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Study the Levels of GPCR , GLP-1 and Related Hormones Controlled and Uncontrolled in Diabetic Patient's

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Abstract:
The aim of the present study is to evaluate the change in the levels of glucagon, GLP-1 and GPCR in diabetic patient's and diabetic with dyslipidemia as metabolic syndrome. The study included 75 male aged ranged (30-50) years and with BMI (25-29) kg/m^2 which divided into three groups as follows: group one (G1): consist of 25 subjects as healthy control group. Group two (G2): consist of 25 patient's with diabetes mellitus and group three (G3): consist of 25 patient's with diabetic and dyslipidemia as metabolic syndrome. Serum was used in determination of FBG, lipid profile, insulin, glucagon, GLP-1 and GPCR. Whole blood was determination of HbA1c. The results revealed significant elevation in FBG and HbA1c in G2 and G3 comparing to G1. While non -significant elevation was found in FBG and HbA1c in G3 comparing to G2. The results also, showed no significant elevation in each of TC, TG, LDL and VLDL in G2 comparing to G1. Whereas, significant elevation was noticed in these parameters when G3comparing to G2 and G1. Also, the levels of HDL showed no significant reduction in G2 comparing to G1, while significant reduction was found in G3 comparing to G2 and G1. The results also, revealed no significant elevation in insulin levels in G2 comparing to G1. While significant elevation was found in G3 comparing to G2 and G1. Also, the results illustrated significant elevation in glucagon levels in G2 comparing to G1. While significant reduction was seen in G3 comparing to G2. Significant reduction in GLP-1 and GPCRlevels was found in G2 comparing to G1. While significant elevation in these parameters noticed in G3 comparing to G2 and G1. The conclusion could be drawn from this study that dyslipidemia affecting GLP-1 and GPCR levels that may be these patient's at high risk for cardiovascular disease.
Key Words: GPCR, GLP-1, Diabetic patient's with Metabolic Syndrome.

Introduction:

Diabetes mellitus (DM) is a metabolic disordercaused by a deficiency in producing insulin or inefficient action of this hormone, which leads to chronic hyperglycaemia and other disorders such as vascularalterations, myocardic infarction, nephropathies, retinopathies, and neuropathies[1,2].

Metabolic syndrome is a major public healthproblem and a multiple risk factor for cardiovasculardisease. It consists of atherogenic dyslipidemia (elevated triglycerides and low high-density lipoprotein[HDL]), and elevations of blood pressure and glucose[3,4].Hyperinsulinemiaand several biomarkers was found associated with metabolic syndrome includingoxidized low-density lipoprotein cholesterol and C-reactive protein [5].

GPCRs are made up of a single polypeptidechain of up to 1100 amino acid residues, which pass through theplasma membrane seven times. GPCR membrane topology results inan extracellular N-terminal domain, seven transmembrane α-helicesjoined by three Extracellular Loops and three Intracellular Loopsfollowed by an intracellular C-terminal domain that interactswith G proteins.

GPCRs are classically divided into threeclasses: A, B and C based on their sequence homology and functionalsimilarities[6].

Glucagon-like peptide-1(GLP-1) isproglucagon- divided peptides released from enteroendocrine L-cells in response to nutrient ingestion. Recently, preclinical and clinical studies havedemonstrated that the role of GLP-1 is not specific toglycol metabolism; it is also involved in cardiovascular and neuroprotection effects[6,7].There are studies supporting that GLP-1 can regulate signaling pathways coupled to cell proliferation and apoptosis[8,9]. The GLP-1R belongs to the family B GPCRs, also known asthe secretin receptor family and is made up of only 15 members[10].GLP-1 exerts its actions though the GLP-1 Receptor (GLP-1R), which mediates its effects through the Gαs subunit, whichin turn activates Adenylyl Cyclase. Recent study demonstrated the involvement of Gαsand subsequent accumulation of cyclic adenosine monophosphate (cAMP)in glucose-induced insulin secretion [11].

