

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Distribution of plasma copeptin levels and influence of obesity in children and adolescents

This is a pre print version of the following article:

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1767398> since 2021-01-19T10:03:51Z

Published version:

DOI:10.1007/s00431-020-03777-3

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

“DISTRIBUTION OF PLASMA COPEPTIN LEVELS AND THE INFLUENCE OF OBESITY IN THE PEDIATRIC AGE ”

Gerdi Tuli ^{1,2}, Jessica Munarin ^{1,2}, Daniele Tessaris ^{1,2}, Silvia Einaudi ^{1,2}, Patrizia Matarazzo ^{1,2}, Luisa de Sanctis ^{1,2}

1Department of Pediatric Endocrinology, Regina Margherita Children’s Hospital, Turin, Italy

2Department of Public Health and Pediatric Sciences, University of Turin, Italy

Corresponding author:

Gerdi Tuli MD,

Piazza Polonia 94, 10126, Turin, Italy

Tel + 39 011 313 5687

Fax + 39 011 313 5459

gerdi.tuli@unito.it

Co-authors:

Jessica Munarin (Jessica.munarin@edu.unito.it)

Daniele Tessaris (daniele.tessaris@unito.it)

Silvia Einaudi (seinaudi@cittadellasalute.to.it)

Patrizia Matarazzo (pamatarazzo@cittadellasalute.to.it)

Luisa de Sanctis (luisa.desanctis@unito.it)

Abstract

In the last years, a more stable AVP surrogate, called copeptin, has been used as an adjuvant diagnostic tool in adults and seems to be promising also in the pediatric age. The aim of this study is to present plasma copeptin distribution in a large pediatric cohort and to observe the influence of fluid drinking and obesity on its measurement.

A cohort of 128 children and adolescents was split in two groups on the basis of nocturnal liquid thirsting (Group A) or free access of oral fluids in the 6-8 hours before the withdrawal (Group B).

At all the distribution percentiles copeptin levels were higher ($p<0.0001$) in Group A, as well as plasma sodium level and osmolality ($p=0.02$ and $p=0.008$, respectively). The influence of BMI on copeptin levels was investigated by dividing the cohort in non-obese (Group C) and obese children (Group D). Copeptin levels were higher in group D ($p=0.03$).

Conclusion: Copeptin measurement could be indeed an useful tool for the diagnostic pathway of dysnatremic conditions, but its interpretation should take into consideration the hydration status. Furthermore, it might be a promising marker also for obesity and metabolic syndrome, even if this hypothesis needs further studies to be confirmed.

Key words: copeptin, distribution, AVP related disorders, pediatric age, obesity

INTRODUCTION

Arginin-vasopressin (AVP) or anti-diuretic hormone (ADH) is the main hormone driving water and sodium homeostasis maintenance [1-10]. AVP-related disorders are represented by a heterogeneous group of conditions often characterized by severe neurological symptoms, mostly due to dehydration and dysnatremia, even life threatening if not promptly recognized and correctly treated.

An inappropriate AVP secretion associated with hyponatremia configures the syndrome of inappropriate antidiuretic hormone secretion (SIADH); its diagnosis is often challenging, as its laboratory features overlap with those of the cerebral/renal salt wasting syndrome (C/RSW), a rare and controversial but severe hyponatremic disorder mostly seen in patients with cerebral tumours [11-16].

Conversely, hypernatremia is the common finding of an insufficient AVP secretion, as observed in central diabetes insipidus (CDI), or insufficient AVP action, despite increased release, in case of AVP receptor resistance (nephrogenic diabetes insipidus, NDI) [17-20]. The biochemical features are not always helpful in distinguishing them from primary polydipsia (PP). AVP plasma concentration have been considered helpful in the diagnostic pathway of all these conditions, but the structural instability, its very short plasma half-life and, last but not least, the long lasting laboratory processing have limited its use in the clinical practice [29-32]. To differentiate them, a water deprivation test (WDT) is often required, even if the results interpretation can be cumbersome, especially in the presence of partial CDI [17-28].

Recent studies have regarded plasma copeptin investigation in the differential diagnosis pathway of either hyponatremic and hypernatremic AVP release disorders as it is a stable and fast-available measured surrogate of plasma AVP [33-35].

