



# Study the Levels of Glucagon Like Peptide-1(GLP-1) and Related Parameters in Iraqi Hyperlipidemia Patients with Diabetes Mellitus.

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## **Abstract**

The glucagon-like peptide-1 is secreted by intestinal L cells in response to nutrient ingestion. It regulates the secretion and sensitivity of insulin while suppressing glucagon secretion and decreasing postprandial glucose levels , additionally, glucagon-like peptide-1 delays gastric emptying and suppresses appetite. The impaired secretion of glucagon-like peptide-1 has negative influence on hyperlipidemia, diabetes and insulin resistance related diseases the levels of its secretion change with the intake of different nutrients. Some drugs also have influence on GLP-1 secretion .

**Key words:** Hyperlipidemia , glucagon like peptide -1(GLP-1)

## Introduction

Hyperlipidemia is a condition excess in concentration of one or more serum of lipids , at most triglyceride(TG) and total cholesterol (T.ch) , inside the body, the hyperlipidemia is also called hyperlipoproteinemia , the only way for the survival the particles lipid soluble in the circulatory system is attached to the protein[16].This is the only way that these lipids can remain dissolved while in circulation. There are different types of hyperlipidemia depending on which lipid levels are high in blood, it can be divided into three subcategories. [4] : hypercholesterolemia, hypertriglyceridemia and familial combined hyperlipidemia.

Dyslipidemia is shared in T2DM patients with other futures of insulin resistance like hypertension with abdominal obesity. It is a well-recognized and changing risk factor that should be discovered early to know aggressive cardiovascular preventive management. In the liver, fatty acids are changed to triglyceride (TG) which are loaded and excreted in the form of VLDL , reduced levels of HDL are also correlated with T2DM, as a result of increased destruction. Hyperglycemia and dyslipidemia affect the development of coronary heart disease (CHD) and raises the mortality rate in diabetic patients[20].

Glucagon like peptide-1 (GLP-1) is a gastrointestinal hormone excreted from the enteroendocrine L-cell in response to nutrient ingestion. once released into the circulation, GLP-1 elicits a potentiation of glucose-stimulated insulin secretion from the  $\beta$ -cells within the pancreatic islets, known as the incretin effect [3,5] , that used now in the pharmaceutical [7]. the GLP-1 consisted of a 42 amino acids produced from the transcription product of pro-glucagon gene that has a half-life of less than 2 minutes[11], due to rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) [15]. GLP-1 has two biologically active forms : GLP-1 [7–37] and GLP-1 [7–36] amide . biological activity of GLP-1decreased soon after secretion because decomposition by di-peptidyl peptidase-4 (DPP-4) [14]. Physiological roles of GLP-1 are increasing of insulin secretion from beta cells , decreasing of glucagon secretion from alpha cells ,GLP-1 increasing the mass of  $\beta$ -cells and the gene expression of insulin , delays gastric emptying and inhibition of acid excretion in the stomach(this delays and protracts carbohydrate absorption and contributes to a satiating effect) and decreasing of food consumption by elevation satiety in the brain [30] .

The study aimed to determine the levels of GLP-1 in dyslipidemia patients that no study found on these patients , also to found the relation of GLP-1 with atherogenic index of plasma (AIP), glucagon and insulin.

## Materials and Methods

One hundred and thirty five subjects were enrolled in this study , their age range was within (40-70) years , they were divided into three groups as follow:- group one ( $G_1$ ) considered as a control group consists of (22) males and (23) females with BMI ( $26.48 \text{ Kg/m}^2$ ) , group two ( $G_2$ ) hyperlipidemia patients that consists of (22)males and (23)females with BMI ( $27.11 \text{ Kg/m}^2$ ) . Group three ( $G_3$ ) that represent hyperlipidemia patients with T2DM that consists of (22) males and (23) females with BMI ( $27.5 \text{ Kg/m}^2$ ), patients groups don't administrate any treatment .Samples were collected from Hyperlipidemia patients at Al-Karama Hospital / Baghdad during the period from November 2015 to February 2016. Smokers, alcoholics, patients with cardiovascular disease, insulin treatment , kidney disease and hepatic failure were excluded.

