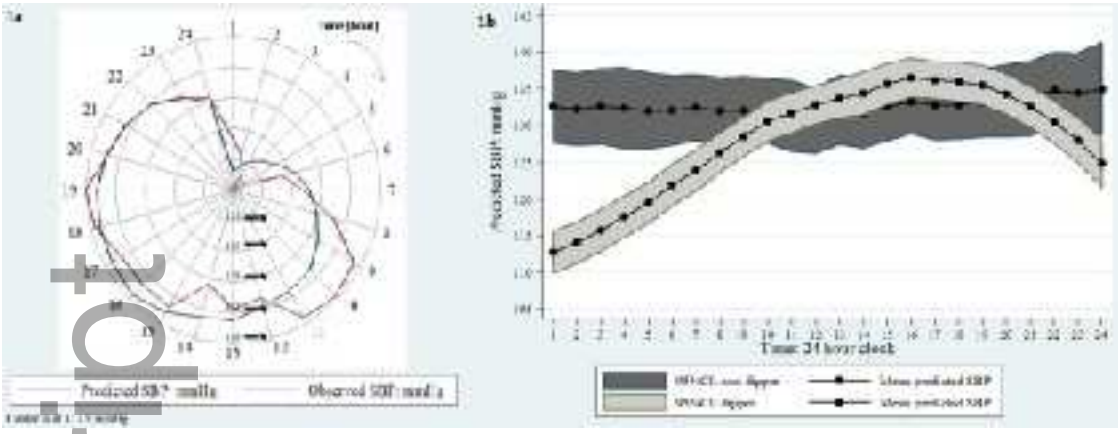
Figure 1a): Radar plot illustrating the model-predicted systolic blood pressure (SBP) compared to the observed SBP, over 24hours. Figure 1b): Predicted systolic blood

This article is protected by copyright. All rights reserved

pressure in dippers and non-dippers on an hourly basis: there was an interaction between dipping status with time, such that between the hours of 23:00 and 08:00 there was a significant difference on systolic blood pressure of up to 20mmHg between dippers and non-dippers as modeled by a non-linear function.

Author Manuscript

This article is protected by copyright. All rights reserved



cep_12852_f1a-b.tif

Author Manuscript

This article is protected by copyright. All rights reserved