It has been shown that copeptin is very helpful in distinguishing between hypernatremic disorders (CDI, NDI and PP), but less helpful in hyponatremia (large overlap between SIAD/hyper - or hypovolemic hyponatremia). [36-48]. Similar data have been reported from our group in a small number of patients in pediatric age, even if these preliminary data need to be confirmed in larger cohorts [43].

Furthermore, some authors have reported the data about the use of copeptin measurement in hypertonic saline solution or arginine stimulation test with promising results in adults but to date there are no reported data about the use in pediatric age [49-50].

In pediatric age, copeptin plasma values have been considered as a prognostic factor in many conditions, such as septic shock, polmonitis, stroke, heart and kidney failure and brain traumatic injury [51-61]; higher copeptin levels have been described in insulin-resistant obese children [62].

However, few data exist to date about plasma copeptin distribution in the pediatric age, ranging between 2.4-8.6 pmol/L [8, 43]. Previous studies from our experience in 53 children not suffering from AVP-related disorders showed significant difference between the free access to fluids and the fluid thirsting for at least 6-8 hours population [43].

The aim of this study is to present plasma copeptin distribution in a larger pediatric cohort either by considering the fluid intake and the BMI.

MATERIAL AND METHODS

Study population

Plasma copeptin levels have been measured in 128 children and adolescents not suffering from any AVP related disease, referred to the Department of Pediatric Endocrinology of the Regina Margherita Children's Hospital of Turin in the period July 2016-May 2018.

The referral reason was suspected puberty or growth disorder which was not confirmed after hormonal basal and dynamic evaluation, all patients were free of other comorbidity, outpatient clinic and the access was planned after the first clinical evaluation by a pediatric endocrinologist.

Exclusion criteria were the presence of hypo or hypernatremia, abnormal urinary or plasma osmolality, type I diabetes mellitus, hypo or hypercalcemia, hypokaliemia, hypo or hyperthyroidism, hypo or hypercorticism, kidney and heart diseases, recent episodes of nausea or vomiting, infectious diseases, brain traumatic injury, any treatment interfering with the AVP release system and nocturnal enuresis.

Plasma samples for copeptin investigation were collected early in the morning; the cohort was then split in two groups on the basis of nocturnal liquid thirsting at a home setting for at least 6-8 hours (Group A) or free access to liquids (limited to a maximum of 300 ml of water) in the 6-8 hours before the withdrawal (Group B).

The main anthropometric parameters height, weight and body mass index (BMI) have also been considered in the studied population and allowed the distinction in non-obese (BMI <95° percentile, Group C) and obese children (BMI > 95° percentile, Group D [63], accordingly to BMI Cole percentiles.

Ethical approval from the Ethics Committee of the City of Health and Science University Hospital of Turin and written informed consent from the families were obtained before the study start.

Laboratory sample for plasma copeptin

Plasma samples for copeptin evaluation were collected into EDTA tubes. The peptide measurement was performed with an immunoluminometric assay (BRAHMS CT-proAVP LIA; B.R.A.H.M.S. GmbH, Hennigsdorf Germany) with lower detection limit 0.4 pmol/L and functional assay sensitivity less than 1 pmol/L. Intra and inter-assay have a CV% of <8% and <10% respectively.

Statistical analysis and graphs

Statistical analysis and graphs were performed by Graphpad 7 software (GraphPad Software, La Jolla, CA, USA) using T-Student for the means comparison.

RESULTS

Distribution of plasma copeptin levels in pediatric age

In the 128 children and adolescents (mean age 9.63 ± 3.36 years, 42 boys, 86 girls) with normal plasma sodium and osmolality, mean plasma copeptin level was 6.76 ± 3.18 pmol/L (range 2-14.9 pmol/L).

The demographic and biochemical features of the studied population, divided in Group A (fluids thirsting for at least 6-8 hours) and Group B (free access to fluids) are represented in Table 1.

Plasma copeptin level in Group A was 10.26 ± 0.43 pmol/l whereas in Group B was 5.16 ± 0.18 pmol/L ($p < 0.0001$) (Fig. 1).

Plasma sodium level was 141.3 ± 1.63 mmol/L in Group A, whereas 140.5 ± 1.81 mmol/L in Group B ($p = 0.02$). Significant difference was observed between the 2 groups also for plasma osmolality (285.6 ± 5.89 mOsm/kg vs 283.5 ± 2.99 mOsm/kg respectively, $p = 0.008$).

Plasma copeptin distribution in percentiles for each group is represented in Table 2.