Five mL of blood was collected by venipuncture using 10mL disposable syringe, from both fasting patients and control. Biochemical tests including fast blood sugar, lipids profile, glycosylated hemoglobin, insulin, glucagon and glucagon like peptide-1,were estimated in serum for all patients and controls. Body mass index , atherogenic index of plasma and HOMA-IR were calculated as a part of the study.

HbA<sub>1c</sub> is determined in whole blood for controls and patients groups . the other parameters were determined in serum that FBS and lipid profile were determined by using enzymatic method according to the procedure in the hospital. Insulin , glucagon and GLP-1 were determined by ELISA method by using a ready kit from DRG, Germany for insulin , Germany for glucagon and GLP-1 depending on protocol of the manufacture of the kit.

### Statistical Analysis

Results were presented as mean  $\pm$ SEM , t. test was used to determine the differences between two groups, P-value of  $< 0.001$  and  $< 0.05$  considered as highly significant and significant respectively. Person's correlation was used in evaluating correlation relation( $r$ ) between two parameters.

### Results and Discussion

Three groups were enrolled in this study, group one ( $G_1$ ) includes (45) healthy people (both sex), group two ( $G_2$ ) includes (45) patients with hyperlipidemia (both sex) and group three ( $G_3$ ) includes (45) patients with hyperlipidemia and T2DM as complication. Table (1) illustrated age , FBS levels , HbA<sub>1c</sub> and BMI levels for the studied subjects.

Results in table (1) illustrated no significant differences found in BMI among the studied groups.

The results showed no significant elevation of FBS in  $G_2$  compared to  $G_1$  while there was significant elevation in  $G_3$  compared with  $G_1$  and  $G_3$  compared with  $G_2$  .

There was no significant elevation in HbA<sub>1c</sub> in  $G_2$  compared to  $G_1$  while there was significant elevation in  $G_3$  compared to  $G_1$  and  $G_3$  compared to  $G_2$ .

The suitable indicator to how we can control the level of blood glucose at the past months is HbA<sub>1c</sub> , in the diabetes patients, it has been used to observe the influence of regimen exercise during the period of treatment of diabetes, increased amounts of HbA<sub>1c</sub> are found in RBCs of patients with diabetes mellitus because their HbA was linked with higher glucose concentration during the (120) days of the life time of red blood cells [13,8].

### Lipid profile and Atherogenic Index of plasma (AIP) in studied groups:-

Results in table (2) illustrated the levels of lipid profile (T.ch , TG, HDL, LDL and VLDL) and Atherogenic Index of plasma (AIP) in  $G_1$ ,  $G_2$  and  $G_3$ .

Results showed significant elevation in total cholesterol for  $G_2$  and  $G_3$  compared to control group , while  $G_3$  showed no significant elevation compared to  $G_2$  . the increase in total cholesterol in diabetic patients means prevalence of hypercholesterolemia where elevation in non-enzymatic glycosylation of LDL that refers to metabolic inhibition of LDL receptor activity was reported as an illustration for this observation [33].

Results showed significant elevation in T.ch , TG , LDL and VLDL in  $G_2$  and  $G_3$  compared to control group , while  $G_3$  showed no significant elevation compared to  $G_2$ .

Result also showed significant reduction of HDL in  $G_2$  and  $G_3$  compared to control group , while  $G_3$  showed no significant reduction compared to  $G_2$  . Each degradation of one mg HDL will correlate 2% of increase coronary artery disease [28], which is due to the death of patients with T2DM [21].

The impaired removal of LDL and chronic deficiency of insulin that may be associated with those highly atherogenic particles [2], high level of TG has been related with an increased LDL particles and increased cardiovascular risk [22].

Results of our study are in agreement with previous study that demonstrated strong relationship between AIP and lipoproteins particles size , therefore, AIP could be considered as an indicator of atherogenic lipoprotein status [23] .

## Insulin , HOMA-IR , Glucagon and Glucagon like peptide-1(GLP-1) in studied groups

The results in table (3) illustrated the levels of insulin , HOMA-IR , glucagon and glucagon like peptide-1 (GLP-1) in  $G_1$ ,  $G_2$  and  $G_3$

Results showed no significant difference for insulin in  $G_2$  compared to control group, while  $G_3$  showed significant reduction in insulin level compared to control group and  $G_2$ .

