Impact of hyponatremia on muscle strength, gait and balance, and cognitive function: a prospective observational study

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) [1].
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	A

Project Leader:
Gregor Lindner M.D.
Department of General Internal Medicine
Bürgerspital Solothurn
Schöngrünstrasse 42
4500 Solothurn
Switzerland
Tel: +41/32 627 31 21
Email: lindner.gregor@gmail.com

PROTOCOL SIGNATURE FORM

Study Title	**Impact of hyponatremia on muscle strength, gait and balance, and cognitive function: a prospective observational study**

The project leader has approved the protocol version ***1.4 (dated 14.05.2019)***, and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [30, 31], current version of the World Medical Association Declaration of Helsinki [32] and the principles of Good Clinical Practice.

Project leader:

Site
Bürgerspital Solothurn
Schöngrünstrasse 42
4500 Solothurn
Switzerland

Name: PD Dr. med. univ. Gregor Lindner

Date: _____ Signature: _____

TABLE OF CONTENTS

GLOSSARY OF ABBREVATIONS

BASEC	*Business Administration System for Ethical Committees*
CRF	*Case report form*
FOPH	*Federal Office of Public Health*

HRA	*Human Research Act*
HRO	*Ordinance on Human*

1 BACKGROUND AND PROJECT RATIONALE

Hyponatremia, defined as a serum sodium level below <136 mmol/L, is an often encountered disorder in hospitalized patients, with a prevalence of about 10% of patients presenting to the emergency department 1-3]. While the excess mortality seen in hyponatremic patients has long been attributed to the severity of the underlying disease, as it is potentially true in heart failure and other conditions, recent studies have shown that hyponatremia itself has a negative impact on patient outcomes, irrespective of the type and severity of the underlying disease 4-8]. Even a slight decrease of the serum sodium level was shown to be independently associated with adverse outcomes, such as mortality or increase in length of ICU/hospital stay 6, 8]. To date, the mechanisms leading to worse prognosis in patients with hyponatremia remain largely unknown. Evidence suggests that patients with hyponatremia may be more prone to falls resulting in an increased incidence of fractures in such patients 9-11]. In addition, chronic hyponatremia may be associated with decreased bone density and therefore a higher risk of fractures 12-14]. A small recent study showed an association between hyponatremia and psychomotor disturbances, such as attention deficits and gait difficulties 15].
The above mentioned effects of acute hyponatremia might be explained by cellular hyperhydration, the same mechanism that also leads to cerebral edema [3]. In chronic hyponatremia, compensatory mechanisms, such as a shift of organic and inorganic osmotically active substances from the intracellular to the extracellular space, have already occurred and decrease cellular edema [3, 16. However, resting membrane potential is a function of sodium and potassium concentrations. Thus, hyponatremia might directly influence nerve conduction velocity and muscle strength.
In summary, limited evidence suggests that hyponatremia appears to influence neurologic functions leading to attention deficits, gait disturbances, and a higher risk of fractures. Given the low quality of existing data, the association between hyponatremia and these adverse outcomes must be further examined, preferably in an adequately powered prospective study.

Preliminary studies

I. In a large study including multiple intensive care units in Austria, our group demonstrated that even mild decreases in serum sodium (i.e., serum sodium 130 – 135 mmol/L) were associated with an increased mortality, adjusting for age, admission diagnosis, and severity of illness as measured by the Severe Acute Physiology Score (SAPS) II 6].
II. Another study by our group showed that hyponatremia at the time of hospital admission is often not noticed and consequently, not or inadequately treated during hospitalization 11].
V. Refardt and coworkers demonstrated an increase in cognitive function but could not show an improvement in gait after correction of sodium levels [29].
VI. Vandergheynst and coworkers could show no improvement in strength after correction in moderate hyponatremia, but could show impaired nerve conduction with significant improvement through correction in severe hyponatremia [PMID 26835607].
VII. Albabtain and cowerkers found a correlation between hyponatremia and impaired cognitive function in patients with heart failure but none for impaired mobility [PMID 27988787].
VIII. Murthy and coworkes did a metaanalysis regarding bone density and fractures in hyponatremia, showing a significantly increased risk for osteoporosis, all-site fractures, mortality and duration of hospital stay in Patients with hyponatremia [PMID 30720342].
IX. Usala and coworkers conducted a metaanalysis regarding osteoporisis and prevalence of fractures in diabetic patients with hyponatremia, showing a significantly increasd risk for osteoprosis and fractures in hyponatremia [PMID 30746503]
X. Corona and coworkers showed in a metanalysis an increased risk for fractures even in mild hyponatremia [PMID 29920727].

