Serum Dipeptidyl peptidase-4 Activity and its Relation to Insulin Resistance in Type 1 Diabetic Adolescents

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Diabetes and Insulin 1

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Amany Ibrahim has no relevant financial or non financial relationships to disclose

INTRODUCTION AND OBJECTIVES

- IR is recognized as a prominent feature of T1D. IR was linked to a higher risk to alterations in lipid profiles, obesity and poor diabetic control and subsequently the development of micro- and macrovascular complications [1]. This made IR a therapeutic target in patients with T1D [2].
- Dipeptidyl peptidase-4 (DPP-4) is a widely expressed enzyme on almost all cell surfaces. It deactivates many bioactive peptides involved in glucose regulation; glucose-dependent insulinotropic polypeptide (GIP) and Glucagon-like peptide-1 (GLP-1) regulating insulin release (figure (1)) [3]. DPP-4 inhibitors were approved for the use in T2D. DPP-4 inhibition not only improved metabolic control in patients with T2D through prolonging the incretin effect of GLP-1 and GIP, but also suppressed the inflammatory pathways mediating the endothelial dysfunction and the subsequent vascular complications complicating diabetes [4].
- This study aimed at evaluating serum DPP-4 level in adolescent T1D patients compared to controls and investigating the relationship between DPP-4 level and the development of IR in these patients.

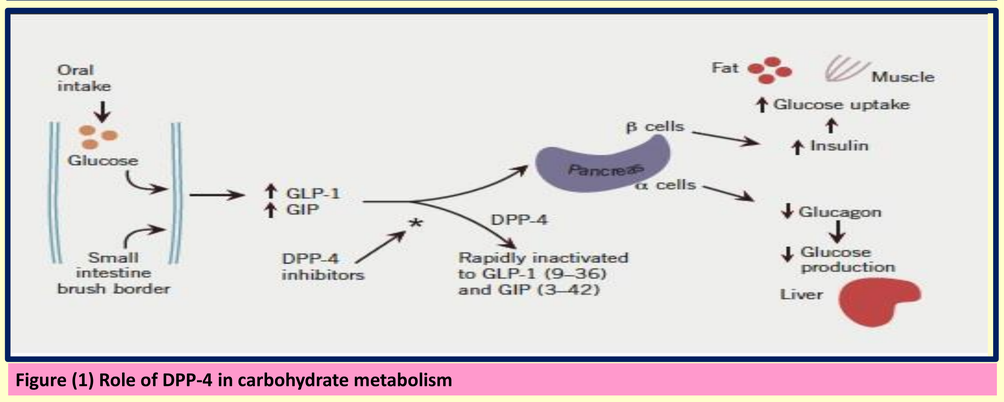

Figure (1) Role of DPP-4 in carbohydrate metabolism

METHODS

- 50 adolescents with T1D following in the outpatient clinic of Diabetic Endocrine Metabolic Pediatric Unit (DEMPU) over a period of one year were compared to 80 healthy adolescents.
- After informed parental consent, detailed medical history was initially taken including age, diabetes duration, insulin dose as well as complications. Clinical examination including anthropometry (weight, height and BMI was calculated and SDS for weight, height and BMI were obtained, Waist circumference and blood pressure measurement.
- Recent laboratory results including urine A/C ratio, fasting lipid profile including; TC, TG, HDL and LDL were obtained from the medical records. Mean HbA1C levels over the preceding year were calculated. Serum DPP-4 level was assessed by ELISA technique.
- The equation for estimated glucose disposal rate (eGDR): eGDR (mg/kg/min) = 21.158 – [3.407 x hypertension status (yes=1; no=0)] – [0.09 x WC (cm)] – [0.551xHbA1c (%)] [5].
- Some definitions used:
  - Poor glycemic control was defined by HbA1C<7.5% [6].
  - Abnormal lipid profile (dyslipidemia) the following cut-offs were used: TG level >130mg/dl, TC level >200 mg/dl, LDL >130mg/dl or HDL <40mg/dl [7].
  - The eGDR is inversely correlated to IR; so that the lower the eGDR levels, the greater the IR (eGDR<9 as a definition of insulin resistance) [8].