The aim of the present study is to evaluate the change in the levels of glucagon, GLP-1 and GPCR in diabetic patient's and diabetic with dyslipidemia as metabolic syndrome. The study also aimed to investigate the associations of these parameters with diabetic patients and diabetic with metabolic syndrome.

Material and Method:

The study included 75 male aged ranged (30-50) years and with BMI (25-29) kg/m^2 which divided into three

groups as follows: group one(G1): consist of 25 subjects as healthy control group. Group two(G2): consist of 25 patient's with diabetes mellitus and group three(G3): consist of 25 patient's with diabetes mellitus and dyslipidemia as metabolic syndrome. Serum was used in determination of FBG, lipid profile (total cholesterol (TC), triglyceride (TG), and high density lipoprotein (HDL)), insulin, glucagon, GLP-1 and GPCR. Whole blood was used in determination of HbA1c. FBG, lipid profile, HbA1c were determined according to the procedure using in the laboratory of hospital. Friedewald equation was used in determination of LDL and VLDL.

LDL-c (mg/dI) = Total cholesterol- (HDL-c + VLDL-c), VLDL-c(mg/dI) =TG/5[12].

Insulin, glucagon, GLP-1 and GPCR were determined by using a ready kit based on

ELISA techeniqe[13]. Results expressed as mean± SD. T-Test was used to the differences between the groups. P-value of ≤0.05 considered significant and ≥0.05 considered non significant.

Results and Discussion:

The data in table (1) represented the levels of HbA1c, FBG, TC, TG, HDL, LDL and VLDL in all studied groups

Table (1): levels of HbA1c, FBG, TC, TG, HDL, LDL and VLDL in all studied groups.

Groups / Parameters	G1 N=25	G2 N=25	G3 N=25	P1	P2	P3
FBG(mg/dI)	98.54±20.3	119.20±33.26	125.94±35.61	S	S	NS
HbA1c%	5.2±1.21	9.9±1.38	12.33±2.49	S	S	NS
TC(mg/dI)	112.6±14.93	159.5±32.84	368.3±69.62	NS	S	S
TG(mg/dI)	96.84±16.16	120.67±44.07	390.99±56.40	NS	S	S
LDL(mg/dI)	33.6±5.31	87.90±30.42	259.87±64.63	NS	NS	S
HDL(mgldI)	59.60±12.14	48.54±8.67	28.13±5.56	NS	S	S
VLDL(mg/dI)	19.6±2.41	25.12±8.16	78.18±10.12	NS	S	S

(S) : significant, (NS): non significant

The results revealed significant elevation in FBG and HbA1c in G2 and G3 comparing to G1. While non significant elevation was found in FBG and HbA1c between G3 comparing to G2. The results in table (1), also, shown no significant elevation in each of TC, TG, LDL and VLDL in G2 comparing to G1. Whereas, significant elevation was noticed in these parameters when G3 comparing to G2 and G1. No significant reduction was found in HDL levels in G2 comparing to G1, while significant reduction was found in G3 comparing to G2 and G1.Hyperglycemia increases the risk of microvascular complications , while dyslipidemia is a major risk factor for macrovascular complications in patients with type 2 diabetes. Elevated low-density lipoprotein cholesterol is a major risk factor for CVD. As such, management of LDL-C is the primary goal of therapy for diabetic dyslipidemia [14,15]. In addition, the different components of diabetic dyslipidemia (plasma lipid and lipoprotein abnormalities) are believed to be metabolically linked [16].A central pathophysiological feature of type 2 diabetes (T2D) and the metabolic syndrome is fasting dyslipidemia that is characterized by enhanced (VLDL) production, formation of atherogenic small dense LDL, and decreased HDL-cholesterol[17].

Table(2) showed the levels of insulin, glucagon, GLP-1 and GPCR in all studied groups. The showed no significant elevation in insulin levels in G2 comparing to G1. While significant elevation was found in G3 comparing to G2 and G1. Also, the results illustrated significant elevation in glucagon levels in G2 comparing to G1 and significant reduction was seen in G3 comparing to G2. Results also, showed significant reduction in GLP-1 and GPCR levels in G2 comparing to G1. While significant elevation was found in these parameters in G3 comparing to G2 and G1.

