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Plasma copeptin in children and adolescents with type 1 diabetes mellitus in comparison to healthy controls

Ralf Schiel [a,*], *Thomas Johannes Perenthaler* [a], *Antje Steveling* [b], *Günter Stein* [c]

[a] *MEDIGREIF-Inselklinik Heringsdorf GmbH, Department of Diabetes and Metabolic Diseases, Ostseebad Heringsdorf, Germany*
[b] *Ernst-Moritz-Arndt-University, School of Medicine, Internal Medicine A, Greifswald, Germany*
[c] *Friedrich-Schiller-University, School of Medicine, Internal Medicine, Nephrology, Jena, Germany*

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ABSTRACT

In a cohort of children and adolescents with type 1 diabetes mellitus the trial tested the hypothesis that copeptin levels are associated with kidney function, biometrical data and quality of diabetes control.

Patients and methods: A total of 141 subjects were recruited to participate in the trial: 80 patients with type 1 diabetes (13.0 ± 3.4 years, HbA1c 7.85 ± 1.42%) and 61 healthy controls (12.4 ± 2.8 years). Clinical and socio-economic data were assessed. A sandwich immunoassay (B.R.A.H.M.S. GmbH/Thermo Fisher Scientific, Hennigsdorf/Berlin, Germany) was used for measuring plasma copeptin levels.

Results: The mean concentration of copeptin in the diabetic patients was 4.75 ± 3.46 pmol/l. There was a strong inverse correlation between copeptin and GFR ($r = -0.86$, $p = 0.021$), as well as with total cholesterol ($r = -0.23$, $p = 0.041$), LDL-cholesterol ($r = -0.24$, $p = 0.036$), but not with serum creatinine, albuminuria, HbA1c, blood glucose, MAGE, CRP, systolic or diastolic blood pressure or age, diabetes duration, weight, height and BMI. Comparing patients with a diabetes duration of ⩾7 years ($n = 45$) with those with a diabetes duration <7 years ($n = 35$), patients with a longer duration of diabetes had higher copeptin levels (5.24 ± 2.26 vs 4.13 ± 2.86, $p = 0.045$). Performing multivariate analyses only GFR could be identified as a parameter associated with copeptin (R-square = 0.05, $\beta = -0.23$, $p = 0.032$). In the healthy controls mean copeptin concentration was 5.56 ± 3.15 pmol/l. The copeptin concentration and GFR were inversely correlated as well ($r = -0.61$, $p = 0.034$). However, other correlation and multivariate analyses revealed no further significant results. Comparing patients with type 1 diabetes mellitus with the healthy controls, the diabetes patients revealed no significant difference with respect to copeptin ($p = 0.24$), serum creatinine (49.8 ± 11.9 vs 50.4 ± 11.0 μmol/l, $p = 0.53$) or GFR (102.4 ± 23.3 vs 104.5 ± 19.1 ml/min, $p = 0.47$). On the other hand, patients with type 1 diabetes had lower concentrations of CRP (1.66 ± 3.91 vs 3.21 ± 3.04 μg/ml, $p = 0{,}013$), triglycerides (0.88 ± 0.53 vs 1.13 ± 0.60 mmol/l, $p = 0.010$), and a lower ratio of LDL-/HLD-cholesterol (1.73 ± 0.69 vs 2.32 ± 0.80, $p < 0.001$), as well as lower body weight (51.3 ± 18.0 vs 60.3 ± 15.7 kg, $p = 0.002$) and BMI (19.7 ± 3.8 vs 23.2 ± 2.9 kg/m^2, $p < 0.001$). In contrast to the controls, the diabetes patients had higher blood glucose levels at the time of examination (8.2 ± 3.8 vs 4.7 ± 0.5 mmol/l, $p < 0.001$), higher HDL-cholesterol

* *Corresponding author at:* MEDIGREIF-Inselklinik Heringsdorf GmbH, Department of Diabetes and Metabolic Diseases, Setheweg 11, D-17424 Ostseebad Heringsdorf, Germany. Fax: +49 38378/780555.
E-mail address: r.schiel@medigreif-inselklinikum.de (R. Schiel).
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levels (1.59 ± 0.34 vs 1.26 ± 0.24 mmol/l, $p < 0.001$), as well as higher education and higher educational levels of the mothers.

Conclusions: The present trial revealed a clear association between GFR and copeptin in children and adolescents with type 1 diabetes mellitus. Hence, copeptin can be considered as a marker of renal function.

