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Abstract

Background: Our aim was to explore biological variation of serum sodium levels as a method of quantifying health risk in older adults. We investigated whether dynamic changes in serum sodium levels could provide additional prognostic information to standard predictors of mortality in older people.

Design: Analysis of routinely collected clinical datasets containing information on demographics, hospitalisation, biochemistry, haematology, and physical function for Dundee in-patient rehabilitation services, between 1999 and 2011.

Participants: Older people admitted to inpatient rehabilitation following an acute medical or surgical hospitalisation. Five dynamic measures of sodium levels homeostasis - minimum, maximum, standard deviation, and minimum and maximum deviation from mean - were derived for each individual, using biochemistry data from the year preceding their rehabilitation discharge. Cox regression models tested for associations with time to death. Covariates included age, sex, discharge Barthel score, co-morbid diagnoses, haemoglobin, albumin and eGFR.

Results 3021 patients were included (mean age 84 years, 1776 (58.8%) females). 1651 (54.7%) patients experienced hyponatraemia, and 446 (14.8%) became hypernatraemic. Mean sodium was correlated with all mean, minimum and SD of sodium. Kaplan Meier survival curves showed that those without sodium perturbations had the best mortality outcomes, whilst those with both hyponatremia and hypernatremia had the worst. Multivariate cox regression showed that standard deviation and hypernatraemia were significant predictors of death in non-adjusted models, but not fully adjusted models.

Conclusions All dynamic measures of dysnatraemia were associated with increased mortality risk, but failed to add predictive value to established static measures after adjusting for covariates.

Keywords: Frail Elderly, Sodium, Mortality, Hypernatremia, Hyponatremia

Introduction

Serum sodium levels are subject to complex, multisystem controls, including the cerebral, gastroenterological, renal and cardiovascular systems. As such they may provide a useful integrative measure of whole-body homeostatic control. In current clinical practice, the concept of frailty (operationalised via static measures of function and deficit) is recognized as a key determinant of adverse outcomes for older people[1, 2, 3]. However, functional decline is inherent in the diagnosis of frailty, and we can only establish this state of physical weakness following the clinical history and examination of an affected patient. We propose that dynamic (i.e serial) biomarker measurements – such as fluctuations in an individual's sodium levels – may model physiological responses to stressors in real-time and biological variation for an individual[4], offering the opportunity for risk stratification at an earlier stage, prior to physical detereroration setting in.

Whilst frailty is undoubtedly a useful concept in caring for older people, it is not a well-defined entity. In fact, the two most established models of frailty – the frailty index (a model of deficit accumulation) [2], and the phenotype model (using specific functional criteria to define a syndrome) [3] – rarely identify the same individuals as frail [5]. Our novel approach, using routinely collected biochemical data, aims to identify objective biomarkers of ageing. The advantages of this would be twofold, with both clinical and academic implications. Firstly we may be able to add additional prognostic value to traditional risk-prediction models, aid decision-making, and allow for earlier detection of declining function, before frailty has become established[4, 6]. Secondly, it may give insight into the biological processes that underpin

ageing. Both are of relevance given the shift in goals towards maintaining health and maximising quality of life in older individuals [4,7].

Serum sodium is frequently measured in older people, both to assess acute and chronic illness, as well as to monitor hydration and medication side-effects (e.g. diuretics and renin-angiotensin-aldosterone system inhibitors). Serial sodium levels are therefore readily available in routinely collected clinical datasets, and disorders of sodium balance are seen with increasing frequency in older patients [8]. Quantifying these imbalances and variation could offer insight into an individual's homeostatic capacity, and offer advantages over the routinely used, but sub-optimal, concept of "static" biomarker readings, referring to single measurements.

The aim of this analysis was therefore to examine whether dynamic measures of serum sodium levels, which vary with a predictable standard deviation around a "biological setpoint" for a given individual, could be used to predict poor health outcomes and all-cause mortality in older people.

