AENSI Journals

Australian Journal of Basic and Applied Sciences

ISSN:1991-8178

Journal home page: www.ajbasweb.com

Glucagon Like Peptide- 1 and C-peptide levels and their relationship with some physiological and biochemical variables of non-insulin-dependent diabetes mellitus (type 2) patients

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ARTICLE INFO

Article history:
Received 25 August 2014
Received in revised form
19 September 2014
Accepted 29 October 2014
Available online 16 November 2014

Keywords:
Diabetes Mellitus, GLP-1, and C-peptide .

ABSTRACT

Background: Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both these abnormalities results in metabolic syndrome and the most common problem in diabetic patients is atherosclerosis and cardiovascular disease which is induced by hyperglycemia, hyperlipidemia, and glycated hemoglobin are independent risk factors for cardiovascular disease. **Objective:** The aims of this study is to recognition the levels of Glucagon Like Peptide-1, C-peptide, and some physiological variables in type 2 diabetic pateints like FBG, HbA_{1c}, BMI, AIP, cholesterol, triglyceride, HDL-C, LDL-C, and VLDL-C also study the correlations between them. **Results:** The results of this study of type 2 diabetic patients for both genders males and females showed significant decreasing ($P < 0.05$) in GLP-1 levels compared with control group but there is no signification ($P > 0.05$) between males and females for both diabetes and control groups, while the levels of C-peptide were significantly elevated ($P < 0.05$) in diabetic patients than control group, the C-peptide levels were significantly elevated ($P < 0.05$) in females than males for both diabetes and control groups, the correlation analysis showed significantly positive correlation between GLP-1 and C-peptide for both males and females of patients group but there is no any significant correlation between these hormones in control subjects, also there are significant negative correlation between GLP-1 and each of LDL-C, FBG, and HbA_{1c} and also there is significantly positive correlation with AIP in males of diabetic group, in males of control group there is only significant positive correlation with AIP. In females there is significant positive correlation with BMI in patient group and significant positive correlation with triglyceride in control group. As for C-peptide there is significant negative correlation with LDL-C and positive correlation with AIP in males of diabetic group, in females of diabetic group there is significant positive correlation with BMI, but there is no any correlation between C-peptide and other variables in control group, from this we conclusion that there is strong association between these hormones and some physiological variables in type 2 diabetic patients. **Conclusion:** The significant decrease in GLP-1 levels and significant increase in C-peptide levels were noted in diabetic patients with significant correlation between these two peptides and BMI for both males and females. A significant correlation was noted between GLP-1 and lipid profile in females diabetic patients.

To Cite This Article: Prof. Dr. Haider K. Zaidan and Asma'a H. Mohamed., Glucagon Like Peptide- 1 and C-peptide levels and their relationship with some physiological and biochemical variables of non-insulin-dependent diabetes mellitus (type 2) patients. ***Aust. J. Basic & Appl. Sci.,*** *8(17):595-600, 2014*

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both, the combination of these varies result in chronic hyperglycemia which led to macro-microvascular disease (American Diabetes Association, 2014), the type 2 diabetes is no autoimmune destruction of β-cells and individuals do not need insulin treatment to survive, which includes individuals who have insulin resistance and usually have relative rather than absolute insulin deficiency (Shoback , 2011 ; American Diabetes Association, 2014), Obesity is thought to be the major cause of type 2 diabetes in people who are genetically predisposed to the disease, can managed by increasing exercise and dietary changes (Smyth and Heron, 2006).

Glucagon Like Peptide-1(GLP-1) is an incretin hormone (7-36) amid and (7-37) producing from intestinal L-cells in response to meal intake as a results of increase the levels of nutrient derived from carbohydrate, lipid,

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and protein leading to insulin secretion, the half-life of this hormone is ~ 2 minutes then goes degradation by the dipeptidyl peptidase-4 (DPP-4) (Holst, 2007; Drucker *et al*., 2006). Its ability to induce insulin output before food intake in type 2 diabetic patients make it useful as a treatment; it control on appetite, gartering empty, and inhibit glucagon secretion helping in weight loss (Torekov *et al*., 2011).

C-peptide composed of 31 amino acid considered to be biologically inert but some studies suggests that it has its own biological activity, it secretes from β-cells along with insulin in equimolar amounts (Marques *et al* ., 2004 ; Wahren , 2004), it has protective function by prevent diabetic neuropathy, apoptosis, atherosclerosis (Lina and Johansson, 2008), exert as cardioprotective (Young *et al* ., 2000 , and this because it has receptors on human kidney, endothelial cells, and fibroblasts (Rigler *et al*., 1999).

