Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 1077–1080

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Association of fasting glucagon-like peptide-1 with oxidative stress and subclinical atherosclerosis in type 2 diabetes

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ARTICLE INFO

Article history:
Received 28 December 2018
Accepted 18 January 2019

Keywords:
Glucagon-like peptide-1
Oxidative stress
Atherosclerosis
Type 2 diabetes

ABSTRACT

Aim: Glucagon-like peptide-1(GLP-1) is a gut hormone that beside its main function in glucose homeostasis may play a role as an anti-oxidant and anti-atherosclerotic factor. The aim of this study was to estimate fasting total GLP-1 level in type 2 diabetes (T2DM) patients and to determine its relation with oxidative stress and atherosclerotic vascular changes.
Methods: The study included 60 T2DM male patients with age $\geq$40 and 30 healthy male subjects matched for age. All of them were subjected to measuring of fasting total GLP-1, 8-iso prostaglandin F2α (8-iso PGF2α) as a marker of oxidative stress and carotid intima media thickness (CIMT) as a marker of subclinical atherosclerosis.
Results: Fasting total GLP-1 was not significantly different in diabetics in comparison with healthy subjects ($p = 0.52$). Fasting total GLP-1 was found to have significant negative correlations with both 8-iso PGF2α ($p < 0.05$) and CIMT ($p < 0.001$).
Conclusion: Endogenous fasting GLP-1 appears to have anti-oxidant and anti-atherosclerotic effects in T2DM.

1. Introduction

Glucagon-like peptide-1 (GLP-1) is a hormone released from gut-specific cells called neuroendocrine cells in response to nutrients [1]. It plays a major role in glucose homeostasis through stimulation of insulin release and inhibition of glucagon secretion in a glucose-dependent manner, reduction of gastric emptying rate [2] and suppression of the appetite [1].

Besides that important role, it exerts multiple non-glycemic effects [3]. Anti-oxidant effect of GLP-1 is one of its non-glycemic actions that was demonstrated in in vitro experimental conditions [4,5], in vivo models of ischemia [6] and in human umbilical vein endothelial cells [7].

Oxidative stress is a biochemical imbalance in which production of reactive oxygen species (ROS) exceeds the capacity of naturally-existing antioxidant mechanisms [8]. It is believed that oxidative stress plays an important role in the development of vascular complications in diabetes particularly T2DM [9]. 8-Iso-prostaglandin F2 alpha (8-iso-PGF2α) is a prostaglandin-like substance formed by peroxidation of arachidonic acid by ROS [10] and it is considered a reliable marker of oxidative stress [11].

The abundant expression of GLP-1 receptors in the wall cells of blood vessels and in inflammatory cells that play crucial role in the process of atherosclerosis like macrophages and lymphocytes raises the question about the link between GLP-1 and atherosclerosis [12]. Indeed, the anti-atherosclerotic effect of GLP-1 was demonstrated in mice [13] and in a cell culture of human primary coronary artery smooth muscle cells [14] but the association between endogenous GLP-1 and atherosclerosis in human is still in need to be more investigated [15].

The aim of this work was to study the circulating fasting level of total GLP-1 in T2DM patients compared to healthy control subjects and to determine its association with oxidative stress (represented

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https://doi.org/10.1016/j.dsx.2019.01.031
1871-4021/

by 8-iso $PGF_2\alpha$) and atherosclerotic vascular changes (represented by CIMT) in subjects with T2DM.

2. Materials and methods

2.1. Study subjects

This cross-sectional observational study was conducted on a cohort of 60 T2DM male patients. Patients with history of acute infection, malignancy, metabolic or endocrinal disease other than T2DM, renal impairment, hepatic impairment, cardiac failure and those who use incretin mimitics, enhancers or metformin were excluded at the start of the study. The control group included 30 non-diabetic subjects matched for age, sex and other exclusion criteria. This study was approved by Ethics Committee, Faculty of Medicine, Alexandria University. Informed consent was obtained from every participant.