Materials and Methods

Study Population and datasets

Our study was based on a population of patients over 65 years of age, who underwent in-patient rehabilitation in the Dundee Medicine for the Elderly service between 1999 and 2011, after surviving an acute hospital admission for a range of non-specific medical and surgical illnesses,

stroke and fractured neck of femurs [8, 9]. We included all patients who were alive at the time of discharge from rehabilitation, and who had both admission and discharge 20-point Barthel scores available [10]. The analysis used routinely collected, linked datasets on this cohort held by the Health Informatics Centre, University of Dundee. Use of this data was approved by the East of Scotland Research Ethics committee and the local Data Protection Officer. Routinely collected clinical datasets from the Dundee Medicine for the Elderly Rehabilitation service, Scottish Morbidity Record 01, laboratory results, community prescription dispensing data, death records from the Scottish register of deaths, and data from the Scottish Care Information – Diabetes Collaboration were combined (as previously described), anonymised, and held in a Safe Haven environment by the Health Informatics Centre, University of Dundee [11].

Dynamic Measures of Sodium Homeostasis

We examined all serum sodium levels taken during the year prior to a patient being discharged from rehabilitation services, and derived mean, minimum, maximum and the standard deviation (SD) values for each individual. Maximum sodium levels were taken as the highest sodium reading in the specified time period. Hypernatremia was defined as sodium>145mmol/L on any reading, and hyponatremia as sodium <135mmol/L. We derived the maximum deviation above and below the mean sodium level by comparing the mean sodium level across the whole year with the highest and lowest sodium levels in this period. Variability in sodium levels was measured on an individual basis by calculating the SD of all their sodium readings in the year-long period. With these measures we aim to model the individual setpoint, and the variation around this set point, for each patient.

Covariates

Baseline demographic data included age, gender, hospitalisation dates and length of rehabilitation stay. Death dates were obtained from death certificate records held by the Scottish General Records Office. Previous hospitalisation due to myocardial infarction, stroke, chronic heart failure or chronic obstructive pulmonary disease (COPD) was taken from Scottish Morbidity Record (SMR01) data on hospital discharges, using ICD-9 and ICD-10 codes. The presence of diabetes mellitus was taken from the SCI-DC record, containing details on all patients in Scotland diagnosed with Diabetes Mellitus (DM). Estimated glomerular filtration rate (eGFR) was based on the first serum creatinine value measured after admission to the rehabilitation unit, calculated using the Modificaiton of Diet in Renal Disease 4-variable (MDRD4) equation [12]. Albumin and haemoglobin levels were derived from linked, routinely collected laboratory data, once again based on the first measurement following rehabilitation admission. Community prescription data (held by Health Informatics Centre linked datasets) quantified medication use. 20 point Barthel score, a validated measure of basic activities of daily living, was routinely assessed on admission to, and discharge from, the rehabilitation unit [10].

Statistical Analyses

SPSS v22 (IBM, New York, USA) was used for all analyses. A 2-sided $p<0.05$ was taken as significant for all analyses. Descriptive statistics for population characteristics were calculated as frequencies and proportions, or as mean values with standard deviations. Correlations were performed to generate Pearson's correlation coefficients.

Linear regression was used to illustrate the relationship between our chosen measures of sodium and discharge Barthel score. For each dynamic measure of sodium homeostasis we ran separate models adjusting for different covariates – firstly age, sex and admission Barthel score; and secondly adding in previous myocardial infarction, previous stroke, previous hospitalisation for heart failure (CHF), previous hosptialisation for chronic obstructive pulmonary disease (COPD); previous cancer diagnosis; previous diabetes mellitus diagnosis; haemoglobin, serum albumin and eGFR by MDRD4 equation [12]. All models included the mean sodium level, with forced entry of all covariates.

Kaplan-Meier survival plots were constructed to show differences in survival between consistently normatraemic patients, and those that became hypernatraemic, hyponatraemic, or both. Cox regression models were constructed to test whether measures of sodium homeostasis were independently associated with time to all-cause death. Again, for each dynamic measure of sodium homeostasis we ran separate models adjusting for different covariates – firstly age and sex, then adding discharge Barthel score, and finally all other baseline covariates (previous admission with MI, stroke, CHF, COPD; previous cancer diagnosis; previous diabetes mellitus diagnosis; haemoglobin, serum albumin and eGFR by MDRD4 equation). All models included the mean sodium level, with forced entry of all covariates.