No difference was present between boys (n=42) and girls (n=86), for which mean copeptin level was 6.96 ± 0.5 pmol/L vs 6.65 ± 0.34 pmol/L respectively ($p = 0.61$).

Copeptin levels in obese children

The biochemical data relative to the non-obese (group C, 102 children, 28 boys and 74 girls, age 9.3 ± 3.32 years) and obese children (Group D, 26 children, 14 boys and 12 girls, age 10.94 ± 3.28 years) are represented in Table 3.

Plasma copeptin level was 6.4 ± 0.31 pmol/l in Group C, 7.931 ± 0.61 pmol/L in Group D ($p = 0.03$, Fig. 2); no significant difference was observed for plasma sodium and osmolality between groups (Table 3).

DISCUSSION

AVP related disorders comprise different clinical conditions which may be life-threatening when hyponatremia or hypernatremia become severe. In case of hyponatremia, the differential diagnosis between the SIADH and C/RSW syndrome is challenging but fundamental, as their treatment is quite the opposite. Also, the distinction of partial diabetes insipidus and PP may be challenging and the management of the two conditions is quite different.

Thus, AVP plasma measurement may be useful in the diagnostic pathway of all these derangements, but its in vitro instability and its short half-life make the laboratory results almost useless. In the last years, the dosage of an AVP surrogate, called copeptin, has been used thanks to its higher stability and fewer required pre-analytical procedures [29-33].

Copeptin values in healthy adults range from 1 to 13 pmol/L and the serum levels are very sensitive to the osmotic and hemodynamic stimuli similarly to AVP. Copeptin levels significantly decrease even after little oral fluid intake as 200-300 mL or by hypotonic saline infusion whereas the water deprivation alone or followed by hypertonic saline infusion leads to copeptin levels increase [64, 65, 69]

Males show slightly higher values of copeptin with minimal difference in median values, whereas age or circadian rhythm do not interfere with its serum levels as well as food intake or menstrual cycle. In a previous paper, we showed the distribution of plasma copeptin levels in 53 children and adolescents without AVP-related diseases, indicating ranges between 2.4-8.6 pmol/L for the pediatric age [43].

In the current study we have enlarged our cohort of controls not suffering from any AVP-related diseases to

establish a more defined distribution in the evolutive age.

Plasma copeptin levels have been measured in a cohort of 128 children who were split in two groups on the basis of the orally ingested fluids; in the first group children who had been fluid thirsting for at least 6-8 hours were included, while free access to fluids was permitted in the other group. Copeptin, sodium and osmolality levels significantly differed in the two groups, even if sodium and osmolality were in the normal reference range in both groups. This strengthens the fact that even small fluctuations of sodium and osmolality within the normal reference range may lead to significant changes in the AVP release, which is really sensitive either to the hydration state [9,33-35]. Subjects with free access to fluids showed lower values all over the percentiles of the copeptin levels distribution than subjects with fluid deprivation, highlighting that oral intake, even of little fluid amounts, leads to significant copeptin values decrease and should be taken in consideration when interpreting its plasma levels.

Previous papers have reported similar mean copeptin levels, without showing a percentile distribution. In 2 studies on the use of copeptin as a marker for community acquired pneumonia and after brain traumatic injuries, fluid thirsting control cohorts displayed mean levels of 9.0 ± 2.7 and 9.6 ± 3 pmol/l respectively [51,55]. In 2 other papers analyzing copeptin as a marker for febrile seizures and in patients with type 1 diabetes mellitus, the control cohorts with fluid free access showed mean levels of 5.6 pmol/l and 5.56 ± 3.15 , respectively [53, 59].

The relationship between copeptin levels and obesity [66-70], as well as its association to metabolic and cardiovascular risk factors, has been already explored in the adult age and in animal models. AVP normally acts through V1 receptor to maintain water and salt homeostasis, to control blood pressure variations and to promote the hepatic gluconeogenesis and glycogenolysis, whereas its action through the V3 receptor induces glucagon or insulin secretion. A positive correlation between plasma copeptin levels and the metabolic syndrome parameters was already described in the pediatric age [61] and higher copeptin levels have been described in obese children [62]. Our data, within a cohort of subjects with normal serum sodium and osmolality, indicate significantly higher copeptin levels in obese children than in the not obese counterpart. The significant differences in the ages of the two groups might be explained by the fact that obesity onset mostly occurs in adolescence. Thus, plasma copeptin levels might be an important indicator of glucose metabolism dysfunction related to the BMI. However, further studies with larger cohorts and metabolic parameters analysis are needed to confirm this hypothesis.