2.2. Methods

All the subjects of this study were submitted to full medical history, thorough clinical examination including the anthropometric measures and measurement of fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), lipid profile, fasting total GLP-1, 8-iso PGF2α and CIMT. Blood samples were drawn from a peripheral vein after an overnight fasting for 12 h. Samples for (GLP-1 and 8-iso PGF2α) were centrifuged and the separated serum was kept frozen and stored at −80 °C until assayed. Fasting total GLP-1 was measured using a kit of ELISA technique supplied by RayBiotech, Inc. (USA), 8-iso PGF2α was measured using a kit of ELISA technique supplied by Cloud-Clone, Corp. (USA). Assessment of bilateral common carotid artery intimal medial thickness was done by using a standardized Doppler ultrasonic device (7.5 MHz; ARIETTA S70, Hitachi Aloka Medical America Inc., USA). Measurement of CIMT was made at a point on the far wall of the common carotid artery (CCA), 2 cm proximal to the bifurcation, from a longitudinal scan plane that showed the intima-media boundaries most clearly [16]. Average values derived from data of both sides were used for the analysis [17].

2.3. Statistical analysis

Statistical analyses were performed using SPSS software (18.0 version). Data normality was tested using Kolmogrov-Smirnov and Shapiro-Wilk tests. Quantitative data were presented as mean ± SD and median (minimum-maximum).The statistical significance between means was estimated by Mann-Whitney *U* test (2 independent samples). Spearman's correlation coefficient (r) was used to measure the strength of the association between two numerical variables. Chi-Square test was used to determine if there is a significant relationship between two categorical variables. Differences were considered statistically significant at $p<0.05$.

3. Results

Demographic and anthropometric parameters of the two groups are presented in Table 1 with no statistically significant difference between the both groups as regards age, smoking habits, body mass index (BMI), waist circumference and waist/hip ratio.

The laboratory and radiological parameters of both groups are showed in Table 2. FPG, HbA1c, total cholesterol (TC), triglycerides (TG) and low density lipoprotein (LDL) were significantly higher in diabetics in comparison with healthy subjects ($p < 0.05$). High density lipoprotein (HDL) was significantly lower in diabetics ($p < 0.001$). No statistically significant difference between diabetics and the control group as regards fasting total GLP-1 level (714.7 ± 358.4 pg/ml vs. 706 ± 218.9 pg/ml, $p = 0.52$).8-iso PGF2α was significantly higher in diabetics in comparison with the control group (594.7 ± 460.7 pg/ml vs. 304 ± 243.6 pg/ml, $p = 0.002$). CIMT was also significantly higher in diabetics in comparison with the control group (0.77 ± 0.14 mm vs. 0.58 ± 0.08, $p < 0.001$).

Table 1
Comparison between the two groups according to the demographic and anthropometric parameters.

	Cases N = 60		Control group N = 30		P value
Age (years)					
Mean. ± SD	49.3 ± 9.3		46.6 ± 3.55		0.94
Median (min. - max.)	46.5 (40–75)		46.5 (41–52)		
Smoking	%	No.	%	No.	0.64
Non smokers	35	21	40	12	
Smokers	65	39	60	18	
BMI (kg/m2)					
(Mean. ± SD.)	27.8 ± 4.5		26 ± 4		0.51
Median (min. − max.)	26.5 (19.5 −40.7)		24.9 (18.9 −33.2)		
Waist circumference(cm)					
(Mean. ± SD.)	98.68 ± 11.3		98.13 ± 8.1		0.83
Median (min. − max.)	100 (80 −119)		99 (80–112)		
Waist/Hip ratio					
(Mean. ± SD.)	1.01 ± 0.05		0.99 ± 0.04		0.07
Median (min. − max.)	1.02 (0.87 −1.14)		0.98 (0.93 −1.08)		

BMI= Body mass index.

Table 2
Comparison between the two groups according to the laboratory and radiological parameters.

	Cases No = 60	Control group No = 30	P value
FPG (mg/dl)			
(Mean. ± SD.)	153.4 ± 39.2	85 ± 6.75	<0.001*
Median (min.- max.	142.5 (85–325)	85.5 (72–95)	
HbA1c (%)			
(Mean. ± SD.)	7.78 ± 0.9	5.2 ± 0.3	<0.001*
Median (min.- max.)	7.8(6–11)	5.2(4.2–5.6)	
TC. (mg/dl)			
(Mean. ± SD.)	194.4 ± 43.4	172.9 ± 25.4	0.03*
Median (min.- max.)	183.5 (146–400)	174.5 (133–225)	
TG (mg/dl)			
(Mean. ± SD.)	170.5 ± 121.75	101.2 ± 36.68	<0.001*
Median (min.- max.)	142 (61–780)	93.5 (52–173)	
LDL (mg/dl)			
(Mean. ± SD.)	106.8 ± 22	95.2 ± 15.8	0.003*
Median (min.- max.)	102(74–182)	90 (79–146)	
HDL (mg/dl)			
(Mean. ± SD.)	43 ± 6.9	51.5 ± 8.6	<0.001*
Median (min.- max.)	43(26–63)	51.5 (39–74)	
Fasting total GLP-1			
(Mean. ± SD.)	714.7 ± 358.4	706 ± 218.9	0.52
Median (min.- max.)	600(200–2000)	650 (400–1320)	
8-iso $PGF_2\alpha$ (pg/ml)			
(Mean. ± SD.)	594.7 ± 460.7	304 ± 243.6	0.002*
Median (min.-max)	520(50–1900)	235(50–940)	
CIMT (mm)			
(Mean. ± SD.)	0.77 ± 0.14	0.58 ± 0.08	<0.001*
Median (min.-max)	0.8(0.6–1.2)	0.6 (0.5–0.7)	