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

Our broad objective is to prospectively examine in a prospective study whether an association exists between hyponatremia and psychomotor deficits. The specific aims are:

A) To measure muscle strength by use of a dynamometer in patients presenting with moderate to severe hyponatremia (serum sodium ≤ 125 mmol/L) at the emergency department before and after correction of hyponatremia (serum sodium ≥ 135 mmol/L).
B) To test for balance and gait disorders before and after correction of hyponatremia
C) To investigate whether presence of hyponatremia is associated with cognitive impairment that isreversible after correction of serum sodium.

Our hypothesis is that hyponatremia is associated with reduced muscle strength, impaired balance, and cognitive impairment, and that the correction of the serum sodium will lead to an improvement of these parameters.

2.2 Primary and secondary endpoints

A) Muscle strength in pounds and kilogram before and after correction of hyponatremia.
B) Results for the Tinetti performance-oriented mobility assessment (POMA) to evaluate static and dynamic balance abilities during and after correction of hyponatremia.
C) Results for the Montreal Cognitive Assessment (MOCA) test to assess mild cognitive impairment before and after correction of hyponatremia.

Muscle strength at handgrip will be measured at time of presentation at our clinic with a serum sodium ≤ 125 mmol/L and 24 to 48 hours after correction of hyponatremia at a serum sodium ≥ 135 mmol/L using the Jamar ® hydraulic hand dynamometer, Lafayette Instrument, Lafayette, IN, USA. Strength will be measured in pounds and kilograms thrice at baseline and after correction of hyponatremia, respectively. The best result of each test will be used for the analysis. The test will be conducted by either Drs. Woitok or Lindner.
The Tinetti POMA, a simple, easily administered test, will be used to measure patients' gait and balance taking about 10 to 15 minutes [19]. Scoring of the Tinetti Assessment Tool is done on a three point ordinal scale with a range of 0 to 2. A score of 0 represents the most severe impairment, while a 2 would represent patient independence. The individual scores are then combined to form three measures; an overall gait assessment score, an overall balance assessment score, and a gait and balance score. The test has been validated in several studies and found to be a useful screening tool for gait instabilities and prediction of falls [20-22]. The Tinetti POMA form is shown in the Appendix. The test will be performed at baseline and 24 to 48 hours after correction of hyponatremia. The test will be conducted by either Drs. Woitok and Lindner.
The MOCA is a 30-point test administered in about 10 minutes designed to identify mild cognitive impairment [23]. The test is validated for a large variety of diseases ranging from frontotemporal dementia to HIV or chronic obstructive pulmonary disease [24-27]. The MOCA form is shown in the Appendix. The test will be performed at baseline and 24 to 48 hours after correction of hyponatremia. The test will be conducted by either Drs. Woitok and Lindner.

2.3 Project design

We will conduct a single-center, prospective, observational study at the General Hospital Solothurn. The study will be conducted at the Department of Emergency Medicine, where patients will be screened for hyponatremia, and the Department of General Internal Medicine, where screening will occur both in the inpatient and outpatient services.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

Sample size was calculated on basis of the MOCA test. To achieve a power of 90% and a two-sided alpha level of 0.05, the sample size needed to detect a difference of 5 points (shown difference between normal individuals and those with mild cognitive impairment) between the baseline and post-correction MOCA scores would be 44 patients [23]. Thus, we plan to enroll a total of 50 patients.

Inclusion criteria

Consecutive patients aged 18 years or above presenting with moderately to severe hyponatremia (serum sodium ≤ 125 mmol/L after correction for blood glucose), who give informed consent.