Many Authors have investigated the copeptin levels in adults and their utility in the diagnostic pathways of AVP related diseases as well as their potential role as prognostic marker in various clinical conditions as acute myocardial injury, kidney and heart failure, stroke and sepsis [7,9,31-42,44-48]. While the direct measurement of copeptin can be helpful to promptly diagnose a nephrogenic diabetes insipidus (NDI), an osmotic stimulation by water deprivation test (WDT) or a hypertonic saline infusion are required to distinguish between primary polydipsia (PP) and central diabetes insipidus. Despite many authors have established its utility in the adult clinical practice, few data on copeptin as a tool in AVP-related diseases

diagnosis have been produced so far and, overall, few data nowadays exist on plasma level distribution in developmental age [43, 51-62].

CONCLUSION

The present study further strengthens the fact that plasma copeptin level could be regarded as an useful indicator of AVP system function and water and sodium homeostasis; it should therefore be included in the diagnostic pathway of the pathological conditions involving the AVP release, especially when hypernatremia is present.

It has been demonstrated to be very sensible to plasma sodium and osmolality variations, as well as to orally or intravenous administered fluids.

In the present study we have presented plasma copeptin distribution in percentiles in a children population not suffering from any AVP release system disorders, in order to have normal copeptin values as references in the suspicion of AVP release disorders.

By considering the anthropometric variables in our control population, we can postulate that copeptin might be a promising marker also for other conditions such obesity and the metabolic syndrome in the pediatric age, even if this hypothesis needs further studies to be confirmed.

Authors contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by G.T. and E.M. The first draft of the manuscript was written by G.T. and all authors commented on previous versions of the manuscript. D.T. and S.E performed final statistical analysis. P.M and L.dS. performed the final revision of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Statements.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: There is no funding source.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: Informed consent was obtained from all parents of individual participants included in the study.

REFERENCES

1. Jain A (2015) Body fluid composition. *Pediatr Rev* 36(4):141-150.
2. Ruth JL, Wassner SJ (2006) Body fluid composition: salt and water. *Pediatr Rev* 27(5):181-187.
3. Ranadive SA, Rosenthal SM (2011) Pediatric disorders of water balance. *Pediatr Clin North Am* 58(5):1271-1280.

