

## Novel Biomarker in Polycystic ovary syndrome (PCOS) infertile females with Diabetes Mellitus prone to atherosclerosis

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### Abstract:

The study aimed to evaluate Glucagon-Like Peptide-1 levels in Polycystic ovary syndrome(PCOS) infertile female with Diabetes Mellitus (DM) and compare the results with control group , also , to find the correlation for GLP-1 with Luteinizing hormone(LH), Follicle stimulating hormone(FSH) and LH/FSH ratio that may be used in prediction atherosclerosis in these patients. The study included nineteen women with age ranged(30-40) years and BMI ranged between (30-35) Kg/m<sup>2</sup>. Subjects were divided into two groups: group(1) consist of (45)females as a healthy control and group(2) consist of (45) infertile females with PCOS and DM as complication . Fasting serum glucose was determined by using commercial kits (Biolabo SA-France); LH , FSH , prolactin were determined by ELISA, fasting serum insulin was determined by using ELISA kit(DRG-Germany).Insulin-resistance(IR) calculated by (HOMA-IR) . FSH , LH , LH/FSH ratio and prolactin levels for all studied groups were measured . A highly significant elevation in prolactin, LH and LH/FSH ratio was found when G1 comparing with G2 . While significant reduction seen in FSH levels in G2 comparing to G1 . A high significant elevation in Fasting blood glucose , % HbA1C levels in patients group when comparing to healthy control . Results revealed a highly significant elevation in insulin,HOMA-IR and glucagon, while there are a significant reduction in GLP-1levels. There is significant positive correlation was found in GLP-1 levels with (FSH) in G1 ,while a significant negative correlation was observed in levels of GLP-1 and (FSH) inG2. A significant negative correlation was found in GLP-1 levels and (LH) in G1 ,while a significant

positive correlation was found in GLP-1 levels with (LH) in G2 . Results illustrated significant negative correlation was seen in levels of GLP-1 with LH/FSH ratio in G1, while there are a significant positive correlation in GLP-1 levels with LH/FSH ratio in G2 . The conclusion could be drawn from this study that GLP-1 has a correlation with LH , FSH which may be considered as a marker in PCOS patients with DM that prone to atherosclerosis .

**Key word: GLP-1 , insulin resistance , PCOS**

**Abbreviations:**

<b><i>Code</i></b>	<b><i>word</i></b>
<b>BMI</b>	Body mass index
<b>DM</b>	Diabetes Mellitus
<b>ELISA</b>	Enzyme-linked immunosorbent assay
<b>FBG</b>	Fasting blood glucose
<b>FSH</b>	Follicle stimulating hormone
<b>GLP-1</b>	Glucagon-Like Peptide-1
<b>HOMA-IR</b>	Homeostasis model assessment for insulin resistance
<b>HbA1c</b>	Glycated hemoglobin
<b>IR</b>	Insulin-resistance
<b>LH</b>	Luteinizing hormone
<b>PCOS</b>	Polycystic ovary syndrome

**Introduction :**

The PCOS is endocrine disorders of premenopausal females <sup>(1-3)</sup> that causes oligomenorrhea and hormonally related infertility . The PCOS etiology characterized by its reproductive endocrine abnormalities of hyperandrogenism and chronic anovulation with the exclusion of specific diseases of the ovaries, adrenals, and pituitary <sup>(4)</sup> . LH is secreted in a pulsatile manner by gonadotropic cells of the anterior pituitary , regulated by the hypothalamus . LH stimulates the production of testosterone in males and estradiol in females which in turn have a negative feedback effect on gonadotropins . Females with menstruating LH in synergy directly with FSH affects ovarian follicles leading to increase steroid production and estimation ovulation .Ovulation happened when a positive feedback effect on estrogen producing the pre-ovulatory LH surge <sup>(5)</sup> FSH and LH are secreted under the effect of gonadotropin releasing hormone (GnRH) . The ratio of circulating levels of LH /FSH levels are controversial criterion for characterizing a subgroup of infertile females with PCOS and abnormalities at the level of the hypothalamic-pituitary -ovarian axis <sup>(6)</sup> . IR found to be associated with PCOS leading to increased risk for the type 2 diabetes mellitus in early age <sup>(7,8,9)</sup> . Glucagon-like peptide-1(GLP-1) is L cell-derived

