Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

**Might Podocyturia Be an Early Marker for Diabetic Nephropathy in Males**

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**MON-680**

Renal involvement can develop before detection of microalbuminuria in type 2 diabetes. There is an interest in finding biomarkers to detect diabetic nephropathy (DN) earlier and identify progression risk. Podocyturia emerge as a marker for early kidney damage however standardization problems hamper its widespread use. We aimed to investigate the value of podocyturia for the detection of early DN. Herein we report our preliminary results.

Our study population was composed of three type 2 diabetic patient groups and a healthy control group. Diabetic groups were defined as follows; group 1: patients without microalbuminuria who had HbA1c <7%; group 2: patients without microalbuminuria who had HbA1c >8.5%; group 3: patients with diabetic retinopathy who had proteinuria >1g/day and/or microalbuminuria >300 mg/day and group 4: healthy volunteers without any known disease. Patients with glomerular filtration rate (GFR) below 30 ml/min were excluded.

GFR was calculated using the abbreviated MDRD formula. Microalbuminuria was measured in 24 hour urine. Number of podocytes in the urine was determined by immunocytochemical staining of podocalyxin. Due to the known expression of podocalyxin in the female genital tract, only males were included. Statistical analyses were carried out using Statistical Package for the Social Sciences version (SPSS) 24.0 and statistical significance was set as p<0.05.

We examined a total of 119 patients (mean age 57.35 ± 12.75 yrs.). Patient distribution in each group was as follows; group 1: 24(20%); group 2: 26(22%); group 3: 24(20%) and group 4: 45(38%) patients. There was no significant difference in mean age (p=0.582) and duration of diabetes (p=0.517) between the diabetic groups. The mean GFR was significantly lower in group 3 than in group 1 and 2 (p<0.001, p:0.007; respectively). The median podocyte measurement in urine was 0.25 (IQR: 0-2.68) podx/ml in group 1; 0.37 (IQR: 0-0.12) podx/ml in group 2; 1.37 (IQR: 0.56-5.18) podx/ml in group 3; 0.0 (IQR: 0-0.75) podx/ml in group 4. The mean number of podocytes in urine was significantly different between the 4 groups (p=0.001). In posthoc analysis with Bonferroni correction, the mean podocytes measurement was significantly higher in group 3 than in group 1 and 4 (p=0.033, p=0.001; respectively).

According to our preliminary results; podocyturia assessed by podocalyxin immunostaining does not seem to be increased in male diabetic patients without proteinuria. Further studies on larger patient groups and using different podocyte markers might clarify the value of podocyturia as an early marker of DN.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS I

**Pyridoxal 5'-Phosphate Cerebrospinal Fluid Abnormalities in Hypophosphatasia Before and After Enzyme Replacement Therapy**

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**SAT-382**

**Introduction:** Hypophosphatasia (HPP) is an inborn error of metabolism due to deficiency of tissue non-specific alkaline phosphatase (TNSALP), characterized by a wide range of metabolic and skeletal abnormalities.
of skeletal and neurological symptoms. Little is known about the mechanism of neurologic involvement, but it may result from inefficient hydrolysis of vitamin B6 (pyridoxal 5′-phosphate, PLP), which is involved in neurotransmitter synthesis and is markedly elevated in HPP. However, it remains unknown what PLP levels are in the cerebrospinal fluid (CSF) of patients with HPP. We report two cases: (1) one with pre- and post-treatment CSF PLP levels and (2) one with pre-treatment CSF PLP and neurotransmitter levels.

Case 1: A 30-year-old man with extensive fracture history presented with seizure-like activity. Laboratory evaluation while on no B6 supplementation was notable for low ALP (14 U/L, ref: 40-150), high plasma PLP (362 mcg/L, ref: 5-50), and high CSF PLP (16 mcg/L), with a low CSF/plasma PLP ratio (0.04, ref: 0.1-0.7[1]). Genetic testing showed a pathogenic variant of TNSALP (Het c.1133A>T, p.Asp378Val, rs 121918008). After initiation of enzyme replacement therapy (ERT), her plasma and CSF PLP levels normalized to 6.3 and 1.4 mcg/L, respectively, with a ratio of 0.23. She reported improvement in energy level and seizure-like activity after several months of ERT.

Case 2: A 34-year-old man with no history of skeletal pathology presented with diffuse musculoskeletal pain, weakness, and loss of sensory function attributed to generalized peripheral neuropathy. Laboratory evaluation while on no B6 supplementation was notable for low ALP (23 U/L), high plasma PLP (496 mcg/L), and high CSF PLP (17 mcg/L) with a low CSF/plasma PLP ratio (0.03). CSF neurotransmitter levels were also low, including 5-hydroxyindoleacetic acid (40 nmol/L, ref: 67-140) and homovanillic acid (115 nmol/L, ref: 5-50), and high CSF PLP (29 mg/dL, n 0.50 to 1.60), elevated insulin (90.1 mU/L, n 3.0 to 19.0), suppressed beta-hydroxybutyrate (0.16 mmol/L, n 0.02 to 0.27), and suppressed free fatty acids (0.27 mmol/L, n 0.50 to 1.60). C-peptide level resulted undetectable (<0.1 ng/mL, n 0.8 to 3.5) raising suspicion for exogenous insulin administration. History revealed an older brother with type 1 diabetes mellitus treated with insulin glargine and lispro. Only one caregiver was present in the hospital, who denied knowledge of exogenous insulin administration. Hypoglycemia persisted despite placement of a continuous 1:1 sitter, high-dose intravenous glucose (glucose infusion rate up to 21.6 mg/kg/min), and treatment with diazoxide. A repeat insulin measurement with the Roche Diagnostics assay specific for human insulin was performed on a critical sample and resulted elevated (13.9 uIU/L, n 2.6 to 24.9), suggestive of endogenous insulin. However, an extensive study of commercial human insulin immunoassays by Heurtault et al., including the Roche Diagnostics assay, has demonstrated cross-reactivity with insulin analogues and their metabolites [1]. Given persistent concern for exogenous insulin administration, the patient’s caregiver was asked to leave the bedside for an extended period of time which resulted in normoglycemia. Diazoxide and dextrose-containing IV fluids were discontinued. Patient maintained normoglycemia for the remainder of the admission and was discharged in the care of child protective services.

Conclusions: Cross-reactivity exists in human insulin immunoassays with insulin analogues and their metabolites complicating the determination of endogenous versus exogenous insulin as the cause of hyperinsulinemic hypoglycemia. It is important to know the cross-reactivity of the assay used if a diagnosis of surreptitious insulin administration is suspected. Separation of patient and possible perpetrators and involvement of child protective services is essential in suspected cases of exogenous insulin administration. Evaluation in cases where self-injection of insulin is suspected may be more difficult to decipher, and inclusion of c-peptide measurement at the time of hypoglycemia is critical.

Reference: [1] Heurtault B, Reix N, Meyer N, et al. Extensive study of human insulin immunoassays: promises and pitfalls for insulin analogue detection and quantification. Clin Chem Lab Med. 2014; 52:355-362.