Results illustrated no significant differences found in HOMA-IR among the studied groups. It has been found that insulin resistance may be responsible for low HDL production in patients with T2DM , which is caused by alterations in hepatic function and elevation in activity of hepatic lipase ,that facilitates HDL clearance[6].

Results showed significant reduction in glucagon and GLP-1 in  $G_2$  compared to  $G_1$  , while there was high significant reduction in  $G_3$  compared to  $G_1$  and  $G_2$  .

The primary actions are to regulate insulin and glucagon secretion only when plasma glucose exceeds normal fasting levels. Thus, the deficiency of GLP-1 is now considered as part of the pathophysiology of type 2 diabetes [18].

GLP-1 controls the heart rate (HR) and blood pressure (BP) by , synthetic human GLP-1 injected into the jugular vein of male rats acutely increased systolic and diastolic BP, as well as HR , after 25 min from GLP-1 injection , would return to basal levels , the pre-treatment with phentolamine or propranolol did not prevent the elevation in BP and HR[25].

Studies demonstrated an increased myocardial glucose uptake during a hyperinsulinemic euglycemic clamp[19,34].

Other study suggested recently , that GLP-1 enhanced acetylcholine induced for earm the flowing of blood , but there was no effect on flowing of blood caused by sodium nitroprusside in healthy human subjects (T2DM Patients) with stable Coronary artery disease have approached an improvement in endothelial function which is expressed by an increase in flowing of blood mediated vasodilation of the brachial artery, regardless of changes of blood pressure systolic and diastolic during a hyperinsulinemic clamp as a response to GLP-1 . However, the improvement mediated GLP-1 in flowing of blood considerably attenuated after two months period of better glycemic control [17].

Cardiac insufficiency ( class II/ IV ) has been presented in diabetic and non-diabetic patients , an improvement of left ventricular ejection fraction , the ventilation of myocardial and oxygen consumption and quality of life are caused by GLP-1 infusion [27] . In T2DM patients with chronic heart failure , infusion of exenatide decreases Pulmonary capillary wedge pressure (PCWP) and increases both inotropism and chronotropism . These satisfactory results require additional clinical experiments for clarification if these effects will result or not in reduced mortality [32].

According to the primary and mechanistic clinical evidence , results indicated consistently toward beneficial effects of GLP-1R agonists and GLP-1 analogues on CVD in T2DM patients [26].

The homeostasis of triglyceride level in blood was caused by the directly effects of GLP-1 by decreasing of lipid stores in hepatic and adipose tissue [9] . Indeed , the reduction of high plasma triglyceride levels and hepatic triglyceride stores , it is because of the exogenous increases of plasma GLP-1 including inhibitors of the enzyme DDP-4 and the long acting GLP-1 receptor agonists . as GLP-1 is synthesized in L-cells (which are located in the small intestine), it has been suggested that GLP-1 may affect lipid absorption in intestinal and thus postprandial triglyceride excursions[10].

In the brain, the central regulation may be useful in homeostasis of triglyceride regulation , the autonomic nervous system composed of parasympathetic and sympathetic nerves ,it is related to metabolism of triglyceride by organization of adipose tissue activation and homeostasis of liver triglyceride [9].

Results showed highly significant reduction in table (3) in  $G_3$  compared to  $G_1$  and  $G_2$  in glucagon and GLP-1 levels, high significant negative correlation of GLP-1 with AIP in  $G_1$  was found, high significant positive correlation in  $G_2$  was found, significant positive correlation in  $G_3$  was found, No significant negative correlation was found of GLP-1 with insulin in  $G_1$  and  $G_2$ , while high significant positive correlation in  $G_3$  was noticed, high significant negative correlation of GLP-1 with glucagon in  $G_1$  and  $G_3$ , while significant negative correlation in  $G_2$  was found.

As of our knowledge, this is the first time, that GLP-1 is determined in hyperlipidemia patients with diabetes, that may be considered as biomarker for this disease.