Table (2): levels of insulin, glucagon, GLP-1 and GPCR in all studied groups.

(S) : significant, (NS): non significant

Groups / Parameters	G1 N=25	G2 N=25	G3 N=25	P1	P2	P3
Insulin(µIV/ml)	5.34±1.29	8.24±2.46	20.68±5.93	NS	S	S
Glucagon(mg/ml)	81.2±13.6	189.30.9	125.16±25.6	NS	S	S
GLP-1(mg/ ml)	2.38±0.08	1.69±0.06	4.85±0.99	S	S	S
GPCR (mg/ ml)	1.78±0.03	0.87±0.07	3.79±0.86	S	S	S

Insulin normally acts as a negative regulator of VLDL production, decreased hepatic insulin sensitivity in T2D results in the overproduction of these triglyceride (TG)-rich apolipoprotein B100 (apoB100) containing particles. This ultimately leads to the fasting hypertriglyceridemia that is associated with enhanced cardiovascular risk[18]. Another study suggested that in addition to impaired insulin secretion, type 2 diabetic patients also have elevated levels of glucagon, which worsens hyperglycemia by increasing glucose production by the liver[19].

In recent study, GLP-1 receptors are expressed in the pancreas, brain, heart, vascular, lung, kidney and gastrointestinal tract. Previous study suggest that circulating levels of GLP-1 may affect systemic metabolism in multiple organs including cardiovascular systems as a multifunctional hormone[20]. Other study demonstrated that GLP-1 receptor agonists have wide-ranging cardiovascular actions, such as modulation of heart rate, blood pressure, and myocardial contractility [21].

GLP-1 has been found to exert cardioprotective actions in Experimental models of dilated cardiomyopathy, hypertensive, heart failure, and myocardial infarction[22]. De Marinis et al. reported mat the expression of GLP-1 receptors in alpha-cells cells and that GLP-1-induced suppression of glucagon release is dependent of PKA and independent of glucose or paracrine effects mediated by insulin or somatostatin [23]. On the other hand, de Heer et al. [24] have previously demonstrated that GLP-1 inhibitory effect on glucagon secretion is mediated by somatostatin acting on somatostatin receptor subtype-2 (SSTR-2).

The in cretin hormone glucagon-like peptide-1 (GLP-1) has been recently implicated in decreasing postprandial dyslipidemia in rodent models and diabetic patients by reducing intestinal lipoprotein production [25,26]. Cardiovascular biomarkers in T2D patients were also shown to improve significantly after GLP-1 receptor (GLP-1R) agonism as indicated by reduced plasma TG, as well as reduced LDL-cholesterol and total cholesterol levels[27]. The GLP-1 R in central GLP-1R activation has been shown to regulate both hepatic glycogen storage and peripheral lipid deposition [28,29].

Recent study demonstrated that dysfunctional glucagon secretion to the pathogenesis of diabetes has been widely recognized and, for that reason, targeting glucagon and not only insulin secretion abnormalities in the treatment of T2D has gained increased interest. The well-established actions of GLP-1 as a negative regulator of glucagon and as a positive regulator of insulin and the availability of GLP-1RA provide the opportunity of targeting both main hormones implicated in diabetes pathophysiology[30]. Other recent study suggested that GLP-1decreased hepatic lipid synthesis and also requires an intact parasympathetic signaling pathway[31].

Alpha cells not only secret glucagon, but they also express the glucagon receptor, which is itself a GPCR, thus, glucagon is both secreted by and acts on alpha cells to regulate their own secretion. Along with the glucagon receptor, it is likely that alpha cells express addition GPCR that play roles in glucagon secretion thus GPCR that regulate glucagon secretion may be excellent targets for diabetes therapies due to their overall importance in the regulation of islet function[32,33].

The conclusion could be drawn from this study that dyslipidemia affecting GLP-1 and GPCR levels that may exhibit predictive information for CVD in patient's with dyslipidemia which is one causes of metabolic syndrome.

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