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RESEARCH ARTICLE

Preserved C-peptide secretion in patients with type 1 diabetes and incipient chronic complications is associated with lower serum resistin and higher uric acid levels

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Abstract

Background and aims Previous studies suggested that long-term perseverance of beta-cell function in patients with type 1 diabetes (T1DM) is associated with lower incidence of microvascular complications. The objective of this study was to evaluate preserved C-peptide secretion in patients with T1DM without overt chronic complications and to explore associations with resistin and uric acid as biomarkers of microvascular complication pathogenesis.

Materials and methods We assessed residual beta-cell function in 164 T1DM patients (male/female = 91/73; age/diabetes duration range = 18–70/1–30 years) using an ultrasensitive C-peptide ELISA assay with detection limit of 2.5 pmol/L and total coefficient of variation (CV) 5,8% (Mercodia, Sweden). Serum level of uric acid was measured by enzymatic method (AU680, Beckman Coulter, USA) while resistin concentration was determined by the ELISA assay (Biovendor, Czech Republic).

Results C-peptide secretors had shorter diabetes duration (5.1 vs. 16 years; $p < 0{,}001$), lower resistin (4.53 vs. 4.93 mg/mL $p = 0.045$), and higher uric acid (259 vs 238 μmol/L, $p = 0.048$) level than T1DM patients with no detectable C-peptide levels, while no differences in routine anthropometric and laboratory variables, including HbA1c, were observed. Although the proportion of C-peptide secretors significantly decreased across categories of diabetes duration (70%, 38%, 17% and 15% for <5, 5–10, 10–20 and 20–30 years of duration, respectively; $p < 0{,}001$), detectable C-peptide was found in 5/23 T1DM patients who were diagnosed with T1DM more than 20 years ago.

Conclusion The results of our study revealed that patients with detectable C-peptide had lower resistin and higher uric acid level compared to patients with undetectable C-peptide.

Keywords Type 1 diabetes · Serum resistin · C-peptide · Uric acid

Introduction

Since the half-life of C-peptide is about ten times longer than of insulin, C-peptide is considered to be a reliable substitute marker of endogenous insulin production [1, 2]. Although type 1 diabetes (T1DM) is a T cell mediated autoimmune disease against pancreatic islet beta cells requiring lifelong insulin treatment because of insulinopenia, some patients with T1DM maintained minimal levels of C-peptide and have a lower risk for development of microvascular complications and with favorable metabolic and clinical outcomes particularly in patients with stimulated C-peptide over 0.2 nmol/L [3, 4]. In addition, in T1DM patients, infusions of synthetic C-peptide slow the progression of microvascular complications [5, 6]. However, C-peptide level is significantly decreased in T1DM patients after five years from diagnosis and associated with factors like age at diagnosis, immune status and metabolic control [7, 8].

Several molecules involved in the signalling cascade of C-peptide are also involved in the regulation of different adipocytokines in adipose tissue [9, 10]. Adipose tissue secretes several adipokines, and the majority of them negatively

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affects insulin secretion and insulin resistance [11]. Besides other adipokines like adiponectin and leptin, the resistin only was found to be associated with T1DM. It may play a role in the process of inflammation and also in the pathophysiology of T1DM [12]. A positive association between C-peptide and leptin and resistin and a negative association between C-peptide and adiponectin were found in T1DM [13]. Resistin also positively correlates with atherosclerosis in T1DM while adiponectin negatively [14].

Uric acid is also involved in the function of the beta-cell and with insulin secretion measured with hyperglycaemic clamp test [15]. Besides, uric acid is also associated with the onset and progression of diabetic complications [16]. In patients with diabetes, serum uric acid values positively correlate with serum C-peptide values but only in those with diabetes duration less than five years and without micro and macrovascular complications [17].

The objective of this study was to evaluate preserved C-peptide secretion in patients with T1DM without overt chronic complications and to explore associations with resistin and uric acid as biomarkers of microvascular complication pathogenesis.

Subjects, materials and methods

We assessed residual beta-cell function in 164 T1DM patients referred to tertiary care specialist diabetes clinic. T1DM was defined according to autoantibodies positivity, age of diagnosis (below 35 years), and insulin treatment initiated within one year of diagnosis. The study included patients with age of 18 to 65 years, with a duration of diabetes of 1 up to 30 years, and without microvascular complications or with earlier stages of microvascular complications (non-proliferative diabetic retinopathy, the second stage of chronic kidney disease (estimated glomerular filtration rate (eGFR) 60–90 ml/min calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, urinary albumin excretion rate (UAE) > 30 < 300 mg/24 h, the first degree of peripheral neuropathy without vegetative neuropathy), all complications stationary at least three months before entering the study.

Serum level of uric acid was measured by the enzymatic method (AU680, Beckman Coulter, USA) while resistin concentration was determined by the ELISA assay (Biovendor, Czech Republic). The C-peptide level was determined using an ultrasensitive C-peptide ELISA assay with a detection limit of 2.5 pmol/L and total coefficient of variation (CV) 5,8% (Mercodia, Sweden).