Exclusion criteria

- Patients who do not give or are not able to give informed consent.
- Patients with concomitant Potassium dysregulation (K+<3.5 mmol/l or K+>5.0 mmol/l)
- Pregnant or Lactating females

3.2 Recruitment, screening and informed consent procedure

If a serum sodium of 125 mmol/L is detected in a blood sample sent from the Department of Emergency Medicine or General Internal Medicine, the Center for Laboratory Medicine will notify the study team (Drs. Lindner and Woitok) responsible for patient enrollment using a dedicated pager. Then, a member of the study team will approach potential participants, inform them about the study goals and procedures, obtain informed consent, and enroll them into the study. Patients enrolled in the Department of Emergency Medicine needing hospitalization will primarily hospitalized in the Department of General Internal Medicine, unless hospitalization at specialist ward is indicated.

3.3 Study procedures

Upon recruitment the following data will be collected:

a.) Clinical data

Of all patients included in the study, we will collect data on age, sex, comorbidities, and current medications taken by the patients.

b.) Serum sodium measurements

Measurements of serum sodium will be performed through the Center for Laboratory Medicine of the General Hospital Solothurn. Sodium determination will be performed by use of ion-selective electrode using the ICT (Na+, K+, Cl-) Sample Diluent Kit, Abbott Laboratories, Chicago, IL, USA. Additionally, serum osmolality, potassium, magnesium, calcium, creatinine, albumin and hemoglobin as well as urine osmolality, sodium, potassium, creatinine and urea will be measured. All of these parameters are standard measurements in case of a severe electrolyte disorder and are part of clinical practice in the care for patients with electrolyte disorders. All laboratory parameters will be measured at baseline and after correction of serum sodium. In order to avoid multiple blood drawings for the patient the parameters mentioned above will be reordered from blood already taken for serum sodium determination.

c.) Physical and cognitive measurements

Afterwards muscle strength, Tinetti score and MOCA score will be measured. Upon correction of hyponatremia these measurements will be repeated. The study is then completed for the individual participant.

See also Appendix 1.

3.4 Withdrawal and discontinuation

Patients are excluded from the project in case of withdrawal of informed consent. Endpoint-specific datasets will be included if complete (see Section 4.2.). Additional patients will be enrolled to compensate for drop-outs. Since the blood samples used are part of clinical routine no further steps are taken, the blood samples will be handled according to usual clinical routine.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

Data will be presented as means and standard deviation or medians and interquartile range as appropriate. Wilcoxon signed ranked tests will be used to compare results on muscle strength, Tinetti score and MOCA scores, since those are not normally distributed and samples will be dependent since every patient serves as his own control. A p-value of ≤ 0.05 will be considered statistically significant. Statistics will be calculated using IBM SPSS Statistics 25, IBM, Armonk, New York, USA.

Based on general Patient count and prevalence of Hyponatremia, the enrollment of the sample size of 50 patients seems realistic in a 12-month period, starting on 01 June 2019.

4.2. Handling of missing data

Partially missing data (e.g. a missing Tinetti-Assesment) would be left out in the specific calculation, but data for the other Endpoints would be used, if complete. If there would be no complete sets of data for any Endpoint the data set would be discarded. Reasons for missing measurements will be stated in the publication.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [32], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [30] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

1 A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

5.4 Procedure for investigations involving radiation sources

This Study does not involve radiation sources.

5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.6 End of project

Upon project termination, the Ethics Committee is notified within 90 days. All health-related data are anonymized upon termination of data analysis.

5.7 Insurance

In the event of project-related damage or injuries, the liability of the Bürgerspital Solothurn provides compensation, except for claims that arise from misconduct or gross negligence.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

This is a prospective, observational study. No invasive interventions will take place and thus, there is no potential harm for the patients. Laboratory parameters will be re-ordered from blood samples already taken as a part of clinical routine, so no additional blood drawings are necessary for study purposes. Only patients who are able to give informed consent by themselves will be included in the study. There will be no compensation for the patients, neither monetary nor in another way.

6.2 Risk-Benefit Assessment

Hyponatremia is a commonly encountered problem in hospitalized patients and is associated with significant morbidity and mortality [1, 2, 10]. The present study could give more insight into the impact of this electrolyte disorder on important body functions, such as muscle strength, gait and balance, and cognition. If hyponatremia is associated with these conditions, specific preventive measures could be taken to avoid complications, such as falls and fractures, which are associated with significant mortality, morbidity, and a socioeconomic burden [18]. Additionally, if the negative influence of hyponatremia on psychomotricity was shown, it could help increase physicians' awareness to correct hyponatremia and eliminate predisposing factors for this condition [17]. Since it is an observational study no specific risks are expected.