### Correlation coefficient of GLP-1 versus AIP, insulin level and glucagon in all studied groups:

The value of correlation relation (r) and P-value for GLP-1 versus AIP, Insulin and glucagon level for all studied groups were illustrated in table (4).

A highly significant negative correlation was observed for GLP-1 with AIP in  $G_1$  ( $r = -0.232$ ,  $p < 0.001$ ) as shown in figure(1A), while highly significant positive correlation in  $G_2$  ( $r = +0.133$ ,  $p < 0.001$ ) as shown in figure(1B), in addition, a significant positive correlation in  $G_3$  is ( $r = +0.052$ ,  $p < 0.05$ ). as shown in figure (1C).

No significant negative correlation was observed for GLP-1 and insulin in  $G_1$  and  $G_2$  when ( $r = -0.217$ ,  $r = -0.045$ ) ( $p > 0.05$ ) respectively as shown in figures(2 A,B), whereas a high significant positive correlation in  $G_3$  ( $r = +0.187$ ,  $p < 0.001$ ) as shown in figure(2C).

A highly significant negative correlation was observed for GLP-1 with glucagon in  $G_1$  and  $G_3$  ( $r = -0.131$ ,  $r = -0.124$ ) ( $P < 0.001$ ) respectively as shown in figures (3A,C), whereas significant negative correlation was found in  $G_2$  ( $r = -0.227$ ,  $p < 0.05$ ) as shown in figure (3B).

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**Table (1): Age , BMI, FBS and HbA<sub>1c</sub> for the studied groups**

Groups Parameters	G1 Mean ± SEM	G2 Mean ± SEM	G3 Mean ± SEM	G1&G2 T. test	G1&G3 T. test	G2&G3 T. test
Subject. NO	Male (22) Female (23)	Male (23) Female (22)	Male (22) Female (23)			
Age (years)	44.53 ± 5.11	47.21 ± 7.16	48.29 ± 11.29	NS	NS	NS
BMI(kg/m <sup>2</sup> )	26.48 ± 1.37	27.11 ± 3.2	7.5 ± 3.2	NS	NS	NS
FBS (mmol/L)	5.23 ± 0.48	6.59 ± 1.09	9.75 ± 2.55	NS	S	S
HbA <sub>1c</sub> (%)	5.81 ± 0.36	5.85 ± 0.35	8.57 ± 1.48	NS	S	S

S=significant where  $P \leq 0.05$  , NS=No significant where  $P > 0.05$ .

**Table (2): Levels of lipid profile and AIP for studied groups**

Groups Parameters	G <sub>1</sub> Mean± SEM	G <sub>2</sub> Mean ± SEM	G <sub>3</sub> Mean ± SEM	G <sub>1</sub> &G <sub>2</sub> T. test	G <sub>1</sub> &G <sub>3</sub> T. test	G <sub>2</sub> &G <sub>3</sub> T. test
T.ch (mmol/L)	4.33 ± 0.40	5.58 ± 0.78	7.18 ± 1.34	S	S	NS
TG (mmol/L)	1.32 ± 0.26	2.07 ± 0.58	2.24 ± 0.76	S	S	NS
HDL (mmol/L)	1.29 ± 0.18	1.05 ± 0.25	0.95 ± 0.36	S	S	NS
LDL (mmol/L)	2.49 ± 0.25	4.24 ± 0.80	3.85 ± 0.72	S	S	NS
VLDL (mmol/L)	0.28 ± 0.04	0.40 ± 0.12	0.48 ± 0.17	S	S	NS
AIP	0.07±0.025	0.3 ± 0.11	0.37 ± 0.12	S	S	S

S=significant where  $P \leq 0.05$  , NS=No significant where  $P > 0.05$ .



