Nephrol Dial Transplant (2020) 35: 2013–2014
doi: 10.1093/ndt/gfaa147
Advance Access publication 6 August 2020

ndt
Nephrology Dialysis Transplantation

Low-solute intake in chronic asymptomatic hyponatraemia related to syndrome of inappropriate secretion of ADH (SIADH): think about food beyond water intake!

Guy Decaux [1], Wim Musch[1], Fabrice Gankam Kengne[1], Bruno Couturier, [1]Alain Soupart and [1] Frédéric Vandergheynst[1]

[1]Research Unit on Hydromineral Metabolism, Erasme University Hospital, Brussels, Belgium

Correspondence to: Guy Decaux; E-mail: guy.decaux@skynet.be

Urine solute excretion affects water excretion. During antidiuresis, low-solute intake (and excretion) increases the risk of hyponatraemia while high-solute intake increases diuresis and thus lowers the risk of water retention [1–3]. In experimental models of the syndrome of inappropriate anti-diuretic hormone secretion (SIADH), food intake is lower in rats with severe hyponatraemia (±106 mEq/L) than in rats with less severe hyponatraemia (±116 mEq/L) [4]. We hypothesize that in many patients with chronic asymptomatic SIADH low-solute intake contributes to hyponatraemia.

We analysed all patients observed in our department over a period of 15 years with a diagnosis of chronic asymptomatic SIADH who had provided 24-h urine collections while under a normal diet. We included only patients with stable hyponatraemia (≥120 to ≤132 mEq/L) of >1 week duration, not due to cancer or infection, who were asymptomatic and following their usual diet. Patients with polydipsia (>3 L/day), urine osmolality < plasma osmolality, or urine sodium concentration <30 mmol/L were excluded. Control values were obtained from outpatients with normal SNa of similar age (within 5 years) and sex who were following their usual diet. Only patients with normal renal function without diabetes taking no medication affecting solute excretion and with urine sodium >30 mmol/L were selected. This retrospective study was approved by the Ethics Committee of our hospitals (Ref. P2020/062).

Eighty-one patients were included; causes of SIADH were medications (carbamazepine, selective serotonin reuptake inhibitors, antipsychotic, etc.) ($n = 42$), prior cerebral vascular accident ($n = 8$), chronic pulmonary disease ($n = 6$) and idiopathic ($n = 25$). As shown in Figure 1, urine solute excretion was significantly lower in hyponatraemic subjects than in age-matched controls. The lowest values were observed in elderly women with a mean SNa of 123 ± 1.5 mEq/L presenting a mean solute output value of 441 ± 67 mmol/24 h compared with controls with 698 ± 176 mmol/24 h ($P < 0.01$). Twenty per cent of the patients with mild hyponatraemia (SNa 129 ± 1.5 mEq/L) have a solute output ≤400 mmol/24 h, which was observed in only 3% of the controls ($P < 0.01$), and 35% a value ≤500 mmol/24 h, which was observed in 12.5% of the controls ($P < 0.006$).

We also analysed data obtained during a 5-day hospitalization in a controlled trial using satavaptan to treat asymptomatic hyponatraemia in patients with SIADH [5]: 12 patients were treated with 25 mg/day increasing mean SNa from 125 ± 1.6 mEq/L to 136 ± 1.3 mEq/L on Day 5 ($P < 0.01$); 12 patients were treated with 50 mg/day ($n = 12$), increasing SNa from 127 ± 1.3 mEq/L to 140 ± 1.7 mEq/L ($P < 0.01$). Pooling the data for both experiments, solute output prior to treatment of hyponatraemia was 629 ± 49 mmol/24 h and increased to 755 ± 62 mmol/24 h on Day 5 ($P < 0.02$).

These findings suggest that many patients with chronic asymptomatic hyponatraemia have a daily lower solute excretion (reflecting decreased dietary intake) than normonatraemic patients of similar sex and age. Lower daily solute excretion could contribute to the development of hyponatraemia in patients with a dilution defect like SIADH. For example, if a patient with fixed urine osmolality of 400 mOsm/kg H_2O, on a diet providing 800 mmol of solute daily (half electrolytes and NH_4 and half urea derived from dietary protein) drank 2 L/day she would be able to match fluid intake with urine output; however, if daily solute intake was decreased to 600 mmol/day, urine output would fall to 1.5 L/day (600/400 = 1.5) and 500 mL water would be retained daily, decreasing serum sodium concentration by 2–3 mEq/L/day. Hyponatraemia is particularly frequent in elderly women [6]. In the elderly, antidiuretic hormone levels increase [7] and solute intake decreases, a combination that may contribute to the increased prevalence of hyponatraemia due to idiopathic SIADH.