FPG = fasting plasma glucose, HbA1c = glycosaylated hemoglobin, TC = total choleserol, TG = triglycerides, LDL = low density lipoprotien, HDL = high density lipoprotien, GLP-1 = glucagon-like peptide-1, PGF2 α = prostaglandin F2 α, CIMT = carotid intima media thickness, *indicates a statistically significant difference.

Table 3
Correlations between total GLP-1 and all other parameters in the total sample and diabetic subgroup.

	Fasting total GLP-1			
	Total N = 90		Diabetics N = 60	
	r	p	r	p
Age	−0.058	0.59	−0.086	0.52
BMI	0.1	0.35	0.22	0.09
Waist circumference.	0.041	0.7	0.032	0.81
Waist/Hip ratio	−0.054	0.61	−0.04	0.76
FPG	−0.326*	0.002	−0.45*	<0.001
HbA1c	−0.365*	<0.001	−0.511*	<0.001
TC	−0.068	0.53	−0.012	0.93
TG	−0.086	0.42	0.068	0.61
LDL	−0.016	0.88	0.008	0.95
HDL	−0.073	0.5	−0.096	0.47
8-iso $PGF_2\alpha$	−0.295*	0.005	−0.283*	0.029
CIMT	−0.475*	<0.001	−0.507*	<0.001

r: correlation coefficient, *statistically significant.

The correlations between fasting total GLP-1 and the other studied parameters are illustrated in Table 3. GLP-1 has statistically significant negative correlations with FPG ($p < 0.01$), HbA1c ($p < 0.001$), 8-iso PGF2α [$r = -0.295, p = 0.005$ in the total sample and $r = -0.283$, $p = 0.029$ in diabetic subgroup(Fig. 1)] and CIMT [$r = -0.475, p < 0.001$ in the total sample and $r = -0.507$, $p < 0.001$ in diabetic subgroup(Fig. 2)]. No statistically significant correlations were found between GLP-1 and age, BMI, waist circumference, waist/hip ratio, TC, TG, LDL and HDL

4. Discussion

In the current study we demonstrated that there was no statistically significant difference between T2DM patients and healthy subjects as regards fasting GLP-1 level. This agrees with what was reported by Yabe et al. [18] who conducted a study to evaluate fasting and postprandial GLP-1 secretion in diabetics and found no significant difference between them and healthy subjects. Moreover, a recent meta-analysis including 22 studies done by Calanna et al. [19] showed that there was no significant difference between T2DM patients and controls in regard of fasting GLP-1.

However, Alssema et al. [20] demonstrated that fasting GLP-1 level was significantly higher in T2DM patients in comparison with normoglycemic subjects and suggested that higher fasting GLP-1 level in diabetics may reflect a compensatory mechanism to overcome the loss in islet response. In contrast, Lastya et al. [21] showed that fasting GLP-1 level was significantly lower in subjects with T2DM patients than those with normal glucose tolerance and explained the difference by suggesting impaired GLP-1 secretion and accelerated GLP-1 metabolism in T2DM patients.

