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Persons with latent autoimmune diabetes in adults express higher dipeptidyl peptidase-4 activity compared to persons with type 2 and type 1 diabetes

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ABSTRACT

Aims: We aimed to determine serum dipeptidyl peptidase-4 (DPP-4) activity in a group of persons with latent autoimmune diabetes in adults (LADA) and to compare it with persons with type 1, type 2 diabetes and healthy controls.
Methods: DPP-4 activity measurement was performed in 67 persons (21 with type 1, 26 type 2 and 19 with LADA) and 13 healthy age and gender matched controls.
Results: Persons with LADA showed highest DPP-4 activity among the study groups (32.71 ± 3.55 *vs* 25.37 ± 2.84 *vs* 18.57 ± 2.54 *vs* 18.57 ± 2.61 U/L $p < 0.001$). Mean glutamic acid autoantibody in persons with LADA was 164.32 ± 86.28 IU/mL. It correlated with DPP-4 activity ($r = 0.484$, $p = 0.013$). Furthermore, DPP-4 activity correlated with waist circumference ($r = 0.279$, $p = 0.034$) and glycated haemoglobin A1c ($r = 0.483$, $p < 0.001$), as well as with LDL cholesterol ($r = 0.854$, $p < 0.001$) and total daily insulin dose ($r = 0.397$, $p = 0.001$). In the multinomial regression analysis DPP-4 activity remained associated with both LADA (prevalence ratio 1.058 (1.012–1.287), $p = 0.001$) and type 1 diabetes (prevalence ratio 1.506 (1.335–1.765), $p < 0.001$) while it did not show an association with type 2 diabetes (prevalence ratio 0.942 (0.713–1.988), $p = 0.564$).
Conclusions: Persons with LADA express higher DPP-4 activity compared to persons with both type 1 and type 2 diabetes. The possible pathophysiological role of DPP-4 in the LADA pathogenesis needs to be further evaluated.

1. Introduction

Diabetes mellitus reflects a group of carbohydrate, protein and fat metabolism disorders characterized by hyperglycaemia which eventually leads to micro- and macrovascular complication development. Although all forms of diabetes are characterized by hyperglycaemia, the pathogenic mechanisms by which hyperglycaemia arises widely differ. American Diabetes Association categorized diabetes mellitus mainly as type 1, type 2 diabetes and the others [1]. Type 1 diabetes mellitus (T1DM) is an autoimmune (AI) disease in which absolute insulin deficiency and consecutive hyperglycaemia result from immune-mediated destruction of insulin-secreting pancreatic islet cells [1,2]. Although the majority

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of persons with T1DM experience the acute disease onset under the age of 30 years, during the last decades an accumulating body of literature led to the recognition that predominant, autoantibody mediated form of T1DM might appear at any age [2–4].

Latent autoimmune diabetes in adults (LADA) represents a form of autoimmune diabetes that resembles type 1, but has a later onset and slower progression towards absolute insulin dependency. There are controversies regarding this type of the disease and its terminology which is why several attempts have been made for better characterization and classification [4]. Uncertainties concern almost all aspects of this disease, including: nomenclature, diagnostic criteria, epidemiology, natural history, pathogenesis along with genetic, metabolic and immunological aspects. Clinical phenotype in persons with AI diabetes ranges from diabetic ketoacidosis to diabetes that can be controlled with diet alone [5] and the three criteria namely: age at diagnosis, autoantibody positivity and need for insulin treatment conventionally used to define adult-onset AI diabetes are non specific. Because autoantibodies to tyrosine phosphatase-like insulinoma-associated protein 2 (IA2) have been reported to be rather infrequent, the diagnosis basically relies on identifying glutamic acid decarboxylase autoantibody (GADA), which is the best single marker for screening [6]. Time to insulin treatment is dependent on local clinical judgment and not on the disease process [7], finally, as already mentioned, the disease might appear at any age which is not possible to establish the correct diagnosis without Ab screening that is not routinely performed. Consequentially, there is no clear management strategy in terms of LADA therapy and prevention. Even though ~10% of adults with presumed type 2 diabetes (T2DM) at diagnosis in fact have LADA, so far there are only few studies evaluating therapeutic interventions for LADA, using a hypoglycaemic or an immunomodulatory agent. An ideal therapeutic approach would aim not only to obtain a good metabolic control, but also to protect residual β-cell mass and function. Conversely, even in persons on insulin, glycaemic control is suboptimal, suggesting that insulin alone may not be sufficient [8].