peptide in intestinal endocrine . The receptors of GLP-1 are found in islet beta-cells, brain, cardiovascular system, and lung <sup>(10)</sup> . GLP-1 decreases blood glucose levels during hyperglycemia by induced insulin secretion and lowering glucose-dependent glucagon secretion <sup>(11,12)</sup> . GLP-1 promotes satiety and delays gastric emptying through central mechanisms, thereby reducing postprandial glucose levels <sup>(13)</sup> . Results in animal and human studies revealed that GLP-1 have important effects on the cardiovascular , gastrointestinal systems and the central nervous systems . Also , native GLP-1 has limited pharmacological value due to its low-lying half-life which attributed to degradation by the dipeptidyl peptidase-4 <sup>(14)</sup> . The study aimed to evaluate GLP-1 levels in PCOS infertile female with DM and compare the results with control group , also to found the correlation for GLP-1 in LH , FSH , and LH/FSH ratio that may be used in prediction atherosclerosis in these patients .

### **Materials & Methods:**

The study included nineteen women with aged ranged (30-40) years and BMI ranged between (30-35) Kg/m<sup>2</sup>. Subjects were divided into two groups: group(1) consist of (45) females as healthy control and group (2) consist of (45) infertile females with PCOS and DM as complication diagnosed by physicians' at consultant clinic of the high institute for Infertility and Assisted Reproductive Technologies , AL-Naharine University . Blood samples were obtained between days 2 and 3 of the menstrual cycle for glycated hemoglobin (HbA1c) , glucose, insulin, hormones (FSH , LH , prolactin , glucagon, GLP-1) of venous blood were collected from each subject in the study after 12 hours fast . Samples were immediately centrifuge and serum was separated and frozen until assayed . Fasting serum glucose <sup>(15)</sup>, was determined by using commercial kits( Biolabo SA-France); LH , FSH , prolactin <sup>(16)</sup> determined by ELISA kit(Biomerieux vidas, France) ,fasting serum insulin <sup>(17)</sup> was determined by using ELISA kit (DRG-Germany) . Insulin resistance was estimated by HOMA-IR estimated by the formula <sup>(18)</sup> : [ fasting glucose × fasting insulin ] / 22.5 . Also LH /FSH ratio was calculated . T-test was used to calculated the differences of mean . Results were expressed as mean ± SD and P≤ 0.05 and 0.001 were considered significant and high significant respectively .

### **Results & Discussion :**

#### Analytical parameters:

The mean ± SD and T-test of descriptive parameters for G1 and G2 with aged ranged (30-40) years and BMI ranged between (30-35 ) Kg/m<sup>2</sup> are presented in table (1) . Results showed FSH , LH , LH/FSH ratio and prolactin levels for all studied groups . A highly significant elevation in prolactin ,LH and LH /FSH ratio were found when G1 comparing with G2 , while significant reduction seen in FSH levels in G2 comparing to G1 .

**Table(1) : Descriptive parameters for studied groups**

<b>Groups</b> <b>Parameters</b>	<b>G1</b> <b>n = 45</b>	<b>G2</b> <b>n = 45</b>	<b>T-test</b> <b>G1 vs G2</b>
<b>FSH (mU/ml)</b>	7.25± 0.72	3.69 ± 0.49	1.48318E-44
<b>LH (mU/ml)</b>	4.82 ± 0.82	11.79 ± 1.97	2.58126E-37
<b>Prolactin (ng/ml)</b>	12.41 ± 1.29	21.77 ± 2.41	7.60985E-39
<b>LH /FSH ratio</b>	0.67 ± 0.14	1.63 ± 0.28	1.65499E-34
<b>FBG ( mg/dl)</b>	95.92 ± 4.06	251.19 ± 50.20	1.53255E-35
<b>% HbA1c</b>	5.10 ± 0.60	10.41 ± 1.50	2.14991E-37

\* (S)significant differences which p-value < 0.05 , (HS) high significant differences which p-value < 0.001 , (NS) No significant differences which p-value > 0.05 .