MATERIALS AND METHODS

The study subjects included 60 diabetic patients (30 male and 30 female) aged between (35-65 year) the infection with type 2 diabetes were diagnostic by specialized doctor, and excluded the cases of insulin intake, DMT1, maturity-onset diabetes of the youth (MODY), surgical removal of the thyroid gland, infection with Hepatitis, cancer, renal failure, heart failure, complications of diabetes retinopathy, nephropathy, neuropathy, and the cases of smoking, alcoholic patients, and pregnant women were ruled out the study. In contrast, the control group included 28 healthy people (14 male and 14 female) aged between (35-65 year) represents healthy control group.

Collection of Blood Samples:

Blood samples were collected from healthy control and diabetic patients in the morning between 08:00 and 10:00 O'clock after a period of fasting 8-10 hours . The study was conducted between November 2013 – April 2014 in general Al-exandria hospital in Babylon province / Iraq, some of studies was done in Babylon University- College of Science laboratories, the collection was performed by using disposable glass and plastic tube each one marked with special number .

Measurements and Tests:

A.Measurements :-

Body Mass Index (BMI):

This was based on heights were measured in centimeters by using listed stripe and weights were measured in kilograms by using a digital balance. Body mass index (BMI) was calculated using the formula BMI= weight (kg)/ height^2 (m)^2 (Han *et al*., 2006).

B. Tests :-

Determination of fasting blood glucose:

Serum glucose was measured by using the measurement kits (RanDox, United Kingdom), based on the PAP enzymatic determination of glucose (Barham and Trindoer method, 1972), according to the procedure that came along with kit.

Determination of Glycated Hemoglobin (HbA1c):

The measurement kit was produced from (Stanbio, USA) (Abraham *et al*., 1978). Glycohemoglobin is formed progressively and irreversibily in the erythrocyte during its 120-day life .and by using this measurement kit the membranes of erythrocytes are break down and edit hemoglobin associated with glucose and measure its quantity.

Determination of Lipid Profile:

Total cholesterol and triglyceride were measured by enzymatic method from Biolabo and Randox Company respectively, while the HDL-C was measured by using the precipitation method from Randox company. The levels of LDL-C and VLDL-C were analyzed by using Friedewald method (Friedewald and Levy, 1972) as follows :

LDL-C (mmol/L)= Total Cholesterol – HDL-C - (TG/5).

Serum VLDL-C can be calculated by:

VLDL-C (mmol/L) = TG/5 .

Atherogenic index of plasma AIP (mmol/L) = log Triglyceride / HDL-C (Tan *et al* ., 2004)

Hormonal Assay:

Determination of Glucagon-Like Peptide-1 (GLP-1) hormone levels in blood serum:

The ELISA kit is produced from Elabscience company and the measurement is based on Sandwich principle, the levels of this hormone can be measured according to the procedure along with kit.

Determination of C-Peptide hormone levels in blood serum:

This ELISA kit is produced from (Elabscience , China), the measurement is based on Sandwich principle, the levels of this hormone can be measured according to the procedure along with kit.

Statistical Analysis

The statistical analysis was performed by using the statistical package for social sciences (SPSS version 17.0) and found all of arithmetic mean and standard deviation (M ± S.D) by using the T-test to know the signification between the both gender male and female and between the diabetic and control group at p value ($p < 0.05$), also ANOVA – LSD was used to find the signification between the patients groups and control group at p value ($p < 0.05$). Brivaraite correlations were performed by using the pearson correlation coefficient at p value ($p < 0.05$) considered to be statistically significant (Al-Mashhadani and Al-Mashhadani, 1989).

Results:

1.Differences of some physiological and biochemical parameters between Type 2 diabetic patients and control:

The statistical analysis of some physiological and biochemical parameters show significant differences between diabetic groups and control table (4-1). The results shows no significant elevation ($p > 0.05$) in HDL-C between diabetes control groups, the results of GLP-1 show significant elevation ($p < 0.05$) in control than diabetes groups, while other parameters show significant elevation ($p < 0.05$) in diabetes patients than control group.

According to the gender the results of HDL-C, LDL-C, GLP-1, and C-peptide show no significant differences ($p > 0.05$) between males and females, while the results of other parameters show significant elevation ($p < 0.05$) in females than males for both diabetes group and control .

Correlation between GLP-1 hormone levels and some physio-biochemical parameters in type 2 diabetic patients and control:

Correlation analysis in diabetic groups showed an positive correlation between GLP-1 and both BMI and C-peptide in females (r= 0.62, p= 0.001) and (r=0.54, p= 0.002) respectively, in males diabetic patients there were positive correlation between GLP-1 and both AIP and C-peptide were found (r= 0.44, p= 0.01) and (r=0.68, p= 0.001) respectively, also the results of correlation in males showed an inverse correlation between GLP-1 and HDL-C, HbA_{1c}, and FBG were found (r= -0.59, p= 0.001), (r= 0.36, p= 0.04), and (r= 0.54, p= 0.002) respectively. In control group the analysis showed an inverse correlation between GLP-1 and Triglyceride in females (r= -0.54, p= 0.04), in males of control group there was positive correlation between GLP-1 and BMI found to be (r= 0.55, p= 0.04). Other correlations of cholesterol, LDL-C, VLDL-C with GLP-1 show no significant correlation for both groups and for both male and female gender table (4-2).