4. Gizowski C, Bourque CW (2018) The neural basis of homeostatic and anticipatory thirst. *Nat Rev Nephrol* 14(1):11-25.
5. Zimmerman CA, Leib DE, Knight ZA (2017) Neural circuits underlying thirst and fluid homeostasis. *Nat Rev Neurosci* 18(8):459-469.
6. Bankir L, Bichet DG, Morgenthaler NG (2017) Vasopressin: physiology, assessment and osmosensation. *J Intern Med* 282(4):284-297.
7. Rotondo F, Butz H, Syro LV, Yousef GM, Di Ieva A, Restrepo LM, Quintanar-Stephano A, Berczi I, Kovacs K (2016) Arginine vasopressin (AVP): a review of its historical perspectives, current research and multifunctional role in the hypothalamo-hypophysial system. *Pituitary* 19(4):345-355.
8. Bolignano D, Cabassi A, Fiaccadori E, Ghigo E, Pasquali R, Peracino A, Peri A, Plebani M, Santoro A, Settanni F, Zoccali C (2014) Copeptin (CTproAVP), a new tool for understanding the role of vasopressin in pathophysiology. *Clin Chem Lab Med* 52(10):1447-1456.
9. Morgenthaler NG (2014) Copeptin – biochemistry and clinical diagnostic. UNI-MED-Verlag, Bremen.
10. Holmes CL, Landry DW, Granton JT (2003) Science review: vasopressin and the cardiovascular system part 1– receptor physiology. *Crit Care* 7(6):427-434.
11. Cuesta M, Garrahy A, Thompson CJ (2016) SIAD: practical recommendations for diagnosis and management. *J Endocrinol Invest* 39(9):991-1001.
12. Oh JY, Shin JI (2015) Syndrome of inappropriate antidiuretic hormone secretion and cerebral/renal salt wasting syndrome: similarities and differences. *Front Pediatr*. [https://doi: 10.3389/fped.2014.00146](https://doi.org/10.3389/fped.2014.00146).
13. Cuesta M, Thompson CJ (2016) The syndrome of inappropriate antidiuresis (SIAD). *Best Pract Res Clin Endocrinol Metab* 30(2):175-187.
14. Hardesty DA, Kilbaugh TJ, Storm PB (2012) Cerebral salt wasting syndrome in post-operative pediatric brain tumor patients 17(3):382-387.
15. González Briceño L, Grill J, Bourdeaut F, Doz F, Beltrand J, Benabbad I, Brugières 203 L, Dufour C, Valteau-Couanet D, Guerrini-Rousseau L, Aerts I, Orbach D, Alapetite C, Samara-Boustani D, Pinto G, Simon A, Touraine P, Sainte-Rose C, Zerah M, Puget S, Elie C, Polak M (2014) Water and electrolyte disorders at long term post-treatment follow-up in paediatric patients with suprasellar tumours include unexpected persistent cerebral salt-wasting syndrome. *Horm Res Paediatr* 82(6):364-371.
16. Bettinelli A, Longoni L, Tammaro F, Faré PB, Garzoni L, Bianchetti MG (2012) Renal salt-wasting syndrome in children with intracranial disorders. *Pediatr Nephrol* 27(5):733-739.
17. Dabrowski E, Kadakia R, Zimmerman D (2016) Diabetes insipidus in infants and children. *Best Pract Res Clin Endocrinol Metab* 30(2):317-328.
18. Di Iorgi N, Morana G, Napoli F, Allegri AE, Rossi A, Maghnie M (2015) Management of diabetes insipidus and adipsia in the child. *N. Best Pract Res Clin Endocrinol Metab* 29(3):415-436.
19. Bockenhauer D, Bichet DG. Nephrogenic diabetes insipidus. *Curr Opin Pediatr*. 2017 Apr;29(2):199-205.

20. Sands JM, Klein JD (2016) Physiological insights into novel therapies for nephrogenic diabetes insipidus. *Am J Physiol Renal Physiol* 311(6):F1149-F1152. [https:// doi: 10.1152/ajprenal.00418.2016](https://doi.org/10.1152/ajprenal.00418.2016)
21. Djermane A, Elmaleh M, Simon D, Poidvin A, Carel JC, Léger J (2016) Central diabetes insipidus in infancy with or without hypothalamic adipsic hypernatremia syndrome: early identification and outcome. *J Clin Endocrinol Metab* 101(2):635-643.
22. Frasier SD, Kutnik LA, Schmidt RT, Smith FG Jr (1967) A water deprivation test for the diagnosis of diabetes insipidus in children. *Am J Dis Child* 114(2):157-160.
23. Di Iorgi N, Allegri AE, Napoli F, Calcagno A, Calandra E, Fratangeli N, Vannati M, Rossi A, Bagnasco F, Haupt R, Maghnie M (2014). Central diabetes insipidus in children and young adults: etiological diagnosis and long-term outcome of idiopathic causes. *J Clin Endocrinol Metab* 99(4):1264-1272.
24. Robertson GL (2016) Diabetes insipidus: differential diagnosis and management. *Best Pract Res Clin Endocrinol Metab* 30(2):205-218.
25. Kalra S, Zargar AH, Jain SM, Sethi B, Chowdhury S, Singh AK, Thomas N, Unnikrishnan AG, Thakkar PB, Malve H (2016) Diabetes insipidus: the other diabetes. *Indian J Endocrinol Metab* 20(1):9-21.
26. Edate S, Albanese A (2015) Management of electrolyte and fluid disorders after brain surgery for pituitary/suprasellar tumours. *Horm Res Paediatr* 83(5):293-301.
27. Matarazzo P, Genitori L, Lala R, Andreo M, Grossetti R, De Sanctis C (2004) Endocrine 231 function and water metabolism in children and adolescents with treated intra/parasellar tumours. *J Pediatr Endocrinol Metab* 17(11):1487-1495.
28. Matarazzo P, Tuli G, Verna F, Tessaris D, Fiore L, Mussa A, Repici M, Lala R (2010) Management of sodium metabolism derangements in children treated for hypothalamic-hypophyseal tumours. *J. Pediatr Biochem* 4:289-296
29. Robertson GL, Mahr EA, Athar S, Sinha T (1973) Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. *J Clin Invest* 52(9):2340-2352.
30. Kluge M, Riedl S, Erhart-Hofmann B, Hartmann J, Waldhauser F (1999) Improved extraction procedure and RIA for determination of arginine-vasopressin in plasma: role of premeasurement sample treatment and reference values in children. *Clin Chem* 45(1):98-103.
31. Wun T (1997) Vasopressin and Platelets: a concise review. *Platelets*. 8(1):15-22.
32. Preibisz JJ, Sealey JE, Laragh JH, Cody RJ, Weksler BB (1983) Plasma and platelet vasopressin in essential hypertension and congestive heart failure. *Hypertension*. 5(2 Pt 2):I129-38.
33. Morgenthaler NG, Struck J, Alonso C, Bergmann A (2006) Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. *Clin Chem* 52(1):112-119.
34. Balanescu S, Kopp P, Gaskill MB, Morgenthaler NG, Schindler C, Rutishauser J (2011) Correlation of plasma copeptin and vasopressin concentrations in hypo-, iso-, and hyperosmolar states. *J Clin Endocrinol Metab* 96(4):1046-1052.
35. Beglinger S, Drewe J, Christ-Crain M (2017) The Circadian Rhythm of Copeptin, the C-Terminal Portion of Arginine Vasopressin. *J Biomark*. [https:// doi: 10.1155/2017/4737082](https://doi.org/10.1155/2017/4737082)