RESULTS

- Table (1) shows the baseline clinical characteristics and biochemical parameters of T1D patients in comparison to controls.
- Females constituted 58% of the studied T1D subjects. Hypertension was recognized in 36%. Poor glycemic control was found in 86% with a mean HbA1C 10.51±2.43 for the whole studied patients. Regular insulin and NPH in a basal-bolus regimen was the most commonly used regimen (78%) with a total daily insulin dose of 1.3±0.8 IU/kg/day.
- Table (2) showed comparison between males and females in which males showed a significant increase in HbA1C compared to females, while females showed a significant increase in eGDR compared to males.
- Diabetes complications were detected in 34%; 8 patients had nephropathy, 3 patients had polyneuropathy, 17 patients had dyslipidemia, 2 patients had frequent hypoglycemia and only one had glycogenic hepatopathy. In those subjects, the only variable that showed a significant difference over those without complications was SBP.
- Dyslipidemia was found to be the most frequent complication detected in our T1D patients (34%), comparing two groups of patients according to the presence of dyslipidemia; a statistically significant elevation of HbA1C and reduction of DPP-4 levels in the group with dyslipidemia were detected.
- IR was found in 80% of T1D patients (eGDR<9). According to the status of IR; a statistically significant elevation of SBP, DBP, HbA1C, TG and LDL levels and a significant reduction of HDL level in the group with higher eGDR (eGDR>9).
- Serum DPP-4 level showed a significant correlation only with the insulin dose in T1D adolescents (figure 2).
- Tertiles of eGDR showed a statistically significant increase in HDL and significant reduction in SBP, DBP and HbA1C level along tertiles table (3).
- DPP-4 tertiles showed a statistically significant variation of BMI SDS, elevation of insulin dose and a reduction of TC table (4).
- Multivariate regression analysis for factors affecting eGDR revealed that HbA1C, DBP, WC, diabetes duration and insulin dose were influential factors on eGDR in T1D adolescent patients (table 5).

Table (1): Baseline clinical characteristics and biochemical parameters of the study population

	Patients n=50	Controls n=80	P value
Age (y)	14.44 ± 1.76	15 ± 1.73	0.077
Weight SDS†	0.2 (-0.6, 1.1)	1 (0.6, 1.5)	<0.001
Height SDS†	-1.1 (-1.8, -0.2)	0.5 (0.3, 1)	< 0.001
BMI SDS†	0.95 (0.1, 1.7)	1.1 (0.9, 1.6)	0.126
WC (cm)	79.27 ± 6.54	70.01 ± 6.16	< 0.001
SBP (mmHg)	117.56 ± 16.27	104.14 ± 8.72	< 0.001
DBP (mmHg)	78.1 ± 11.96	69.68 ± 7.03	< 0.001
HbA1C (gm%)	10.51 ± 2.43	5.57 ± 0.62	< 0.001
eGDR (mg/kg/min)	6.7 ± 2.37	11.73 ± 0.68	< 0.001
DPP-4 (ng/ml) †	2.85 (1.25, 11)	6 (3, 9)	0.04

Table (2): Comparison between males and females in the Diabetic subjects

	Males	Females	P value
Age (Y)	14.13±1.71	14.66±1.79	0.301
Weight SDS*	-0.2 (-0.8, -0.8)	0.3(-0.5, 1.2)	0.398
Height SDS*	-1.10 (-1.8,-0.10)	-1.1(-1.8, -0.5)	0.602
BMI SDS*	0.8 (0, 1.9)	1 (0.3, 1.6)	0.798
WC (cm)	79.07±4.58	79.41±7.74	0.846
SBP (mmHg)	121.33±13.72	114.83±17.62	0.165
DBP (mmHg)	78.95±10.22	77.48±13.23	0.673
HbA1C (gm%)	11.40±2.29	9.86±2.35	0.025
eGDR (mg/kg/min)	5.81±1.75	7.34±2.56	0.022
sDPP4 (ng/ml)*	2.5(1, 4.7)	3.70(2, 14)	0.181

Table (3): Comparison between the thirds of T1D patients as regards eGDR tertiles

	≤5.9	5.91 - 7.9	>7.9	P value
Age (Y)	14.55 ± 1.92	14.43 ± 1.54	14.32 ± 1.9	0.934
Diabetes duration (Y) †	6.4 (4.2,9.7)	4.9 (3.9, 6)	5.05 (4.3, 7.45)	0.289
Insulin dose (IU/Kg/Day) †	1.5 (1.2, 1.7)	1.1 (1,1.3)	1.3 (1.05, 1.5)	0.051
Weight SDS†	-0.5 (-1.2, 0.6)	0.3 (-0.4, 0.8)	0.25 (-0.15, 1.25)	0.074
Height SDS†	-1.1 (-3.3, 0.2)	-0.8 (-1.7, 0.2)	-1.30 (-1.8, 0.55)	0.103
BMI SDS†	0.4 (-0.1, 1.6)	1 (0.5, 1.5)	1.15 (0.65, 1.9)	0.124
WC (cm)	79.41 ± 6.09	80.21 ± 4.38	78.12 ± 8.8	0.664
SBP (mmHg)	129.82 ± 13.84	113.47 ± 16.84	108.88 ± 9.39	< 0.001
DBP (mmHg)	88.47 ± 10.65	74.76 ± 10.33	70.63 ± 6.23	< 0.001
TC (mg/dl) †	172 (155, 190)	173 (160, 200)	169.5 (141, 181)	0.284
TG (mg/dl) †	95 (80, 140)	110 (50, 150)	75 (53.5, 129.5)	0.666
LDL (mg/dl) †	112 (102, 125)	110 (100, 123)	91.5 (85, 111)	0.059
HDL (mg/dl) †	47 (44, 48)	46 (41, 53)	53.5 (50.5, 62)	0.005
HbA1C (%)	11.98 ± 1.85	10.87 ± 2.35	8.56 ± 1.74	< 0.001
DPP-4 (ng/ml) †	0.3 (0.12, 0.85)	0.25 (0.1, 0.67)	0.32 (0.21, 1.15)	0.944

