Streszczenie w języku angielskim

Title: Assessment of tryptophan metabolism via the kynurenine pathway in patients with type 1 diabetes.

Introduction: The kynurenine pathway (KP) is the main route of tryptophan (TRP) – an exogenous amino acid- metabolism. It leads to the production of many bioactive compounds including kynurenine (KYN), kynurenic acid (KYNA), 3-hydroxykynurenine (3-HKYN), anthranilic acid (AA), 3-hydroxyanthranilic acid (3-HAA), and nicotinamide adenine dinucleotide (NAD+). Significantly higher concentrations of 3-HKYN were reported in patients with diabetic retinopathy, and it has also been shown to be associated with an increased risk of acute coronary incidents. AA, in contrast, is considered a metabolite with antihyperglycemic properties. Literature data indicate that TRP metabolism via KP is impaired in obesity, type 2 diabetes, atherosclerosis and heart failure. However, studies considering changes in TRP metabolism in type 1 diabetes (T1D) are scarce.

Aim: The purpose of the present dissertation was to evaluate alterations in TRP metabolism via KP in patients with T1D compared to healthy subjects and to assess their association with metabolic control parameters.

Study group: Anthropometric parameters, serum levels of CRP, glucose, creatinine and lipids were assessed in all participants. Additionally, in the T1D group, HbA1c and pancreatic endocrine reserve using the glucagon test were determined, as well as the urine albumin/creatinine ratio. Concentrations of TRP, KYN, 3-HKYN, and AA in serum and urine were estimated by high-performance liquid chromatography (HPLC). The results of the urine assays were normalised against urinary creatinine concentration determined by ELISA.

Methods: In all participants, anthropometric parameters, HbA1c (in the T1D group), serum levels of CRP, glucose, creatinine and lipids were assessed. Serum and urine concentrations of TRP, KYN, 3-HKYN, and AA were estimated by high-performance liquid chromatography (HPLC).

Results: The serum of T1D patients showed an increase in TRP, KYN and 3-HKYN concentrations ($p<0.0001$; $p=0.003$; $p<0.0002$) and a decrease in AA concentrations ($p=0.003$), KYN/TRP, and AA/KYN ratio values ($p=0.005$; $p=0.041$) compared to the control group. In the

urine of T1D patients, an approximately 10-fold increase in KYN (p<0.0001) and a decrease in 3-HKYN (p=0.0055) and AA concentrations (p<0.0001) were observed. Participants with inadequately controlled diabetes (HbA1c>7%; n=33) showed an increase in serum KYN concentrations (p=0.011) and a decrease in urinary TRP concentrations (p=0.048) in comparison with those with HbA1c ≤7%. Positive correlations were found between HbA1c, diabetes duration and KYN concentrations (R=0.422, p=0.002; R=0.343, p=0.015) and between AA concentrations and pancreatic endocrine reserve (R=0.72, p=0.005). Multivariable logistic regression analysis revealed the association between KYN concentrations and HbA1C, HDL concentrations and diabetes duration (B=0.178, 95% CI: 0.03;0.326; B=-0.014, 95% CI: -0.027;-0.002; B=0.043, 95% CI: 0.015;0.71, respectively), while BMI and HDL were associated with TRP concentrations (B = 0.937; 95% CI, 0.038–1.836; B = –0.234;95% CI, –0.423 to –0.046, respectively). BMI, age, and GFR were added as potential confounders.

Conclusions: Poor metabolic control of diabetes is associated with impaired TRP metabolism in T1D patients, especially observed at the first step of KP. A shift in TRP metabolism toward the increased formation of 3-HKYN with a concomitant decrease in AA concentrations, may be associated with a greater risk of developing chronic diabetic complications in individuals with T1D. A thorough understanding of the mechanisms underlying the abnormalities described above offers opportunities to develop new therapeutic strategies in T1D.

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