Data are expressed as means ± SD for normally distributed values, as median with range for non-normally distributed values, and percentage. Patients were divided into two groups according to detectable C-peptide levels. Differences between groups were examined, depending on the nature of the data, using parametric (t-test) or nonparametric tests (Mann-Whitney). Chi-square test was used to assess differences between categorical variables.

The study protocol complied with the Declaration of Helsinki as well as with local institutional guidelines and was approved by the local ethics committees.

Results

The characteristics of the study subjects are listed in Table 1. Mean/median values of majority metabolic parameters like BMI, LDL cholesterol, HDL cholesterol, triglycerides, serum creatinine, UAE, eGFR, as well as blood pressure were within the normal range for patients with diabetes. Fifty-seven (34.5%) T1DM patients had preserved beta-cell function determined with C-peptide levels detected with ultrasensitive assay (median = 47.8 (12.1–126.1) pmol/L). Clinical and metabolic characteristics of patients with and without detectable C-peptide are presented in Table 2. C-peptide secretors had shorter diabetes duration (median 5.1 (3–11) vs. 16 (8.3–21) years; $p < 0{,}001$), lower resistin (median = 4.53 (3.73–5.14) vs. 4.93 (4.24–6.59) mg/mL, $p = 0.045$), and higher uric acid (259 (220–301) vs 238 (199–282) μmol/L, $p = 0.048$) than T1DM patients with no detectable C-peptide levels, while no differences in routine anthropometric and laboratory variables, including HbA1c were observed ($p > 0.05$). We also explore the relationship between C-peptide secretion and duration of diabetes. Although the proportion of C-peptide

Table 1 Clinical and metabolic characteristics of all patients

Variable	Value
Age (years)	43 (18–65)
Sex (male/female)	91/73
Duration of diabetes (years)	11 (1–29)
Body mass index (kg/m^2)	24 (17–35)
HbA1c (%)	7.7 ± 1.65
Systolic blood pressure (mmHg)	125 (100–160)
Diastolic blood pressure (mmHg)	68 (48–91)
Total cholesterol (mmol/L)	5.1 ± 0.9
LDL cholesterol (mmol/L)	2.9 ± 0.7
HDL cholesterol (mmol/L)	1.6 ± 0.3
Triglycerides (mmol/L)	0.91 (0.4–4.1)
Serum creatinine (μmol/L)	71 ± 13
eGFR (mlmin^{-1}1.73 m^{-2})	101 ± 17
Urinary albumin excretion (mg/24 h)	6.2 (1.2–31.9)
C-peptide (pmol/L)	33.5 (0–534.3)
Resistin (ng/ml)	4.8 (1.9–10.6)
Uric acid (μmol/L)	245 (134–453)

eGFR, estimated glomerular filtration rate

Data are expressed as mean ± standard deviation or median (range)

Table 2 Clinical and metabolic characteristics of patients without and with detectable C-peptide levels

	without C-peptide ($n = 107$)	with C-peptide ($n = 57$)	P
Age (years)	46 (21–65)	41 (19–65)	0.66
Sex (male/female)	61/46	30/27	0.1
Duration of diabetes (years)	16 (2–29)	5 (1–29)	<0.001
Body mass index (kg/m^2)	25 (19–34)	24 (19–34)	0.2
Hemoglobin A1c (%)	7.6 ± 1.3	7.7 ± 1.8	0.6
SBP (mmHg)	125 (100–160)	123 (100–150)	0.5
DBP (mmHg)	69 (53–91)	65 (48–88)	0.1
Total cholesterol (mmol/L)	5.0 ± 0.9	5.25 ± 0.8	0.3
LDL cholesterol (mmol/L)	2.9 ± 0.7	3.0 ± 0.6	0.3
HDL cholesterol (mmol/L)	1.6 ± 0.4	1.6 ± 0.3	0.9
Triglycerides (mmol/L)	0.87 (0.4–2.2)	0.93 (0.4–2.8)	0.6
Serum creatinine (μmol/L)	71 ± 12	72 ± 13	0.6
eGFR (ml min^{-1} 1.73 m^{-2})	100 ± 16	102 ± 18	0.8
UAE (mg/24 h)	6.2 (1.2–29.8)	6.2 (1.6–31.9)	0.8
Resistin (ng/ml)	4.9 (2.7–9.2)	4.5 (2.0–8.3)	<0.05
Uric acid (μmol/L)	238 (140–358)	259 (148–446)	<0.05

SBP, systolic blood pressure; DBP, diastolic blood pressure; UAE, urinary albumin excretion rate

secretors significantly decreased across categories of diabetes duration (70%, 38%, 17% and 15% for <5, 5–10, 10–20 and 20–30 years of duration, respectively; $p < 0.001$), detectable C-peptide was found in 5/23 T1DM patients who were diagnosed with T1DM more than 20 years ago (Table 3).