6.3 Rationale for the inclusion of vulnerable participants

Vulnerable Participants are not included in the Study.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

All data handling will be undertaken directly by the investigators. For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

Data will be collected on paper CRFs and transferred to a Microsoft Excel file by the investigators. The Paper CRFs will be subsequently stored in a lockable bin. The Excel file will be stored on a dedicated drive accessible only by the study team. The dedicated drive is part of the Hospital IT Structure and thus subject to data backup procedures.

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number. The Code will not include any parts able to identify a subject like name or date of birth.
All patient data will be stored in a lockable bin in an office room at the General Hospital Solothurn. Patient data will be entered into a Microsoft Excel database, Microsoft Corporation, Redmond, WA, USA, and stored electronically on a password-protected computer. Electronic patient data will be encrypted and only the investigators (Drs. Woitok and Lindner) will be able to identify patients by use of a personal identification number for every patient enrolled in the study. Data will be published anonymously.

7.4 Retention and destruction of study data and biological material

Health related data are stored for 10 years after publication of the research project. The blood samples are part of clinical routine and will be handled according to clinical routine. No blood samples will be stored for study purposes.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

There is no funding for the project. The Investigators declare no conflict of interest.

9 REFERENCES

1. Arampatzis S, Frauchiger B, Fiedler GM, Leichtle AB, Buhl D, Schwarz C, Funk GC, Zimmermann H, Exadaktylos AK, Lindner G, (2012) Characteristics, symptoms, and outcome of severe dysnatremias present on hospital admission. The American journal of medicine 125: 1125 e1121-1125 e1127

2. Arampatzis S, Funk GC, Leichtle AB, Fiedler GM, Schwarz C, Zimmermann H, Exadaktylos AK, Lindner G, (2013) Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: a cross-sectional analysis. BMC medicine 11: 83

3. Adrogue HJ, Madias NE, (2000) Hyponatremia. The New England journal of medicine 342: 1581-1589

4. Kovesdy CP, Lott EH, Lu JL, Malakauskas SM, Ma JZ, Molnar MZ, Kalantar-Zadeh K, (2012) Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. Circulation 125: 677-684

5. Bettari L, Fiuzat M, Shaw LK, Wojdyla DM, Metra M, Felker GM, O'Connor CM, (2012) Hyponatremia and long-term outcomes in chronic heart failure--an observational study from the Duke Databank for Cardiovascular Diseases. Journal of cardiac failure 18: 74-81

6. Funk GC, Lindner G, Druml W, Metnitz B, Schwarz C, Bauer P, Metnitz PG, (2010) Incidence and prognosis of dysnatremias present on ICU admission. Intensive care medicine 36: 304-311

7. Doshi SM, Shah P, Lei X, Lahoti A, Salahudeen AK, (2012) Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. American journal of kidney diseases : the official journal of the National Kidney Foundation 59: 222-228

8. Darmon M, Diconne E, Souweine B, Ruckly S, Adrie C, Azoulay E, Clec'h C, Garrouste-Orgeas M, Schwebel C, Goldgran-Toledano D, Khallel H, Dumenil AS, Jamali S, Cheval C, Allaouchiche B, Zeni F, Timsit JF, (2013) Prognostic consequences of borderline dysnatremia: pay attention to minimal serum sodium change. Critical care 17: R12

9. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G, (2006) Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. The American journal of medicine 119: 71 e71-78

10. Arampatzis S, Gaetcke LM, Funk GC, Schwarz C, Mohaupt M, Zimmermann H, Exadaktylos AK, Lindner G, (2013) Diuretic-induced hyponatremia and osteoporotic fractures in patients admitted to the emergency department. Maturitas

11. Hoorn EJ, Rivadeneira F, van Meurs JB, Ziere G, Stricker BH, Hofman A, Pols HA, Zietse R, Uitterlinden AG, Zillikens MC, (2011) Mild hyponatremia as a risk factor for fractures: the Rotterdam Study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 26: 1822-1828

12. Barsony J, Sugimura Y, Verbalis JG, (2011) Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. The Journal of biological chemistry 286: 10864-10875

13. Verbalis JG, Barsony J, Sugimura Y, Tian Y, Adams DJ, Carter EA, Resnick HE, (2010) Hyponatremia-induced osteoporosis. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 25: 554-563