Results

A total of 3021 (of the original 4449) individuals survived to discharge from rehabilitation with complete data on all covariates, and this subset formed our analytic population. Descriptive

statistics are given in Table 1. Mean age was 84 years old, and 58.8% were female. 1651 (54.7%) patients had been hyponatraemic at some point, whilst 446 (14.8%) patients had been hypernatraemic at some point. 484 (16.0%) of our cohort had previously suffered an MI, 201 (6.7%) had suffered a stroke, 249 (8.2%) had CHF, 419 (13.9%) had COPD, 522 (17.3%) had diabetes mellitus and 371 (12.3%) had a previous diagnosis of cancer.

Mean serum sodium levels were moderately correlated with SD values ($r=-0.28$, $p<0.01$). Both mean sodium and SD were closely correlated with minimum ($r=0.77$, $p<0.01$; $r=-0.66$, $p<0.01$ respectively) and maximum sodium levels ($r=0.71$, $p<0.01$; $r=0.34$, $p<0.01$ respectively); sodium variability was weakly correlated with age ($r=-0.09$, $p<0.01$), and with Barthel scores on admission ($r=-0.10$, $p<0.01$) and discharge ($r=-0.05$, $p<0.01$). However, mean sodium was not consistently correlated with these variables, as shown in Table 2.

In multivariable linear regression analysis, higher mean sodium was weakly correlated with poorer discharge Barthel scores (B=-0.048, 95%CI -0.095 to -0.002; p=0.04); this association did not sustain statistical significance after adjustment for comorbidities (B=-0.041, 95%CI -0.088 to -0.006; p=0.08). Dynamic measures of sodium variability were not associated with discharge Barthel score in models also containing mean sodium level (Table 3).

Figure 1 shows survival differences between patients with and without sodium perturbations; those who remained normotraemic had lower mortality rates than all others (log rank test $p<0.001$), whilst individuals who experienced both hyponatremia and hypernatremia had the worst survival.

Table 4 shows the results of multivariate Cox regression analyses, using time to death as the dependent variable. SD of sodium (HR=1.03, 95% CI 1.00 to 1.07; p=0.03), hypernatremia (HR=1.21, 95% CI 1.07 to 1.38; p<0.01), and maximal perturbation from the mean (HR=1.02, 95% CI 1.01 to 1.04; p<0.01) were significantly associated with mortality in non-adjusted models. However, addition of comorbid disease and discharge Barthel score rendered these variables non-significant. Mean sodium level remained a significant predictor of time to death in the fully-adjusted models.

Discussion

We selected five dynamic measures of sodium variability (SD, hyponatremia, hypernatremia, and perturbation from the mean) to model the biological variation of a given individual. Our results show that all five variables are associated with all-cause mortality. These dynamic measures of sodium homeostasis did not, however, add significant predictive value to static measures of sodium homeostasis after adjustment for a range of other variables associated with mortality in older people.

Sodium levels deviating from the normal range are likely to signify inadequate compensation for an acute stressor due to a loss of resilience. However, in addition to an intrinsic loss of homeostatic reserve, increased illness severity may contribute to mortality risk. Dissecting out

the severity of a stressor from the magnitude of response to illness is difficult; in clinical practice, we typically quantify the severity of a stressor by measuring the body's response to the stressor.

Why did dynamic measures not add predictive value to routinely measured static (mean) levels, after taking comorbid disease and function into account? This may, in part, be due to the tight correlation of mean values dynamic measures of sodium homeostasis. In addition, there is a risk of statistical over-adjustment with the inclusion of discharge Barthel score. Hyponatraemia is known to affect both cognition and postural balance, with a consequential increase in falls, fractures and cognitive impairment. Thus, it is possible that dysnatraemias influence mortality via functional impairment. However, the benefit of including Barthel is that we can evaluate whether dynamic measures of sodium fluctuation are of additional prognostic value, over and above current measures of frailty and function.

