Use of copeptin in the diagnosis of polyuria-polydipsia syndrome

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Bettina Winzeler and colleagues[1] investigated whether copeptin measurement after an arginine stimulation test could be a tool to unravel the differential diagnosis of polyuria-polydipsia syndrome. We caution that the high sensitivity and specificity of the test could have partly been due to the selection of included patients.

When evaluating a case of polyuria-polydipsia, physicians start with evaluating the medical history. New-onset polyuria after pituitary surgery or a history with familial central diabetes insipidus makes a clear diagnosis of central diabetes insipidus without the need for additional testing. Including such patients in a cohort to develop a new diagnostic test can result in overestimation of sensitivity and specificity. In the authors' study,[1] 19 (20%) of 96 patients had a history of pituitary surgery, and six (6%) patients had familial central diabetes insipidus.

In clinical practice, the true challenge begins after elimination of these patients, leaving a cohort in which only a few will have a (partial) central disorder, versus the more common primary polydipsia and nephrogenic diabetes insipidus. The authors[1] excluded individuals with nephrogenic diabetes insipidus because they assumed that this condition can be diagnosed when the patient has a copeptin concentration of 21·4 pmol/L or higher.[1,2]

However, in our experience, some patients with partial nephrogenic diabetes insipidus have copeptin concentrations lower than 21·4 pmol/L.[3] Furthermore, it has been suggested that copeptin can be this high merely due to impaired kidney function.[4]

These considerations raise the questions of whether the test is already up for the intended challenge, or whether these promising results should first be confirmed in a cohort that better represents the clinical situation.

We declare no competing interests.

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1 Winzeler B, Cesana-Nigro N, Refardt J, et al. Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study. *Lancet* 2019; **394:** 587–95.
2 Timper K, Fenske W, Kuhn F, et al. Diagnostic accuracy of copeptin in the differential diagnosis of the polyuria-polydipsia syndrome: a prospective multicenter study. *J Clin Endocrinol Metab* 2015; **100:** 2268–74.
3 Zittema D, Boertien WE, van Beek AP, et al. Vasopressin, copeptin, and renal concentrating capacity in patients with autosomal dominant polycystic kidney disease without renal impairment. *Clin J Am Soc Nephrol* 2012; **7:** 906–13.
4 Roussel R, Fezeu L, Marre M, et al. Comparison between copeptin and vasopressin in a population from the community and in people with chronic kidney disease. *J Clin Endocrinol Metab* 2014; **99:** 4656–63.

Authors' reply

We read the comments about our article about arginine-stimulated copeptin measurements in the diagnosis of diabetes insipidus[1] with interest.

When we first designed the study, it was unclear whether arginine would stimulate copeptin at all. In the absence of a reliable diagnostic reference standard, the decision to include patients with an evident diagnosis of central diabetes insipidus was therefore an essential measure to prove the concept.

As implied by Judith E Heida and colleagues, patients with an evident diagnosis or suggestive medical history often present with a complete form of diabetes insipidus. We agree that the most challenging question in clinical practice is the discrimination between partial diabetes insipidus and primary polydipsia. Reassuringly, for this subgroup, the diagnostic accuracy of arginine-stimulated copeptin measurements was high, with an area under the curve of 0·91 using a cutoff of 3·8 pmol/L at 60 min.

We did not include patients with nephrogenic diabetes insipidus because we believe these patients can easily be diagnosed by a random copeptin measurement and do not need dynamic testing.[2] We thank Heida and colleagues for sharing their experience of single cases with partial nephrogenic diabetes insipidus and copeptin concentrations lower than 21·4 pmol/L, which is, indeed, consistent with our experience in clinical practice. The cutoff of 21·4 pmol/L was based on a small number of patients[3] and might have to be adjusted for patients with partial forms of nephrogenic diabetes insipidus in the future.

Nevertheless, the differentiation between these patients and patients with primary polydipsia who typically have very low or suppressed random (without previous fluid restriction) copeptin concentrations should still be straightforward.

The elimination of copeptin has not been clarified in detail, but a renal clearance has been suggested. The study[4] cited by Heida and colleagues showed an inverse correlation of plasma copeptin concentrations with the glomerular filtration rate in patients with impaired kidney function (stage 3 or higher).

When evaluating patients with polyuria-polydipsia syndrome, the first step should always include routine biochemistry to exclude secondary polyuria and assessment of electrolytes and kidney function. In case of moderately or severely impaired kidney function, copeptin concentrations should be interpreted with caution, independently of the diagnostic test used (ie, random, hypertonic saline-stimulated or arginine-stimulated copeptin measurement).

For the rare condition of suspected central diabetes insipidus in a patient with severely impaired kidney function, no data and specific copeptin cutoffs are yet available.


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