Dipeptidyl peptidase-4 (DPP-4) inhibitors represent a new class of oral antidiabetic agents that have shown the potential to preserve β-cell function in mouse models of type 2 diabetes [9,10], in persons with T2DM [11], and even in persons with impaired fasting glucose tolerance [12]. DPP-4 inhibition reduces insulitis as well, and stimulates β-cell function in a non-obese diabetic mouse model of AI diabetes, a classic model of T1DM [13,14]. There is an increased serum DPP-4 activity [15] and expression on terminally differentiated CD4 T-cells [16] in persons with T1DM. Recent trials show that one of the DPP-4 inhibitors, sitagliptin, significantly improves glycaemic control in adult persons with T1DM [17] as well as in persons with LADA [18].

These observations provided a rationale to test the soluble serum DPP-4 activity in LADA, T1DM, T2DM and to compare it with healthy controls.

2. Materials and methods

2.1. Study design

This was a single-centre based study undertaken at University Clinic for diabetes, endocrinology and metabolic disease Vuk Vrhovac, Zagreb, Croatia. The study population comprised clinic- and hospital-based adult persons with diabetes aged >30 years within at least one year from diabetes diagnosis coming for their comprehensive annual review screened for ICA, GAD and IA2 Abs. Persons were stratified into four groups: healthy controls (CTRL), persons with T1DM, T2DM and LADA. Histories and complete physical examination and laboratory tests were performed in all subjects in order to exclude diseases other than T1DM or medications that might affect insulin sensitivity. T1DM was defined by undetectable meal stimulated C-peptide concentrations

Table 1 – Patients anthropometric and laboratory data.

Variable	Type 1 diabetes N = 21	Type 2 diabetes N = 26	LADA N = 19	p
Age (years)	41.6 ± 14.9	53.7 ± 12.5	43.4 ± 11.4	0.09
Diabetes duration (years)	17.65 ± 12.4	20.75 ± 13.95	18.0 ± 13.5	0.003
Waist circumference (cm)	88.3 ± 14.3	99.9 ± 14.1	90.3 ± 16.9	0.03
Body mass index (kg/m^2)	25.9 ± 3.5	28.6 ± 4.5	26.3 ± 4.6	0.07
Systolic BP (mmHg)	128.2 ± 27.1	133.1 ± 19.6	132.8 ± 27.1	0.76
Diastolic BP (mmHg)	76.6 ± 7.8	84.3 ± 15.1	80.8 ± 11.7	0.15
Disease duration (years)	21.1 ± 11.0	20.2 ± 12.8	18.0 ± 8.8	0.83
HbA1c (%)	7.1 ± 1.3	7.3 ± 1.4	7.5 ± 1.3	0.53
HbA1c (mmol/mol)	54 ± 9	56 ± 8	58 ± 9	
Total serum cholesterol (mmol/L)	4.8 ± 0.9	5.7 ± 1.6	5.5 ± 2.4	0.22
HDL cholesterol (mmol/L)	1.8 ± 0.6	1.4 ± 0.4	1.7 ± 0.5	0.23
LDL cholesterol (mmol/L)	2.6 ± 0.7	3.2 ± 2.1	3.4 ± 1.1	0.18
Triglycerides (mmol/L)	1.03 ± 0.52	1.97 ± 2.86	1.27 ± 0.71	0.21
Total daily insulin dose (IU/kg)	0.59 ± 0.13	0.34 ± 0.14	0.51 ± 0.39	<0.001
DPP-4 activity (U/L)	25.37 ± 2.84	18.57 ± 2.54	32.71 ± 3.55	<0.001

Legend: BP-blood pressure; HbA1c-glycated haemoglobin A1c; HDL-high density lipoprotein; LDL-low density lipoprotein; DPP-4-dipeptidy peptidase-4.