The lack of independent association also highlights the difficulty in ascertaining a specific pathological mechanism for increased mortality. Sodium derangement reflects the amalgamation of numerous physiological insufficiencies (decreased thirst sensation, impaired urinary concentrating capacity, insensible water losses, reduced total body water and impaired ability to access water) [13, 14]. Thus it is important to account for baseline comorbidities and biochemistry (Table 1) when interpreting our results.

Extrinsic factors (including polypharmacy, hydration status and medical management) can further influence this. Suboptimal treatment may result in even greater sodium drops, which, in turn, is associated with worse health outcomes [15, 16, 17].

Other studies, covering a range of clinical presentations, have found similar associations between mortality and sodium dysregulation. A hospital based study by Gil et al. showed that hyponatraemic in-patients tended to be older than controls, have greater mortality rates and significantly longer lengths of hospital stay [15]. Cumming et al. [16] examined a group of elderly patients with fragility fractures, and showed that hyponatraemic patients spent a significantly longer time in hospital, and also had (non-significantly) higher mortality rates than normotraemic patients. Both this group [16] and Chua et al. [17] showed that hyponatraemia was associated with a loss of independence. Likewise, other studies have found associations between hypernatraemia and mortality, with rates ranging from 40% to >60% [18, 19].

This ambiguity regarding the precise reason for increased mortality should not detract from the potential utility of sodium levels in a model of biological resilience. The lack of diagnostic specificity may make sodium an even more valuable biomarker. Indeed, Sebastiani et al. [20] showed that the association between non-specific biomarker 'signatures' and measures of disability, morbidity and mortality could determine biological age with greater accuracy. Such markers likely reflect cumulative age-related changes and the saturation of homeostatic reserve. Moreover, using biomarkers may provide an objective element to aid the clinical diagnosis of frailty, and to monitor treatment effects and progression of frailty in an individual.

Strengths and Limitations

Our findings are strengthened by our large and detailed dataset. The cohort consisted entirely of older patients, making it ideal for identifiying novel risk stratification techniques in this population. The non-selective nature of admission diagnoses, reasons for rehabilitation, and evaluation of hypernatraemic, normonatraemic and hyponatraemic patients alongside each other, enhances the generalisability of our results.

Furthermore, at a time where laboratory investigations are increasingly available, and more frequently requested, economic implications should be considered. Our results have showed that individual biological variation in sodium levels does not add to information that can be gleaned from a single sodium reading. Though this suggests that multiple readings from an individual would not be cost effective with regards to risk prediction, we must remember that clinicians rarely request serum sodium levels for risk stratification purposes alone. Our results are unlikely to have a significant impact on expenses, as we investigated the possibility of gleaning new information from routinely collected samples.

However, there were also limitations to our study. There was a degree of selection bias as only rehabilitation in-patients were included; healthy individuals in the community and those who did not survive their initial hospital admission (likely representing the most, and least, resilient individuals), were excluded. Furthermore, a large number of patients were excluded as they did not survive to rehabilitation discharge or did not have Barthel scores calculated, once again excluding individuals who may have been less resilient. Moreover, our study was based on

sodium levels taken as part of standard clinical care, dictated by clinical need. Thus, more data may have been available for less well patients, and those at higher risk of dysnatraemias. Having said this, most patients remained well enough to survive their rehabilitation admission, perhaps countering this effect.

Our data collection and results did not account for treatments given to correct sodium levels. We therefore cannot accurately determine whether our sodium indices are truly representative of homeostasis, or whether they reflect external intervention. However, by focusing on the development of dysnatraemias (rather than their recovery), we reduce the bias that treatment could introduce. It is also possible that other dynamic measures of sodium may outperform our chosen ones. For example, finding the additive sum of values out with 'normal' may be a more sensitive marker for poor outcome.