The LH levels elevated in arrests follicular cells and induced theca-cell mediated androgen production led to increased androgenic environment in the ovary impairs follicular maturation <sup>(19)</sup> . Prolactin (PRL) is structurally related to growth hormone (GH) and human placental lactogen so , like GH prolactin acts on tissues directly and the levels increase in response to sleep and to physical or emotional stress <sup>(20)</sup> . Effect of increase PRL is lowered in normal levels of estrogen in females and testosterone in males <sup>(21)</sup> . About 15% to 20% of females with PCOS and mildly increased in prolactin levels<sup>(22)</sup> .The administration of FSH for ovulation stimulation the progression of a single follicle causing a singleton live birth . Risks linked with ovulation stimulation involved ovarian hyperstimulation syndrome and pregnancy with multiples <sup>(23,24)</sup> . On the other hand , a highly significant elevation in LH/FSH ratio in patient group as compared to control was absorbed . The increased in LH/FSH ratio in this study was agreement with many studies <sup>(25,26)</sup> . More et al . repoted that LH/FSH ratio to show high significant decrease in PCOS with IR compared to PCOS without IR <sup>(27)</sup> . Beydoun et al suggested that an opposite association in LH/FSH ratio with IR , idea that IR and LH/FSH ratio may compose alterative pathway in the pathogenesis of PCOS <sup>(25)</sup> . Results in table (1) revealed high a significant elevation in FBG and % HbA1c levels in patients group when comparing to healthy control . HbA1C reflect the average glucose concentration over the past three months . Recently American Diabetes Association involved HbA1c levels important to marker in diabetes (≥ 6.5 %HbA1c) or elevated risk for diabetes (5.7 - 6.4%) <sup>(28)</sup> . High prevalence of increased HbA1c in patient with PCOS and elevated risk of increased HbA1c associated with PCOS revealed that PCOS itself linked to the abnormal HbA1c status <sup>(29)</sup> .

**Table(2): Levels of Insulin , HOMA-IR , glucagon and GLP-1 for two studied groups**

<b>Groups</b>	<b>G1 n = 45</b>	<b>G2 n =45</b>	<b>T-test G1 vs G2</b>
<b>Parameters</b>			
<b>Insulin (<math>\mu</math>IU/ml)</b>	6.55 $\pm$ 0.88	17.53 $\pm$ 1.56	4.60379E-59
<b>HOMA-IR</b>	27.95 $\pm$ 4.17	195.15 $\pm$ 41.30	2.26508E-44
<b>Glucagon (pg/ml)</b>	88.57 $\pm$ 32.20	225.73 $\pm$ 70.7	6.79807E-20
<b>GLP-1( ng/dl )</b>	0.319 $\pm$ 0.07	0.14 $\pm$ 0.04	5.98276E-25

\* (S)significant differences which p-value < 0.05 , (HS) high significant differences which p-value < 0.001 , (NS) No significant differences which p-value > 0.05 .

Results in table (2) illustrated levels of insulin , HOMA-IR , glucagon and GLP-1 in G2 and G1 . Results revealed highly significant elevation in insulin , HOMA-IR and glucagon ,while there are significant reduction in GLP-1 levels . It was reported <sup>(30,31)</sup> that PCOS women were hyperinsulinemic . The PCOS is identified by IR with hyperinsulinemia . Insulin resistance have a role in the metabolic syndrome <sup>(32)</sup> .