36. Christ-Crain M, Fenske W (2016) Copeptin in the diagnosis of vasopressin-dependent disorders of fluid homeostasis. *Nat Rev Endocrinol* 12(3):168-176.
37. Fenske W, Störk S, Blechschmidt A, Maier SG, Morgenthaler NG, Allolio B (2009) Copeptin in the differential diagnosis of hyponatremia. *J Clin Endocrinol Metab* 94(1):123-129.
38. Boursier G, Alméras M, Buthiau D, Jugant S, Daubin D, Kuster N, Dupuy AM, Ribstein J, Klouche K, Cristol JP (2015) CT-pro-AVP as a tool for assessment of intravascular volume depletion in severe hyponatremia. *Clin Biochem* 48(10-11):640-645.
39. Wuttke A, Dixit KC, Szinnai GG, Werth SC, Haagen U, Christ-Crain M, Morgenthaler NG, Brabant G (2013) Copeptin as a marker for arginine-vasopressin/antidiuretic hormone secretion in the diagnosis of paraneoplastic syndrome of inappropriate ADH secretion. *Endocr* 44:744-749.
40. Fenske WK, Christ-Crain M, Hörning A, Simet J, Szinnai G, Fassnacht M, Rutishauser J, Bichet DG, Störk S, Allolio B (2014) A copeptin-based classification of the osmoregulatory defects in the syndrome of inappropriate antidiuresis. *J Am Soc Nephrol* 25(10):2376-2383.
41. Nigro N, Winzeler B, Suter-Widmer I, Schuetz P, Arici B, Bally M, Blum CA, Nickel CH, Bingisser R, Bock A, Huber A, Müller B, Christ-Crain M (2017) Evaluation of copeptin and commonly used laboratory parameters for the differential diagnosis of profound hyponatraemia in hospitalized patients: 'The Co-MED Study'. *Clin Endocrinol* 86: 456-462.
42. Fenske W, Sandner B, Christ-Crain M (2016) A copeptin-based classification of the osmoregulatory defects in the syndrome of inappropriate antidiuresis. *Best Pract Res Clin Endocrinol Metab* 30(2):219-233.
43. Tuli G, Tessaris D, Einaudi S, Matarazzo P, De Sanctis L (2018) Copeptin role in polyuria-polydipsia syndrome differential diagnosis and reference range in paediatric age. *Clin Endocrinol (Oxf)* 88(6):873-879.
44. Fenske W, Quinkler M, Lorenz D, Zopf K, Haagen U, Papassotiriou J, Pfeiffer AF, Fassnacht M, Störk S, Allolio B (2011) Copeptin in the differential diagnosis of the polydipsia-polyuria syndrome. Revisiting the direct and indirect water deprivation tests. *J Clin Endocrinol Metab* 96(5):1506-1515.
45. Timper K, Fenske W, Kühn F, Frech N, Arici B, Rutishauser J, Kopp P, Allolio B, Stettler C, Müller B, Katan M, Christ-Crain M (2015) Diagnostic accuracy of copeptin in the differential diagnosis of the polyuria-polydipsia syndrome: a prospective multicenter study. *J Clin Endocrinol Metab* 100(6):2268-2274.
46. Timper K, Fenske WK, Katan M, Kühn F, Arici B, Schütz P, Frech N, Rutishauser J, Kopp P, Stettler C, Müller B, Christ-Crain M (2014) Copeptin in the diagnosis and differential diagnosis of diabetes insipidus – the 'Cosip-Study'. *Exp Clin Endocrinol Diabetes*. [https:// doi: 10.1055/s-0034-1372046](https://doi.org/10.1055/s-0034-1372046)
47. Winzeler B, Zweifel C, Nigro N, Arici B, Bally M, Schuetz P, Blum CA, Kelly C, Berkmann S, Huber A, Gentili F, Zadeh G, Landolt H, Mariani L, Müller B, Christ-Crain M (2015) Postoperative Copeptin Concentration Predicts Diabetes Insipidus After Pituitary Surgery. *J Clin Endocrinol Metab* 100(6):2275-2282.
48. M. de Fost, SM. Oussada, GE. Linthorst, MJ. Serlie, MR. Soeters, JH. De Vries, PH. Bisschop, E. Fliers (2015) The water deprivation test and a potential role for the arginine vasopressin precursor copeptin to differentiate diabetes insipidus from primary polydipsia. *Endocr Conn* 4:86-91.