14. Hoorn EJ, Liamis G, Zietse R, Zillikens MC, (2012) Hyponatremia and bone: an emerging relationship. Nature reviews Endocrinology 8: 33-39

15. Josiassen RC, Filmyer DM, Geboy AG, Martin DM, Curtis JL, Shaughnessy RA, Salzman A, Orlandi C, (2012) Psychomotor deficits associated with hyponatremia: a retrospective analysis. The Clinical neuropsychologist 26: 74-87

16. Rose DB, Post TW (2001) Clinical physiology of acid-base and electrolyte disorders. McGraw-Hill, New York

17. Lien YH, (2012) Are we ignoring dysnatremia? The American journal of medicine 125: 1045-1046

18. Weyler EJ, Gandjour A, (2007) [Socioeconomic burden of hip fractures in Germany]. Gesundheitswesen 69: 601-606

19. Tinetti ME, (1986) Performance-oriented assessment of mobility problems in elderly patients. Journal of the American Geriatrics Society 34: 119-126

20. Kloos AD, Kegelmeyer DA, Young GS, Kostyk SK, (2010) Fall risk assessment using the Tinetti mobility test in individuals with Huntington's disease. Movement disorders : official journal of the Movement Disorder Society 25: 2838-2844

21. Kegelmeyer DA, Kloos AD, Thomas KM, Kostyk SK, (2007) Reliability and validity of the Tinetti Mobility Test for individuals with Parkinson disease. Physical therapy 87: 1369-1378

22. Lin MR, Hwang HF, Hu MH, Wu HD, Wang YW, Huang FC, (2004) Psychometric comparisons of the timed up and go, one-leg stand, functional reach, and Tinetti balance measures in community-dwelling older people. Journal of the American Geriatrics Society 52: 1343-1348

23. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H, (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 53: 695-699

24. Freitas S, Simoes MR, Alves L, Duro D, Santana I, (2012) Montreal Cognitive Assessment (MoCA): validation study for frontotemporal dementia. Journal of geriatric psychiatry and neurology 25: 146-154

25. Freitas S, Simoes MR, Alves L, Santana I, (2013) Montreal cognitive assessment: validation study for mild cognitive impairment and Alzheimer disease. Alzheimer disease and associated disorders 27: 37-43

26. Overton ET, Azad TD, Parker N, Demarco Shaw D, Frain J, Spitz T, Westerhaus E, Paul R, Clifford DB, Ances BM, (2013) The Alzheimer's disease-8 and Montreal Cognitive Assessment as screening tools for neurocognitive impairment in HIV-infected persons. Journal of neurovirology 19: 109-116

27. Villeneuve S, Pepin V, Rahayel S, Bertrand JA, de Lorimier M, Rizk A, Desjardins C, Parenteau S, Beaucage F, Joncas S, Monchi O, Gagnon JF, (2012) Mild cognitive impairment in moderate to severe COPD: a preliminary study. Chest 142: 1516-1523

28. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH, (2007) Hyponatremia treatment guidelines 2007: expert panel recommendations. The American journal of medicine 120: S1-21

29. Refardt J, Kling B, Krausert K, Fassnacht M, von Felten S, Christ-Crain M, Fenske W, (2018) Impact of chronic hyponatremia on neurocognitive and neuromuscular function. European Journal of clinical Investigation 48:e13022

30. Ordinance on Human Research with the Exception of Clinical trials (HRO) https://www.admin.ch/opc/en/classified-compilation/20121177/index.html

31. Human Research Act (HRA)
http://www.admin.ch/opc/en/classified-compilation/20121176/201401010000/810.305.pdf

32. Declaration of Helsinki
(https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects)

33. STROBE statement (http://www.jclinepi.com/article/S0895-4356(07)00436-2/pdf)

Appendix 1: Schedule of assessments

Time	***0***	***Corrected sodium***
Visit	*Screening/1st visit*	*2nd visit*
oral and written Information	**+**	
Written consent	**+**	
check inclusion-/ exclusion criteria	**+**	
Medical history	**+**	
Participant Characteristics	**+**	
Serum sodium measurements	**+**	**+**
MOCA	**+**	**+**
Tinetti Assessment	**+**	**+**
Grip Strength	**+**	+