The GLP-1 induced 50–70 % of total postprandial insulin secretion <sup>(33)</sup> . Additionally, GLP-1 has a pancreatic effects, involved elevation insulin biosynthesis, lowering glucagon secretion and lowering beta-cell glucose sensitivity and beta-cell mass <sup>(34,35)</sup> . GLP-1 has insulinomimetic <sup>(36)</sup> and insulinotropic <sup>(37)</sup> effects are predicated on ambient glucose levels, minimizing risks of hypoglycemia and the need for glucose infusion. Therefore, the pharmacological properties of GLP-1 are important to induced myocardial glucose uptake during dysfunction of postischemic contractile .

### **Relationships and correlation coefficients:**

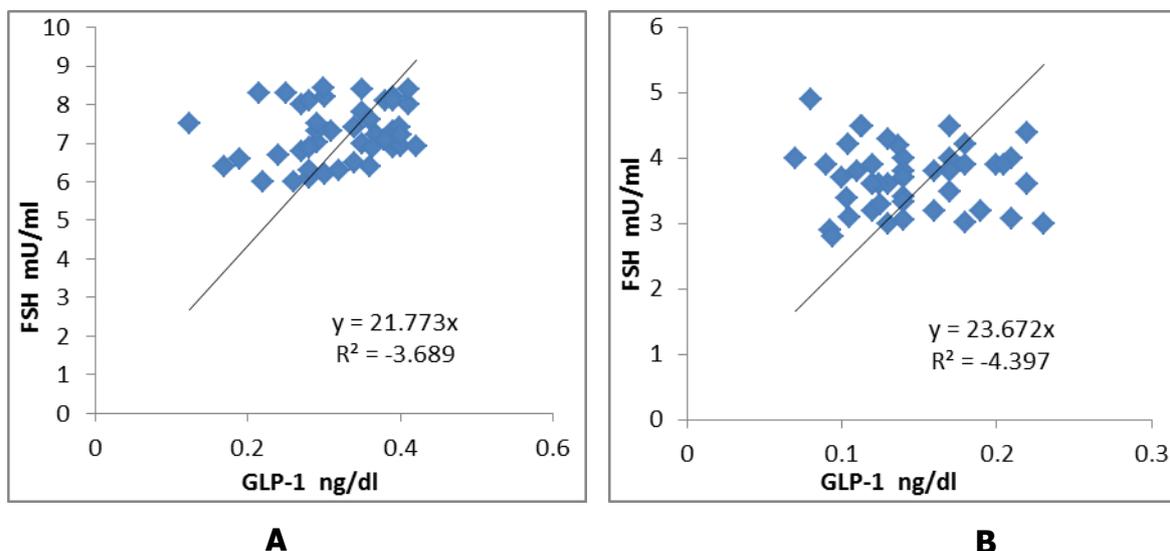
Relationship of GLP-1 with FSH , LH and LH/FSH ratio were studied for studied groups which shown in table (3) .

**Table (3) : Correlation coefficient and p-value for GLP-1 with FSH , LH , and LH/FSH ratio for studied groups**

Groups Parameters	G1		G2	
	r <sub>1</sub>	P – value	r <sub>2</sub>	P- value
GLP-1 vs FSH	0.224	S	-0.058	S
GLP-1 vs LH	-0.222	S	0.127	S
GLP-1 vs LH/FSH	-0.318	S	0.159	S