**Table (3): Levels of insulin, HOMA-IR , glucagon and glucagon like peptide-1 (GLP-1) in all studied groups:**

Groups Parameters	G <sub>1</sub> Mean ± SEM	G <sub>2</sub> Mean± SEM	G <sub>3</sub> Mean± SEM	G <sub>1</sub> &G <sub>2</sub> T. test	G <sub>1</sub> &G <sub>3</sub> T. test	G <sub>2</sub> &G <sub>3</sub> T. Test
Subject.NO	Male (22) Female (23)	Male (23) Female (22)	Male (22) Female(23)			
(Insulin μIU/ml)	13.79 ±3.37	13.34 ±4.27	9.42 ± 6.1	NS	S	S
HOMA-IR	3.41 ± 0.90	3.57 ± 1.13	3.76 ± 1.21	NS	NS	NS
Glucagon (ng\ml)	13.2 ± 4.4	11.23 ±2.73	7.41 ± 3.92	S	HS	HS
GLP-1 (ng\ml)	15.71 ± 2.2	13.12 ± 3.2	5.76 ±0.84	S	HS	HS

S=significant where  $P \leq 0.05$  , NS=No significant where  $P > 0.05$  and HS=highly significant where  $P \leq 0.001$  .

**Table (4) The correlation coefficient of GLP-1 with AIP, Insulin and glucagon level and in studied groups:**

Correlation parameters	Groups		
	G1	G2	G3
GLP-1 vs AIP	HS	HS	S
	r = - 0.232	r = + 0.133	r = + 0.052
GLP-1 vs Insulin Level	NS	NS	HS
	r = - 0.217	r = - 0.045	r = +0.187
GLP-1 vs Glucagon Level	HS	S	HS
	r = - 0.131	r = - 0.227	r = - 0.124

S=significant where  $P \leq 0.05$  , NS=No significant where  $P > 0.05$  and HS=highly significant where  $P \leq 0.001$  .

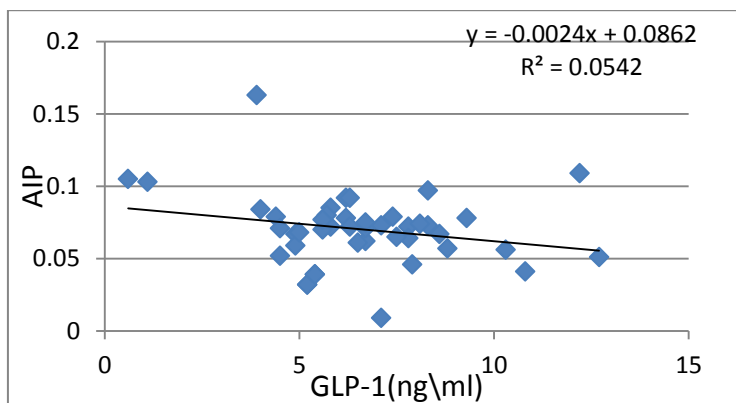


Figure (1A): The correlation relation of GLP-1 with AIP in G<sub>1</sub>.

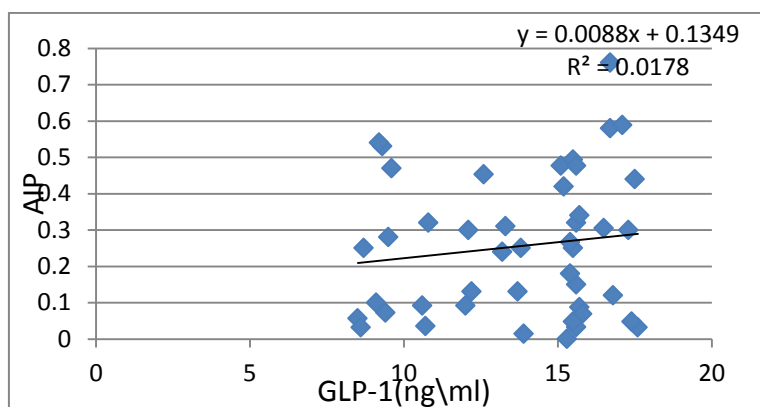


Figure (1B): The correlation relation of GLP-1 with AIP in G<sub>2</sub>.