Correlation between C-peptide and some physio-biochemical parameters in type 2 diabetic patients and control:

In diabetic patients the correlation analysis showed positive correlation between C-peptide and BMI in females was found (r= 0.73, p= 0.001), while in males there were positive correlation between C-peptide and AIP (r=0.40, p= 0.02), also the analysis results showed inverse correlation between C-peptide and HDL (r=0.55, p= 0.001). The analysis results for control group show no significant correlation between C-peptide and other parameters table (4-3).

Table 4-1: Some physiological and biochemical parameters in Type 2 diabetic patients and control subjects .

P value of group	P value of gender	Diabetes (Mean ± S.D.)		Control (Mean ± S.D.)		Group / Indices
		Female	Male	Female	Male	
0.001*	0.02**	6.08 ± 0.43	5.77 ± 0.59	5.79 ± 0.49	5.14 ± 0.60	Cholesterol(mmol/l)
0.001*	0.003*	3.64 ± 0.62	3.15 ± 0.60	2.82 ± 0.31	2.17 ± 0.43	Triglyceride (mmol/l)
0.92	0.37	1.51 ± 0.32	1.42 ± 0.44	1.57 ± 0.47	1.52 ± 0.44	HDL-C (mmol/l)
0.02**	0.26	3.95 ± 0.83	3.75 ± 0.56	3.74 ± 0.42	3.34 ± 0.74	LDL-C (mmol/l)
0.001*	0.009*	0.68 ± 0.13	0.59 ± 0.12	0.56 ± 0.06	0.41 ± 0.10	VLDL-C (mmol/ l)
0.001*	0.001*	0.40 ± 0.11	0.30 ± 0.91	0.25 ± 0.12	0.13 ± 0.07	AIP (mmol/l)
0.001*	0.006*	8.13 ± 0.53	7.64 ± 0.78	5.00 ± 0.67	4.55 ± 0.60	HbA_{1c} %
0.001*	0.02**	9.16 ± 0.63	8.76 ± 0.67	5.98 ± 0.39	4.24 ± 0.24	FBG (mmol/l)
0.001*	0.004*	30.14 ± 1.49	29.04 ± 1.30	26.93 ±	24.73 ± 0.58	BMI

				0.61		(kg/m^2)
0.001*	0.15	23.36 ± 6.27	20.80 ± 7.43	74.8 ± 39.65	63.31 ± 20.28	GLP-1 (pg/ml)
0.001*	0.30	1.72 ± 1.00	1.49 ± 0.67	0.67 ± 0.47	0.50 ± 0.17	C-peptide (ng/ml)

*P value is significant at P < 0.01.
**P value is significant at P <0.05 .
(M±SD): Mean ± Standard Deviation .

Table 4-2: Correlation between GLP-1 hormone levels and some physio-biochemical parameters in type 2 diabetic patients and control subjects.

GLP-1 Hormone (pg/ml) Diabetes groups				GLP-1 Hormone (pg/ml) Control groups				Groups
Female		Male		Female		Male		
P value	r	P value	r	P value	r	P value	r	Indices
0.79	0.04	0.09	-0.31	0.58	-0.16	0.75	0.09	Cholesterol (mmol/l)
0.008*	0.47	0.30	-0.19	0.02**	-0.61	0.23	0.34	Triglyceride (mmol/l)
0.32	-0.18	0.002*	-0.54	0.70	-0.11	0.91	0.03	HDL-C (mmol/l)
0.39	0.16	0.51	0.12	0.23	-0.34	0.74	0.09	LDL-C (mmol/l)
0.55	-0.11	0.15	-0.17	0.001*	-0.76	0.93	0.02	VLDL-C (mmol/l)
0.001*	0.39	0.43	0.14	0.74	-0.09	0.31	0.29	AIP (mmol/l)
0.59	-0.10	0.002*	-0.54	0.88	0.04	0.32	0.28	HbA_{1c} %
0.04**	-0.37	0.002*	-0.55	0.87	-0.04	0.42	0.23	FBG (mmol/l)
0.001*	0.62	0.25	0.21	-0.33	-0.28	0.02**	0.59	BMI (kg/m^2)
0.006*	0.48	0.001*	0.58	0.01**	-0.65	0.11	0.43	C-peptide (ng/ml)

Correlation coefficient (r)
*Correlation is significant at P < 0.01 level (2- tailed).
**Correlation is significant at P < 0.05 level.