Patients with a low-solute intake (≤400–500 mmol/24 h) and a low diuresis (≤1 L/day) will not respond well to water restriction and will be better treated by increasing solute intake with oral urea [8–10]. Loss of appetite for any reason will

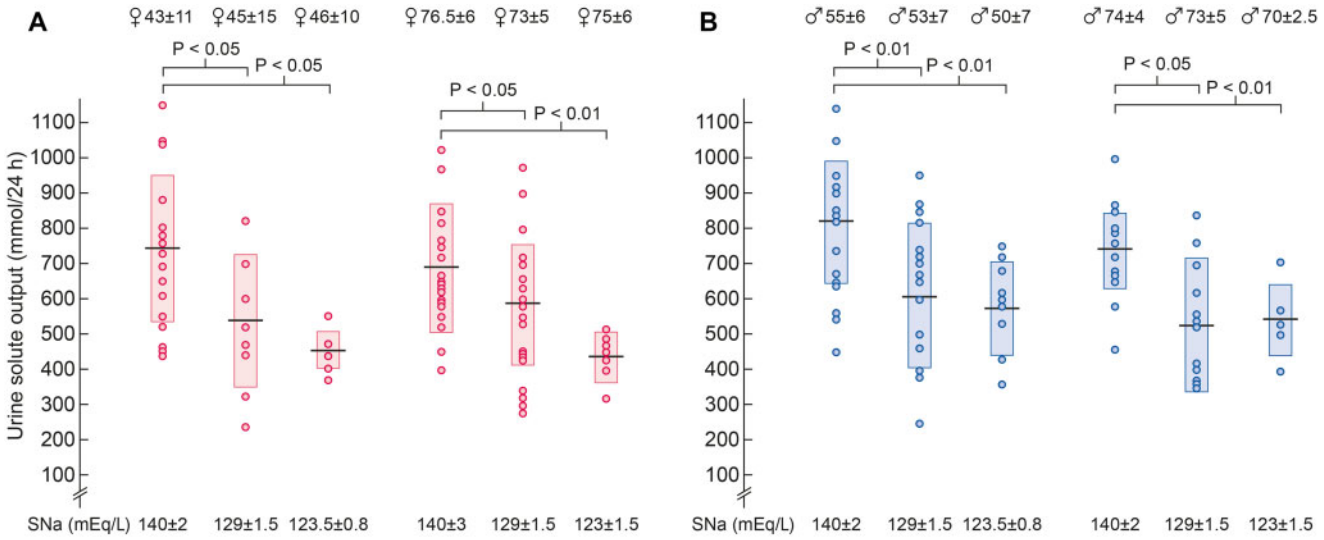

FIGURE 1: Lower urine solute output in patients with chronic asymptomatic hyponatraemia related to SIADH compared with controls of similar age and sex (mean ± standard deviation). The comparison between the groups was performed with a Student's *t*-test.

increase susceptibility to hyponatraemia if there is a urinary diluting defect. Our data suggest that hyponatraemia by itself (particularly SNa ≤125 mEq/L) contributes to loss of appetite and that normalization of SNa will improve urine solute (and water) excretion.

Our findings are limited by methodological problems and should be considered preliminary for several reasons. The selection of patients with SIADH and their normal controls was subject to bias, and we cannot exclude the possibility that conditions underlying SIADH (depression, dementia and frailty) rather than hyponatraemia were responsible for decreased solute excretion. We also could not assure the accuracy of urine collections. Data on patients treated with a vasopressin antagonist are more convincing, because patients served as their own controls. However, these data are also inconclusive because completeness of urine collections was not assured with measurements of urine creatinine excretion. A prospective study should be done to validate our hypothesis that treatment of hyponatraemia improves appetite and increases urine solute excretion, making it easier to maintain a normal serum sodium concentration on a tolerable fluid intake.

AUTHORS' CONTRIBUTIONS

G.D. collected the data, performed the analysis and wrote the article. M.W., F.G.K., B.C. and A.S. collected the data. F.V. collected the data and reviewed the article.

CONFLICT OF INTEREST STATEMENT

None declared. The data presented in this article have not been published previously.

(See related article by Sterns. Managing electrolyte disorders: order a basic urine metabolic panel. *Nephrol Dial Transplant* 2020; 35: 1827–1830)

REFERENCES

1. Berl T. Impact of solute intake on urine flow and water restriction. *J Am Soc Nephrol* 2008; 19: 1076–1078
2. Decaux G, Musch W. Estimated daily urine volume and solute excretion from spot urine samples to guide therapy of hyponatremia in SIADH. *J Clin Med* 2019; 8: 1511
3. Decaux G. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *Semin Nephrol* 2009; 29: 239–256
4. Verbalis JG, Drutarosky MD. Adaptation to chronic hyponatremia in rats. *Kidney Int* 1988; 34: 351–360
5. Soupart A, Gross P, Legros JJ *et al.* Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with satavaptan (SR121463B) an orally active nonpeptide vasopressin V2 receptor or antagonist. *Clin J Am Soc Nephrol* 2006; 1: 1154–1160
6. Upadhyay A, Jaber BL, Madias NE. Epidemiology of hyponatremia. *Semin Nephrol* 2009; 29: 227–238
7. Cowen LE, Hodak SP, Verbalis JG. Age-associated abnormalities of water homeostasis. *Endocrinol Metab Clin North Am* 2013; 42: 349–370
8. Decaux G, Gankam Kengne F, Couturier B *et al.* Mild water restriction with or without urea for the longterm treatment of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Can urine osmolality help the choice? *Eur J Intern Med* 2018; 48: 89–93
9. Rondon-Berrios H, Tandukar S, Mor MK *et al.* Urea for the treatment of hyponatremia. *Clin J Am Soc Nephrol* 2018; 13: 1627–1632
10. Nervo A, D'Angelo V, Rosso D *et al.* Urea in cancer patients with chronic SIAD-induced hyponatremia: old drug, new evidence. *Clin Endocrinol* 2019; 90: 842–848

Received: 25.2.2020; Editorial decision: 27.4.2020