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1. Introduction

It has been shown in both experimental and human studies that the arginine vasopressin stress-adaption system plays an important role in the physiology of volume homeostasis [13]. This stress-adaption system is also consequential in heart failure and kidney dysfunction [14,24,4]. Additionally, activation of the vasopressin system has been documented in patients with type 2 diabetes mellitus. In cross-sectional epidemiological studies the concentration of plasma copeptin has been identified as a surrogate marker for vasopressin. In these studies higher plasma copeptin concentrations were associated with higher albuminuria and a decrease in glomerular filtration rate (GFR) [14,24,4]. Recent findings also indicate an association between vasopressin, its surrogate marker copeptin, and insulin resistance [19,7]. In patients with poorly controlled diabetes mellitus vasopressin is markedly elevated [25]. In healthy subjects vasopressin infusion leads to increased blood glucose levels [20]. In summary, these data suggest a strong association between the human stress-adaption system, vasopressin, copeptin, heart and kidney function and blood glucose regulation.

As of today, all investigations have focused only on adult patients and healthy controls. Using a highly sensitive and validated assay to measure copeptin concentrations in plasma, we tested the hypothesis that copeptin levels are associated with kidney function, biometrical data and quality of diabetes control in children and adolescents with type 1 diabetes mellitus. The results were compared to healthy controls of the same age-range.

2. Patients and methods

Patients were included in the trial if they had type 1 diabetes mellitus [2], were admitted to an in–house rehabilitation in a specialized hospital (MEDIGREIF Inselklinik Heringsdorf GmbH, Ostseebad Heringsdorf, Germany) between 01/04/2014 and 01/04/2015, and the patients along with their parents gave their written consent to participate in the study. Clinical and socio-economic data assessed included age, sex, educational level (primary school, secondary school), familial situation (i.e. living with both parents, living with one parent alone), educational level of the parents, duration of diabetes, kind and strategy of diabetes therapy, insulin dosage, frequency of blood-glucose monitoring, number of hypoglycaemia (blood glucose < 2.7 mmol/l and presence of typical symptoms or blood-glucose <2.2 mmol/l without symptoms [17]) within the preceding 3 months, prevalence of retinopathy, measurement of height (barefoot) and body weight (with light clothes), calculation of body-mass index (BMI) according to the formula BMI = kg/m^2 (Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter [AGA], 2004 [3]) and measurement of blood pressure (sitting position after 10 min resting) according to the guidelines of the World Health Organization (WHO) [9].

For comparison of copeptin levels, blood samples were taken from healthy age-matched children and adolescents attending a mother–child-rehabilitation [15] during the same time period in a specialized hospital too (Mütter-Gesundheit Usedom e.V., part of the MEDIGREIF Inselklinik Heringsdorf GmbH, Ostseebad Heringsdorf, Germany). Also in this group subjects along with their parents gave their written consent to participate in the trial. In these patients, comparable to the cohort of patients with diabetes mellitus, clinical and socio-economic parameters (age, sex, educational levels of patients and parents, familial situation, height, weight, BMI, blood pressure) were assessed.

A total of 141 subjects were recruited (80 patients with type 1 diabetes, 61 controls) to participate in the trial.

3. Laboratory parameters

In patients with diabetes mellitus, blood-glucose (glucose-oxidase-method, Speedy, Müller Gerätebau GmbH, Saalfeld, Germany) and HbA1c (DCA2000®-method, Bayer Diagnostics, Leverkusen, Germany, following DCCT-standard [HbA1c/mean normal] × mean according to the DCCT-standard [22]) were measured in blood samples derived from finger pricking. Additionally venous blood samples were analyzed (Laborgemeinschaft IMD, Prof. Dr. med. G. Menzel, Pappelallee 1, 17489 Greifswald, Germany) from all patients with diabetes and the controls for lipids (cholesterol [enzymatically], LDL-cholesterol [ezymatically], triglycerides [enzymatically]), creatinine (Jaffé-method) and CRP (ultrasensitive KRYPTOR assay, B.R.A.H.M.S. GmbH/Thermo Fisher Scientific, Hennigsdorf/Berlin, Germany). In the cohort of patients with diabetes mellitus microalbuminuria was measured using first morning urine (enzymatically) according to the recommendations of the German Diabetes Association [10]. Mean amplitude of blood-glucose excursion (MAGE) was calculated as mean out of 4 blood-glucose values per day (pre breakfast, pre lunch, pre dinner, at bedtime) assessed over a period of 3 days immediately after admission to hospital.

Of the children and adolescents with type 1 diabetes mellitus one girl (14 years) used as co-medication L-Thyroxine (due to a Hashimoto's thyroiditis with hypothyroidism). Of the healthy controls 2 patients (one girl, 16 years, one boy,

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