Table 4-3: Correlation analysis between C-peptide Hormone and some parameters of control and Type 2 diabetic patients .

C-peptide Hormone (ng/ml) Diabetes groups				C-peptide Hormone (ng/ml) Control groups				Groups
Female		Male		Female		Male		
P value	r	P value	r	P value	r	P value	r	Indices
0.85	0.03	0.82	-0.04	0.73	0.09	0.37	-0.26	Cholesterol (mmol/l)
0.77	-0.05	0.47	-0.13	0.23	-0.33	0.86	0.05	Triglyceride (mmol/l)
0.47	0.13	0.001*	-0.55	0.62	-0.14	0.67	0.12	HDL-C (mmol/)
0.74	0.06	0.09	0.31	0.90	-0.03	0.45	-0.21	LDL-C (mmol/l)
0.45	-0.14	0.34	-0.18	0.20	-0.35	0.93	0.02	VLDL-C (mmol/l)
0.83	-0.04	0.02 **	0.40	0.78	-0.08	0.98	0.006	AIP (mmol/l)
0.19	-0.24	0.15	-0.26	0.23	0.34	0.63	-0.13	HbA_{1c} %
0.15	0.26	0.06	-0.34	0.47	0.20	0.21	0.35	FBG (mmol/l)
0.001*	0.67	0.12	0.28	0.61	-0.14	0.43	0.22	BMI (kg/m^2)

Correlation coefficient (r)
*Correlation is significant at P < 0.01 level (2- tailed).
**Correlation is significant at P < 0.05 level.

Discussion

Glucagon Like Peptide-1 (GLP-1):

The results of this study demonstrate that patients with type 2 diabetes had significantly lower GLP-1 concentrations than control group and there is no significant difference between males and females in diabetic group (table 4-1), this results were came agreement with former studies (Tronier *et al* ., 1985; Nauk *et al* ., 1986; Ioannis *et al* ., 2003), where the decreasing in GLP-1 levels may be due to several factors, desensitization of GLP-1 receptor on β-cells, a negative feedback loop between GLP-1 and insulin secretion (Ioannis *et al* .,

2003), the half-life of circulation GLP-1 was very short ~ 2 minutes, and increased enzymatic degradation by dipeptidyl peptidase-4 (DPP-4) (Freeman, 2009), decreased gastric empting rate (Miholic *et al* ., 1991 ; Qualmann *et al*., 1995).

The correlation study show no significant correlation between decreased levels of GLP-1 and increased lipid profile in diabetic patients only negative correlation with HDL-C and positive correlation with AIP in males of diabetic group this agreed with the finding of (Katja *et al* 2007) were found that the GLP-1 positively associated with coronary atherosclerosis in diabetic patients, it has vasoprotective action in normal subjects (Lehrke and Marx , 2011).

Found from this study that there is positive significant correlation between GLP-1 and HbA_{1c} in males of diabetic patients and this don't agreed with the finding of (Ioannis *et al* ., 2003) they found that the decrease in GLP-1 led to the increase of HbA_{1c} levels.

The relationship between GLP-1 and FBG showed significantly negative correlation in males of diabetes group the increased of FBG induce the secretion of GLP-1 but poor glycemic control, dyslipidemia, and insulin resistance led to the decrease GLP-1 response and this don't agreed with (Mai-Britt *et al*., 2001).

This study showed significantly positive correlation with BMI in females of diabetic group, GLP-1 secretion result in insulin secretion when the blood glucose increase, inhibition of glucagon secretion, and decrease the appetite (Katja *et al*., 2007), but in diabetic patients the decrease GLP-1 secretion causes the opposite effect of all actions above leading to increase obesity .

There is significantly positive correlation between GLP-1 and C-peptide in males and females of diabetic patients this agreed with the finding of (Ioannis *et al*., 2003) where the decrease GLP-1 response led to decrease insulin secretion and related C-peptide.

C-peptide:

The usefulness of C-peptide measurements is to know the endogenous insulin secretion because it secretes along with insulin in equimolar amounts. The results showed significantly high levels of C-peptide in diabetic patients than in control group for both males and females table (4-1) and this agreed with (Bilal *et al*., 2010; Park *et al*., 1997; Andrea *et al*., 2001), they found that the increasing levels of fasting blood glucose FBG, HbA_{1c}, and increase fat depots induce β-cell for more secretion of insulin and C-peptide .

The statistical analysis showed that there is significantly negative correlation between C-peptide and HDL-C in males of diabetic group and significantly positive correlation between C-peptide and AIP in males of diabetic group and this agreed with (Nikolaus *et al*., 2004) he found increased C-peptide deposition in early atherosclerotic lesions and also the chemotactic effects of C-peptide on monocytes, this chemotactic and deposition increase with the presence of higher deposition of lipids in early atherosclerosis lesions.

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