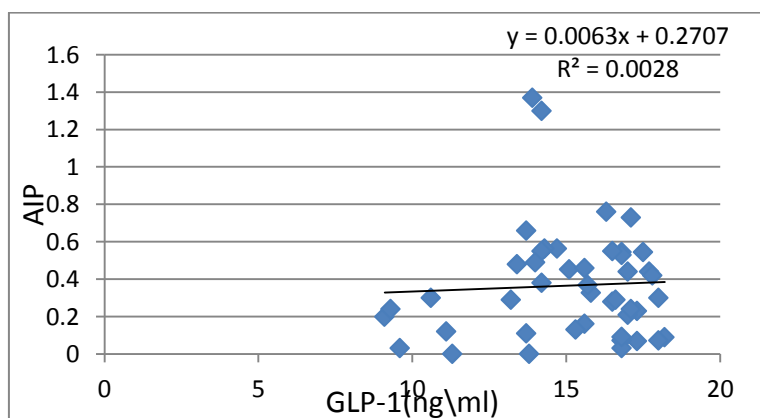


Figure (1C): The correlation relation of GLP-1 with AIP in G<sub>3</sub>.

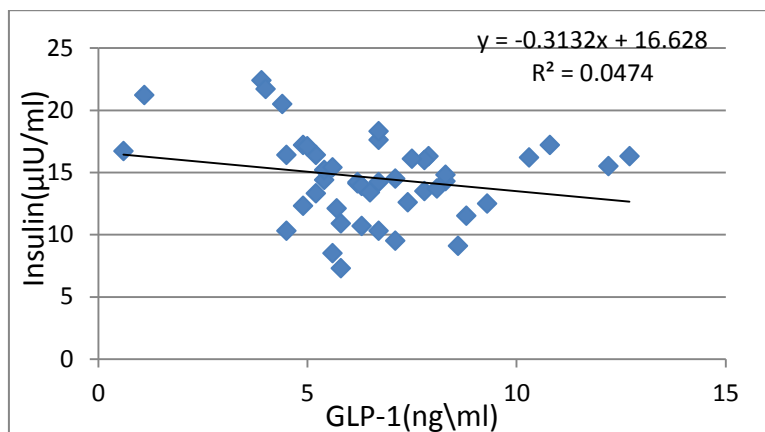


Figure (2A): The correlation relation of GLP-1 with Insulin in G<sub>1</sub>.

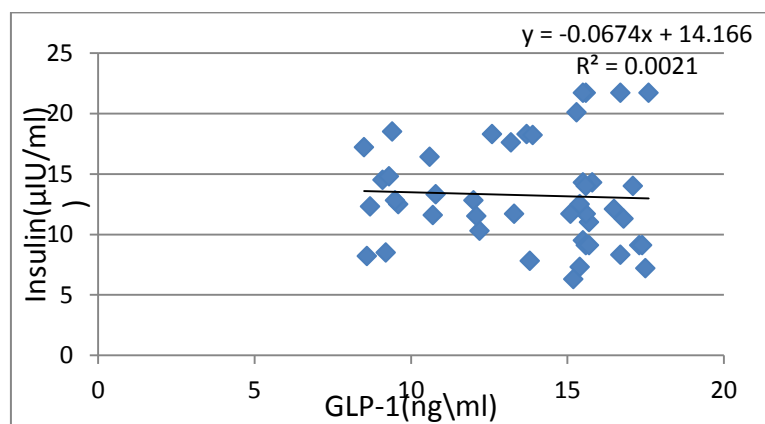


Figure (2B): The correlation relation of GLP-1 with Insulin in G<sub>2</sub>.

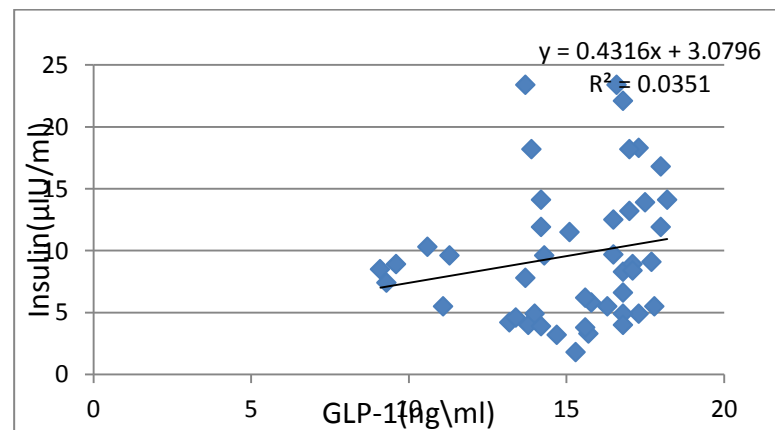


Figure (2C): The correlation relation of GLP-1 with Insulin in G<sub>3</sub>.