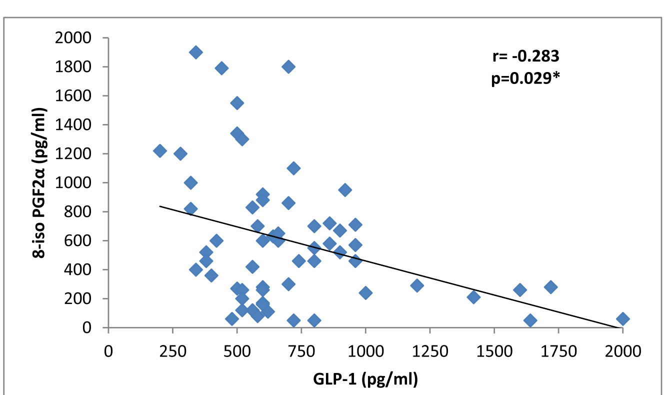

Fig. 1. Correlation between GLP-1 and 8-iso PGF2α in diabetics.

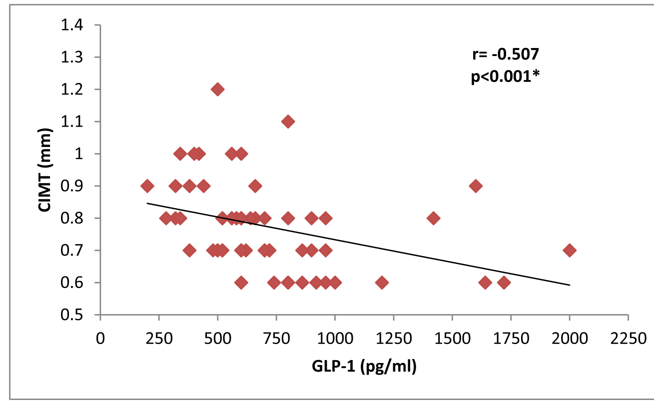

Fig. 2. Correlation between GLP-1 and CIMT in diabetics.

Oxidative stress plays an important role in the progression of diabetes and in the pathogenesis of its complications [22]. GLP-1 was found to play a role in influencing oxidative stress. Improved glucose control, decreased food intake, enhanced insulin secretion and improved insulin sensitivity may be behind this effect but other glucose-independent mechanisms such as reduction of oxygen free radicals level and enhancing the anti-oxidant capacity were also suggested [23].

In this study a significantly negative correlation between fasting GLP-1 and 8-iso $PGF_{2\alpha}$ was detected in both the total sample and diabetic subgroup. This goes in line with what reported Dokken et al. [24] who found that continuous intravenous infusion of GLP-1 for 4 h after cardiac arrest in animals was associated with a significant decrease in 8-iso $PGF2_{\alpha}$.

This also goes in concordance with what reported by ceriello et al. [25] who indicated that achieving a higher level of GLP-1 in T2DM patients by GLP-1 Infusion was associated with a significant reduction of 8-iso PGF2α level. In an another study for Ceriello et al. [26] they found that achieving high level of GLP-1 by GLP-1 infusion was associated with a significant reduction of 8-iso PGF2α in type 1 DM patients who were exposed to acute hypoglycemia and acute hyperglycemia to induce oxidative stress.

Furthermore, Wu et al. [27] noted that treatment of T2DM with GLP-1 receptor agonist for 5 months was associated with significant decrease of 8-iso PGF2α and this reduction was glucose-independent.

CIMT is a measure of early atherosclerosis and vascular remodeling which strongly correlates with standard cardiovascular risk factors [28]. It is considered a dependable marker of subclinical atherosclerosis [29]. The current study showed that there was a strongly negative significant correlation between fasting total GLP-1 and CIMT both in the total sample and diabetic subgroup. This is in good agreement with what revealed by Akiyama et al. [30] Who found a significant negative correlation between fasting GLP-1 and coronary atherosclerosis in human. Moreover, Rizzo et al. [31] and Rizvi et al. [32] clearly mentioned that treatment of T2DM patient with liraglutide, a GLP-1 analog, significantly reduces CIMT. Likewise, our result goes in concordance with what reported by LEADER [33] and SUSTAIN-6 [34] trials in which liraglutide and semaglutide respectively, both GLP-1 analogs, were found to reduce atherosclerotic cardiovascular complications including nonfatal myocardial infarction and nonfatal stroke in T2DM patients.

The anti-atherosclerotic effect of GLP-1 may be explained by suppression of vascular smooth cell proliferation [13], anti-oxidant and anti-inflammatory effects [35] and stimulation of endothelial nitric oxide production [36].

5. Conclusion

In conclusion this study showed that GLP-1 has both anti-oxidative and anti-atherosclerotic effects and this could suggest the effective use of GLP-1 analogs as a first line treatment in T2DM patients with atherosclerotic cardiovascular disease.

Conflicts of interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.01.031.

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