49. Fenske W, Refardt J, Chifu I, Schnyder I, Winzeler B, Drummond J, Ribeiro-Oliveira A Jr, Drescher T, Bilz S, Vogt DR, Malzahn U, Kroiss M, Christ E, Henzen C, Fischli S, Tönjes A, Mueller B, Schopohl J, Flitsch J, Brabant G, Fassnacht M, Christ-Crain M (2018) A Copeptin-Based Approach in the Diagnosis of Diabetes Insipidus. *N Engl J Med* 379(5):428-439.
50. Winzeler B, Cesana-Nigro N, Refardt J, Vogt DR, Imber C, Morin B, Popovic M, Steinmetz M, Sailer CO, Szinnai G, Chifu I, Fassnacht M, Christ-Crain M (2019) Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study. *Lancet* 394(10198):587-595
49. Du JM, Sang G, Jiang CM, He XJ, Han Y (2013) Relationship between 288 plasma copeptin levels and complications of community-acquired pneumonia in preschool children. *Peptides* 45:61-65.
50. Wrotek A, Jackowska T, Pawlik K (2015) Sodium and Copeptin Levels in Children with Community Acquired Pneumonia. *Adv Exp Med Biol* 835:31-36.
51. Stöcklin B, Fouzas S, Schillinger P, Cayir S, Skendaj R, Ramser M, Weber P, Wellmann S (2015) Copeptin as a Serum Biomarker of Febrile Seizures. *PLoS One*. [https://doi: 10.1371/journal.pone.0124663](https://doi.org/10.1371/journal.pone.0124663)
52. Mastropietro CW, Mahan M, Valentine KM, Clark JA, Hines PC, Walters HL 3rd, Delius RE, Sarnaik AP, Rossi NF (2012) Copeptin as a marker of relative arginine vasopressin deficiency after pediatric cardiac surgery. *Intensive Care Med*. 38(12):2047-2054.
53. Lin C, Wang N, Shen ZP, Zhao ZY (2013) Plasma copeptin concentration and outcome after pediatric traumatic brain injury. *Peptides* 42:43-47.
54. Nalbantoğlu B, Yazıcı CM, Nalbantoğlu A, Güzel S, Topçu B, Güzel EÇ, Donma MM, Özdilek B, Mintaş NE (2013) Copeptin as a novel biomarker in nocturnal enuresis. *Urology* 82(5):1120-1123.
55. Coelho R, Levandowski ML, Mansur RB, da Cunha GR, Asevedo E, Zugman A, Salum GA, Gadelha A, Pan PM, Rizzo LB, Manfro G, Mari JJ, Rohde LA, Miguel EC, Bressan RA, Brietzke E, Grassi-Oliveira R (2016) Serum copeptin in children exposed to maltreatment. *Psychiatry Clin Neurosci* 70(10):434-441.
56. Lee JH, Chan YH, Lai OF, Puthuchery J (2013) Vasopressin and copeptin levels in children with sepsis and septic shock. *Intensive Care Med* 39(4):747-753.
57. Schiel R, Perenthaler TJ, Steveling A, Stein G (2016) Plasma copeptin in children and adolescents with type 1 diabetes mellitus in comparison to healthy controls. *Diabetes Res Clin Pract* 118:156-161.
58. Zhao J, Du S, Yang J, Lin J, Tang C, Du J, Jin H (2014) Usefulness of Plasma Copeptin as a Biomarker to Predict the Therapeutic Effectiveness of Metoprolol for Postural Tachycardia Syndrome in Children. *Am J Cardiol* 114(4):601-605
59. Tenderenda-Banasiuk E, Wasilewska A, Filonowicz R, Jakubowska U, Waszkiewicz-Stojda M (2014) Serum copeptin levels in adolescents with primary hypertension. *Pediatr Nephrol* 29(3):423-429.
60. Rothermel J, Kulle A, Holterhus PM, Toschke C, Lass N, Reinehr T (2016) Copeptin in obese children and adolescents: relationships to body mass index, cortisol and gender. *Clin Endocrinol (Oxf)* 85(6):868-873.
61. Cole TJ, Lobstein T (2012) Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr Obes* 7(4):284-294.