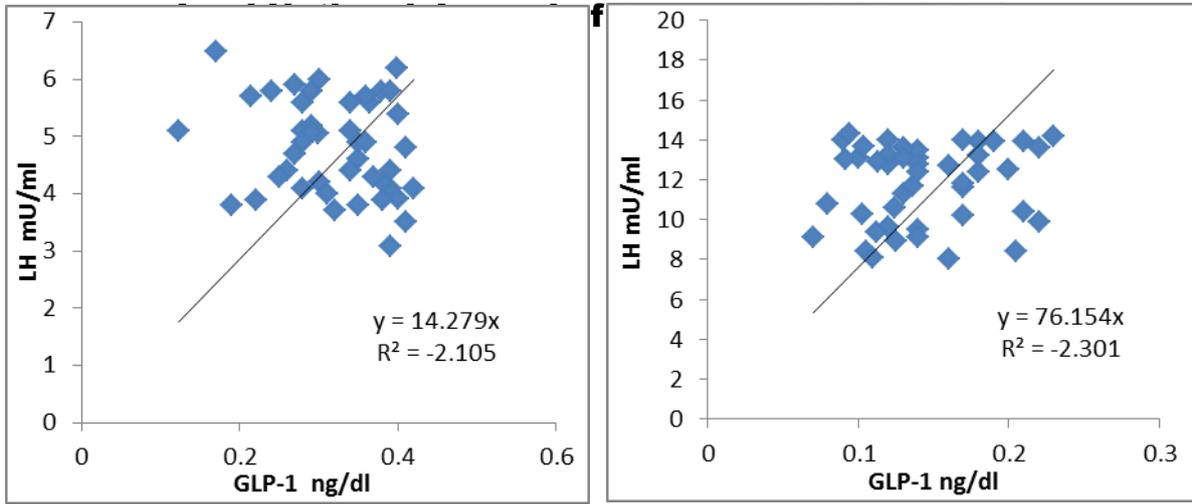
\* (S)significant differences which p-value < 0.05 , (HS) high significant differences which p-value < 0.001 , (NS) No significant differences which p-value > 0.05 .

There is a significant positive correlation was found between GLP-1 levels and (FSH) in G1 as shown in figure (1- A) ,while a significant negative correlation was found in G2 in GLP-1 levels with(FSH) ,as shown in figure (1-B).



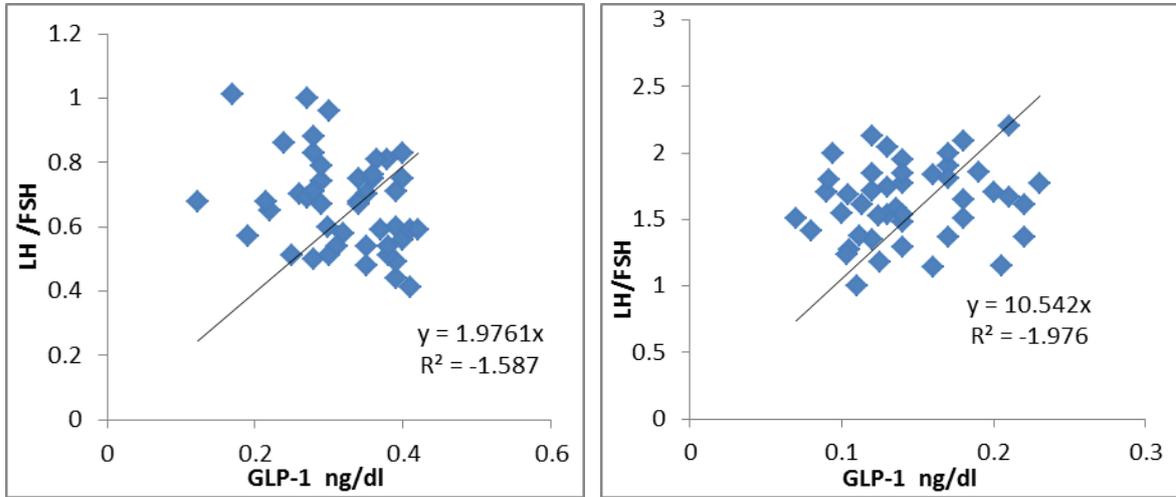
**Figure (1) Correlation between GLP-1 and FSH in**

There is a significant negative correlation was found between GLP-1 levels and (LH) in G1 as shown in figure (2-A) ,while a significant positive correlation was observed in G2 between GLP-1 levels and (LH) , as shown in figure (2 -B).



**A** **B**  
**Figure (2) Correlation between GLP-1 and LH in G1(A),G2(B)**

Results in table (3) illustrated a significant negative correlation was found in GLP-1 levels with LH/FSH ratio in G1 as shown in figures (3-A), while there are a significant positive correlation in GLP-1 levels with LH/FSH ratio in G2, as shown in figures (3-B).