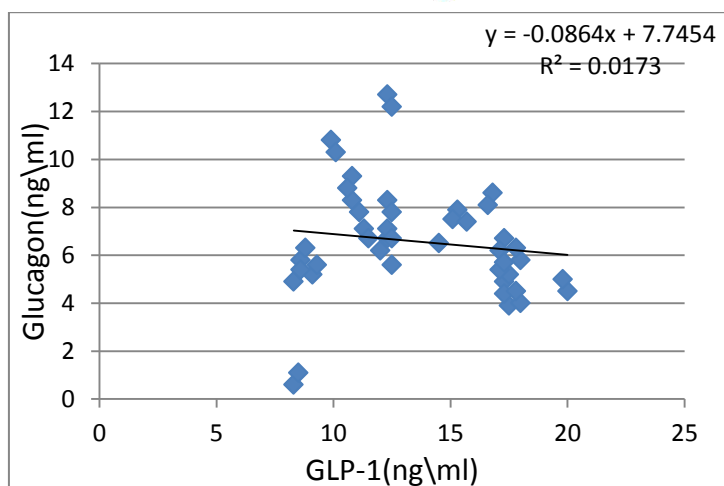


Figure (3A): The correlation relation of GLP-1 with Glucagon in G<sub>1</sub>.

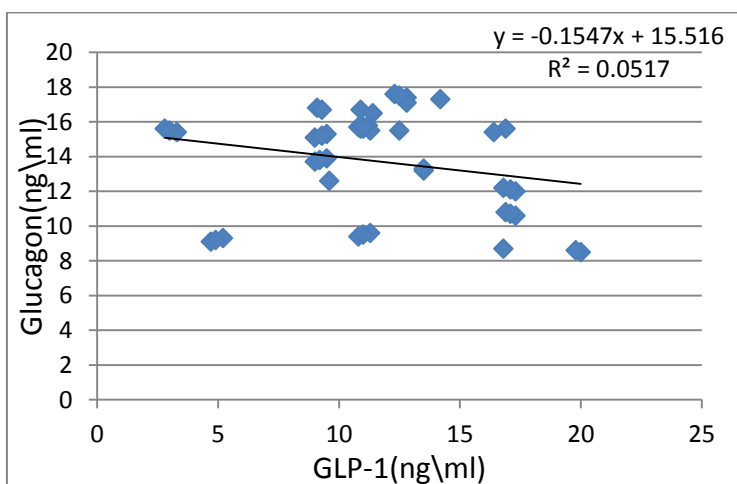


Figure (3B): The correlation relation of GLP-1 with Glucagon in G<sub>2</sub>.

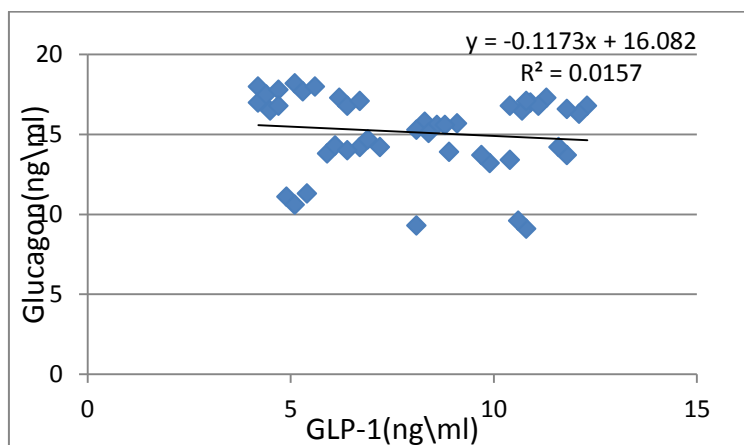


Figure (3C): The correlation relation of GLP-1 with Glucagon in G<sub>3</sub>.