62. Refardt J, Winzeler B, Christ-Crain M (2018) Copeptin and its role in the diagnosis 317 of diabetes insipidus and the syndrome of inappropriate antidiuresis. *Clin Endocrinol (Oxf)* 91(1):22-32
63. Fenske W, Refardt J, Chifu I, Schnyder I, Winzeler B, Drummond J, Ribeiro-Oliveira A Jr, Drescher T, Bilz S, Vogt DR, Malzahn U, Kroiss M, Christ E, Henzen C, Fischli S, Tönjes A, Mueller B, Schopohl J, Flitsch J, Brabant G, Fassnacht M, Christ-Crain M (2018) A Copeptin-Based Approach in the Diagnosis of Diabetes Insipidus. *N Engl J Med* 379 (5):428-439.
64. Enhörning S, Struck J, Wirfalt E, Hedblad B, Morgenthaler NG, Melander O (2011) Plasma Copeptin, a unifying factor behind the metabolic syndrome. *J Clin Endocrinol Metab* 96(7):E1065-1072.
65. Enhörning S, Bankir L, Bouby N, Struck J, Hedblad B, Persson M, Morgenthaler NG, Nilsson PM, Melander O (2013) Copeptin, a marker of vasopressin, in abdominal obesity, diabetes and microalbuminuria: the prospective Malmö Diet and Cancer Study cardiovascular cohort. *Int J Obes (Lond)* 37(4):598-603.
66. Enhörning S, Sjögren M, Hedblad B, Nilsson PM, Struck J, Melander O (2016) Genetic vasopressin 1b receptor variance in overweight and diabetes mellitus. *Eur J Endocrinol* 174(1):69-75.
67. Nakamura K, Velho G, Bouby N (2017) Vasopressin and metabolic disorders: translation from experimental models to clinical use. *J Intern Med* 282(4):298-309.
68. Taskin MI, Bulbul E, Adali E, Hismiogulları AA, Inceboz U (2015) Circulating levels of obestatin and copeptin in obese and nonobese women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol* 189:19-23.
69. Christ-Crain M (2019) Vasopressin and copeptin in health and disease. *Rev Endocr Metab Dis* 20: 283-294

Abbreviations

ADH: anti-diuretic hormone

AVP: arginin-vasopressin

BMI: body mass index

CDI: central diabetes insipidus

C/RSW: cerebral renal salt wasting syndrome

NDI: nephrogenic diabetes insipidus

SIADH: syndrome of inappropriate anti-diuretic hormone secretion

WDT: water deprivation test

“What is Known”

- Copeptin use as a diagnostic tool in AVP-related disorders, such as diabetes insipidus or syndrome of inappropriate secretion of antidiuretic hormone, is well established in adults
- In pediatric age few studies are available but the preliminary data, including our previous study, seems to be promising.

“What is New”

- In this study we represent the distribution of copeptin levels in a pediatric cohort and show the significant influence of fluid ingestion on its plasma levels.
- Also BMI seems to be a significant variable on copeptin levels and may be used as an obesity marker in pediatric age