**A** **B**  
**Figure (3) Correlation between GLP-1 and LH/FSH ratio in G1(A),G2(B)**

The conclusion could be drawn from this study that GLP-1 has a correlation with LH, FSH which may be considered as a marker in PCOS patients with DM that prone to atherosclerosis. The study aimed to evaluate GLP-1 levels in PCOS infertile female with DM and compare the results with control group, also to found the correlation for GLP-1 with LH, FSH, and LH/FSH ratio that may be used in prediction atherosclerosis in these patients.

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## **مؤشرات حيوية جديدة لمتلازمة تكيس المبايض في النساء العقيمات المصابات بداء السكري والمعرضات لتصلب الشرايين**

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### **الخلاصة :-**

تهدف الدراسة لقياس مستويات GLP-1 في متلازمة تكيس المبايض للنساء العقيمات المصابات بداء السكري ومقارنة النتائج مع مجموعة السيطرة وكذلك معرفة العلاقة بين GLP-1 وهرمون انبثاق البويضة من الجريبات (LH) ، الهرمون المنشط للحويصلات المبيضية (FSH) ونسبة الهرمونين LH/FSH التي يمكن استخدامها في التنبؤ بتصلب الشرايين في تلك المريضات . تضمنت الدراسة (٩٠) امرأة معدل اعمارهن بين (٣٠-٤٠) سنة ومؤشر كتلة الجسم لهن يتراوح بين (٣٠-٣٥ كغم/م<sup>٢</sup>) ، تم تقسيمهن الى مجموعتين : المجموعة (١) تتكون من (٤٥) انثى من الاناث الاصحاء ، والمجموعة الثانية تتكون من (٤٥) من الإناث العقيمات اللواتي يعانين من متلازمة تكيس المبايض وداء السكري . تم قياس مستوى السكر في مصل الدم عند الصيام وتم قياس (LH) ، (FSH)

وهرمون الحليب بواسطة ELISA وقيس الانسولين في مصّل الدم عند الصيام باستخدام تقنية الـ(ELISA) ، قيس مقاومة الانسولين بالـ(HOMA-IR) . أظهرت النتائج ارتفاع كبير لمستويات هرمون الحليب ، (LH) ونسبة الهرمونين LH/FSH عند مقارنة المجموعة (١) مع المجموعة (٢) ، بينما بينت الدراسة ان هناك انخفاض كبير في مستويات (FSH) في المجموعة (٢) عند مقارنتها بالمجموعة (١) . الارتفاع الكبير في مستويات سكر الدم والـ HbA1C % في المجاميع المصابة عند مقارنتها مع مجموعة الاصحاء . كشفت النتائج الارتفاع الكبير جدا في مستويات الانسولين ، مقاومة الانسولين والكلوكاكون في حين هناك انخفاض ملحوظ في مستويات الـ GLP-1 . هناك علاقة ايجابية كبيرة متبادلة في مستويات GLP-1 مع FSH في المجموعة (١) في حين هناك ارتباط سلبي كبير لمستويات GLP-1 مع FSH في المجموعة (٢) . كما يلاحظ علاقة سلبية كبيرة موجودة في مستويات GLP-1 مع هرمون LH في المجموعة (١) بينما هناك ارتباط ايجابي كبير في مستويات GLP-1 مع هرمون LH في المجموعة (٢) . يتضح من النتائج ان هناك ارتباط سلبي هام في مستويات GLP-1 ونسبة الهرمونين LH/FSH في المجموعة (١) بينما يكون الارتباط ايجابي في مستويات GLP-1 مع نسبة الهرمونين LH/FSH في المجموعة (٢) . يمكن الاستنتاج من هذه الدراسة بان الـ GLP-1 له علاقة مع (FSH) ، (LH) باعتباره علامة لمتلازمة تكيس المبايض للمريضات المصابات بداء السكري وعرضة للإصابة بتصلب الشرايين .

**الكلمات المفتاحية :-** الكلوكاكون مماثل الببتيد-١ ، مقاومة الانسولين ، متلازمة تكيس المبايض