Moreover, we looked only at serum samples, and not heparinized plasma samples. Whilst it has been demonstrated that there are statistically significant differences between sodium levels in these two samples types, the differences are not clinically important [22]. As such, we would suggest that our results are widely generalisable, and that the risk relationships observed would be applicable to sodium levels of either sample type.

Future work should investigate the physiological basis for trends seen. We have yet to determine whether changes in sodium, are in themselves responsible for the differences in prognosis between individuals, or whether they are simply markers of underlying pathology. Exploring the physiological correlates of these biochemical fluctuations may improve our understanding of the

mechanisms and trajectory of aging [5]. This may provide evidence to strengthen or refute theories of ageing such as inflammation, oxidative stress and/ or mitochondrial dysfunction, so that we can better appreciate the reasons behind the immense heterogeneity seen in the health of older people, and perhaps intervene to boost resilience in this population. Moreover, the clinical utility of novel biomarkers should be assessed against current tools and concepts, such as that of frailty.

Conclusions

Static measures of sodium homeostasis are most useful in predicting mortality and stratifying risk in older people. The individual biologic variations of sodium in dysnatraemia were also associated with increased mortality risk, but failed to add predictive value to single measurement results after adjusting for covariates, making it harder to justify their use in clinical practice. Having said this, they do offer a novel paradigm wherein 'real-time' changes can be illustrated, giving academic insight into processes that underpin ageing, and the opportunity to stratify risk at an earlier stage of the course of an acute illness.

Human Subject Involvement

Linked datasets of routinely collected clinical data were held by the Health Informatics Centre, University of Dundee. The re-use of these routinely collected clinical data did not allow for individual consent to be obtained; management of these data are performed under generic ethics

committee approvals from the East of Scotland Research Ethics committee and the local Data Protection Officer.

Acknowledgements

Author Contributions:

Study concept and design: *MDW, MB, HF, MMMcG*

Acquisition of data: *MDW, PTD, HF, MMMcG*

Analysis and interpretation of data: *MDW, MB, RLS*

Drafting of the manuscript: *MB, MDW, RLS*

Critical revision of the manuscript for important intellectual content*: All authors*

University of Dundee acted as Sponsor for the analysis, but had no input into the design, analysis or writing of the paper.

Conflicts of Interest

There are no financial or personal conflicts of interest that the authors would like to declare.

Table 1. Baseline data on study population (n=3021)

Mean age (years) (SD)	84.1 (7.5)
Female sex (%)	1776 (58.8)
Median length of rehabilitation stay (days) (IQR)	35 (20-65)
Mean Barthel score at discharge (SD)	14.3 (4.7)
Previous myocardial infarction (%)	484 (16.0)
Previous stroke (%)	201 (6.7)
Chronic heart failure (%)	249 (8.2)
Chronic obstructive pulmonary disease (%)	419 (13.9)
Diabetes mellitus (%)	522 (17.3)
Previous cancer (%)	371 (12.3)
Mean Haemoglobin (g/dL)(SD)	12.0 (1.9)
Mean serum albumin (g/L) (SD)	36.6 (4.9)
Mean eGFR (ml/min/1.73m^2) (SD)	62 (25)
Mean Na in year prior to discharge (SD)	137.9 (3.2)
SD of Na in year prior to discharge (SD)	2.7 (1.3)
Mean greatest deviation of Na below mean in year prior to discharge (SD)	4.7 (3.6)
Mean greatest deviation of Na above mean in year prior to discharge (SD)	4.4 (2.8)
No of patients with minimum Na<135 mmol/L in last year (%)	1651 (54.7)
No of patients with maximum Na>145 mmol/L in last year (%)	446 (14.8)
Number of measurements in year prior to discharge (median, IQR)	14 (8-24)

Abbreviations: eGFR, estimated glomerular filtration rate; Na, Serum sodium; SD, Standard Deviation