Discussion

Previous studies documented that preserved C-peptide secretion in T1DM patients has clinical implications including lower risk for development of microvascular complications and that C-peptide modifies secretion of different adipocytokines in human adipose tissue [3, 4, 7, 10]. However, previous studies included patients with advanced chronic complications while we included patients with incipient chronic complications and without nephropathy. It is well known that adipokine serum levels are markedly elevated in chronic kidney disease [18]. In addition, the finding that younger patients have lower levels of C-peptide at diagnosis is well established, and in the present study we included mostly patients diagnosed in adulthood with duration of diabetes up to 30 years. One-third (34.5%) of our T1DM patients had preserved beta-cell function determined with C-peptide levels detected with ultrasensitive assay which is in line with previous studies [19]. Although the proportion of C-peptide secretors significantly decreased across categories of diabetes duration, detectable C-peptide was found in 21% of T1DM patients who were diagnosed with T1DM more than 20 years ago. Previous study that included large numbers of T1DM suggest that after an exponential fall in C-peptide secretion in the first 7 years after diagnosis, there is evidence of stabilization [20]. Finally, C-peptide secretors had shorter diabetes duration, lower resistin, and higher uric acid compared to T1DM patients with no detectable C-peptide levels, while no differences in routine anthropometric and laboratory variables were observed.

Table 3 Relationship between C-peptide secretion and duration of diabetes

	Duration of diabetes (years)				
	< 5	5–10	10–20	20–30	
Patients-total (n)	43	32	56	33	P (trend)
C-peptide secretors (n)	30	12	10	5	<0,001
C-peptide secretors (%)	70	38	18	15	<0,001

In T1DM, C-peptide improves vascular blood flow in skin, increases oxygen and glucose uptake in muscles and normalizes glomerular function [21–23]. The preventing role of C-peptide against reactive oxygen species protects the vasculature from metabolic memory and consequently prevents diabetic complications [24]. C-peptide also bound to the human adipocyte cell membrane and has effects on adipocytokines synthesis and secretion [10]. In contrast to other adipocytokines in humans, resistin is derived in lower levels from adipose tissue and in higher levels in inflammatory cells, especially macrophages [25]. Resistin is associated with inflammation in humans via promotion and activation of endothelial cell, adhesion molecules and cytokines [26]. Resistin is primarily associated with inflammatory markers derived from monocytes and endothelium rather than adipocytes [27].

Although data showed increased serum resistin level in T2DM with microvascular complications, there are no studies that have confirmed relationship between serum resistin level and microvascular complications in T1DM [28, 29]. Previously, we observed in T1DM patients with microalbuminura slightly lower but nonsignificant serum resistin level compared to patients with normoalbuminuria [30]. However, similar to this study, we included patients with eGFR over 60 ml/min and normoalbuminuria while in studies that included T2DM and where resistin was found to be the risk factor for microvascular complications the level of renal function was the main determinants of serum resistin level [31]. In present study we found lower resistin level in patients with preserved C-peptide. Our results are similar to previously published study that found negative association between C-peptide and resistin in T1DM with diabetes duration up to 5 years [13]. However, we used fasting C-peptide level as a biomarker of beta-cell function and fasting resistin level while Pham et al. correlate C-peptide and resistin level after standardized mixed meal test.

Uric acid is also involved in the function of the beta cell and with insulin secretion, and positively correlates with serum C-peptide values [15, 17]. In this study we observed higher uric acid in T1DM patients with preserved C-peptide secretion. The most important mechanism may be association between insulin and renal absorption of urates. Insulin stimulates uric acid reabsorption via regulating urate transporter 1 explaining anti-uricosuric effects of insulin in the diabetic state [32]. Hyperuricemic models can lead to systemic hypertension, arteriolosclerosis as well as albuminuria probably due to the activation of oxidative stress [33]. There is also evidence that uric acid is involved in alteration of the primary function of beta-cell and may inhibit glucose-induced insulin secretion [34]. Results from the study that included patients with type 1 and type 2 diabetes suggest that uric acid behavior is closely related with beta-cell function [17]. In that study, serum uric acid values were in positive correlation with serum C-peptide values in diabetic subjects, but only those with duration of diabetes less than 5 years and without microvascular and macrovascular complications.

The present study has a number of potential limitations. First, our study was cross-sectional, which limited our ability to infer a causal relation between C-peptide level and resistin and uric acid. Second, our analyses were based on a single measurement of C-peptide, resistin and uric acid that may not reflect the relation over time. Third, the small number of patients with preserved C-peptide secretion limited our ability to detect significant differences with other anthropometric and laboratory variables, including HbA1c. Fourth, selection bias is likely because our study was single hospital-based. Finally, a borderline statistical significance and the small effect size warrant confirmation of the observed associations in a larger-scale clinical study.

In conclusion, the results of our study revealed that T1DM patients with detectable C-peptide had lower serum resistin and higher uric acid level compared to patients with undetectable C-peptide. The strength of our study is that we included T1DM patients without microvascular complications or with earlier stages of microvascular complications and there is no influence of comorbidities on the results because renal function is most important determinants of serum resistin and uric acid level. Given the borderline statistical significance and the small effect size detected, future prospective studies are needed to establish should serum resistin and uric acid be investigated as biomarker of beta-cell function in T1DM.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this article.

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