Table (4): Comparison between thirds of T1D patients according to DPP-4 tertiles

	<2.3	2.3 - 5.7	>5.7	P value
Age (Y)	14.32 ± 1.88	14.74 ± 1.95	14.3 ± 1.47	0.741
Diabetes duration (Y) †	6.1 (4, 8.4)	5.1 (3.7, 9.3)	4.85 (3.9, 6.8)	0.761
Insulin dose (IU/Kg/Day) †	1 (0.9,1.3)	1.3 (1.2, 1.6)	1.3 (1.15, 1.5)	0.027
Weight SDS†	0.2 (-0.6, 1.1)	-0.5 (-1.2, 0.3)	0.55 (-0.4, 1.3)	0.035
Height SDS†	-1.1 (-1.9, -0.2)	-0.8 (-2, -0.2)	-1.15 (-1.65, -0.25)	0.542
BMI SDS†	1.1 (0.3, 2)	0.3 (-0.7, 1.2)	1.25 (0.7, 1.85)	0.01
WC (cm)	78.89 ± 6.28	78.73 ± 7.08	80.22 ± 6.67	0.786
SBP (mmHg)	117.26 ± 14.96	116.33 ± 16.24	119.06 ± 18.6	0.896
DBP (mmHg)	78.16 ± 10.01	76.93 ± 13.13	79.12 ± 13.56	0.882
TC (mg/dl) †	177 (160, 205)	175 (157, 97)	161 (138.5, 172)	0.041
TG (mg/dl) †	115 (67, 167)	110 (80, 150)	75 (50.5, 86)	0.094
LDL (mg/dl) †	112 (99, 125)	112 (10, 24)	99.5 (88.5, 110)	0.347
HDL (mg/dl) †	48 (41, 54)	48 (45, 53)	50 (45.5, 55)	0.456
HbA1C (%)	10.65 ± 2.52	11.07 ± 1.39	9.82 ± 2.99	0.345
eGDR (mg/kg/min)	6.76 ± 2.4	6.33 ± 2	6.98 ± 2.73	0.753

Figure (2): Correlation between DPP4 and Insulin Dose in T1D adolescents

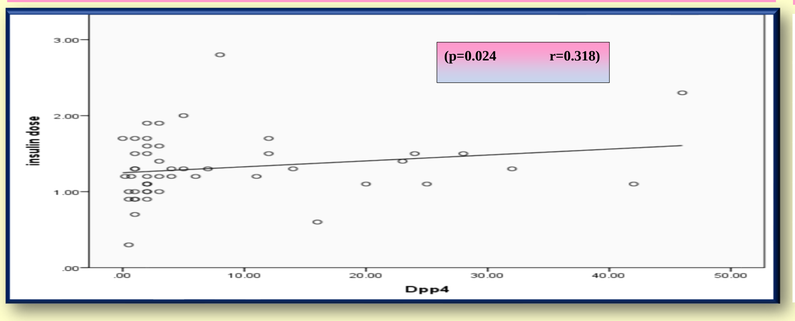

Table (5): Regression analysis for the factors affecting eGDR in T1D patients

	Unstandardized Coefficients		Standardized Coefficients	T	P value
	B	Std. Error	Beta		
HbA1C %	-0.608	0.064	-0.624	-9.533	<0.001
DBP	-0.1	0.013	-0.504	-7.757	<0.001
WC	-0.096	0.024	-0.265	-4.057	<0.001
Diabetes duration	-0.133	0.048	-0.179	-2.751	0.009
Insulin dose	-0.867	0.364	-0.155	-2.38	0.022

CONCLUSIONS

- IR was detected in adolescents with T1D (80% of our patients). IR in T1D was related to poor glycemic control rather than high serum DPP-4 level.
- A significant link between poor glycemic control, dyslipidemia and serum DPP-4 was observed and poor glycemic control resulted in lower eGDR.
- Serum DPP-4 level was related to BMI, insulin dose and changes in lipid profile, especially TG level, which may suggest an important role of serum DPP-4 in lipid metabolism. It seemed to related more to the state of adiposity rather than diabetes process in T1D adolescents.
- Serum DPP-4 seemed to beneficial rather than being harmful and require inhibition

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