Table 2. Correlations between indices of sodium homeostasis and Barthel score

	Mean Na		SD of Na	
	r	p	r	P
Min Na	0.77	<0.01	-0.66	<0.01
Max Na	0.71	<0.01	0.34	<0.01
Mean Na	-	-	-0.28	<0.01
SD of Na	-0.28	<0.01	-	-
Barthel score on admission to rehabilitation	-0.02	0.36	-0.10	<0.01
Barthel on discharge from rehabilitation	-0.05	0.07	-0.05	<0.01
Change in Barthel score between admission and discharge	-0.04	0.03	0.05	0.01
Age	0.02	0.21	-0.09	<0.01

Abbreviations: Na, Serum sodium; SD, Standard Deviation

Table 3. Linear regression: Discharge Barthel as dependent variable, forced entry

	Model 1			Model 2		
	B	95% CI for B	P	B	95% CI for B	P
Mean Na	-0.048	-0.095, -0.002	0.04	-0.041	-0.088, 0.006	0.08
SD of Na	0.004	-0.103, 0.110	0.95	0.001	-0.106, 0.108	0.98
Mean Na	-0.024	-0.082, 0.035	0.43	-0.019	-0.078, 0.040	0.53
Min Na<135	0.195	-0.128, 0.518	0.24	0.169	-0.161, 0.499	0.32
Max Na>145	-0.111	-0.501, 0.280	0.58	-0.134	-0.528, 0.260	0.50
Mean Na	-0.038	-0.084, 0.007	0.10	-0.033	-0.079, 0.013	0.16
Max deviation above mean Na (per mmol/L)	-0.029	-0.089, 0.031	0.34	-0.033	-0.093, 0.028	0.29
Max deviation below mean Na (per mmol/L)	0.051	-0.002, 0.104	0.06	0.048	-0.005, 0.101	0.08

Abbreviations: CI, Confidence Interval; Na, Serum sodium; SD, Standard Deviation

Model 1: Adjusted for age, sex and admission Barthel score

Model 2: As for model 1 with the addition of: previous discharge diagnosis of myocardial infarction, stroke, congestive heart failure, chronic obstructive pulmonary disease, previous cancer diagnosis, previous diabetes mellitus diagnosis, haemoglobin, serum albumin and estimated glomerular filtration rate by MDRD4 equation

Table 4: Multivariate Cox regressions: Time to death after discharge as dependent variable, forced entry

	Model 1			Model 2			Model 3		
	HR	95% CI for HR	P	HR	95% CI for HR	P	HR	95% CI for HR	P
Mean Na	0.99	0.98 – 1.01	0.21	0.99	0.98 – 1.01	0.38	0.99	0.97 – 1.00	0.04
SD of Na	1.03	1.00 – 1.07	0.03	1.01	0.98 – 1.04	0.63	0.99	0.96 – 1.02	0.54
Mean Na	0.99	0.97-1.01	0.16	0.99	0.97-1.00	0.10	0.98	0.96-1.00	0.01
Min Na<135	1.10	0.99-1.23	0.08	0.98	0.88-1.09	0.72	0.95	0.85-1.06	0.38
Max Na>145	1.21	1.07-1.38	<0.01	1.10	0.97-1.25	0.15	1.04	0.91-1.18	0.57
Mean Na	0.99	0.98-1.00	0.12	0.99	0.98-1.01	0.26	0.98	0.97-1.00	0.03
Max deviation above mean Na (per mmol/L)	1.02	1.01-1.04	<0.01	1.01	0.99-1.02	0.60	0.99	0.98-1.01	0.42
Max deviation below mean Na (per mmol/L)	1.00	0.99-1.01	0.99	1.00	0.99-1.01	0.60	1.00	0.99-1.01	0.63

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; Na, Serum sodium; SD, Standard Deviation

Model 1: Adjusted for age and sex

Model 2: As for model 1 with the addition of: previous discharge diagnosis of myocardial infarction, stroke, congestive heart failure, chronic obstructive pulmonary disease, previous cancer diagnosis, previous diabetes mellitus diagnosis, haemoglobin, serum albumin and estimated glomerular filtration rate by MDRD4 equation

Model 3: As for model 2 with the addition of discharge Barthel score

Fig 1: Survival after hypernatremia, hyponatremia, or both in year prior to discharge from rehabilitation

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