International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 08, 2020
ISSN: 1475-7192

Serum Level of Relaxin-2 Correlated to the Diabetic Patients with Coronary Artery Disease

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Abstract

Relaxin has Vasodilatory effects of cardiovascular complication of diabetes through promotes flow and vasodilation in coronary arteries. This study aim to evaluate of relaxin as a biomarker for cardiovascular complication of diabetes. The study included88 Iraqi subjects and divided into three groups: (29) Type 2 diabetes mellitus patients and (29) diabetic patients with CAD compared with (30) healthy person. Serum relaxin-2 was determined by an enzyme immunoassay for quantitative in vitro diagnostic measurement using kit manufactured by Mybiosource (ELIZA kit), insulin by Demeditec (ELIZA kit) and Blood sugar profile including fasting blood sugar and HbA1c were done by Roche/Hitachi cobas c 311device. The mean ± SD of serum Relaxin-2 (pg/ml) of type 2 diabetic (20.65±4.14) and diabetic with CAD(17.95±5.18) patients levels showed a significant decrease ($p<0.05$) in comparison to that level in control group (24.28±7.31). Meanwhile Relaxin-2 level in diabetic patients with CAD demonstrate a highly significant decrease ($p<0.01$) in comparison to that level of control group. However, there is no significant differences ($p\geq0.05$) between T2DM and diabetic with CAD in compare to each other. We concluded that there was a negative correlation between Relaxin-2 and FBS in diabetic patients with CAD.

Keywords: *Type 2 Diabetes Mellitus, Coronary Artery Disease, HbA1c, Insulin; and Relaxin-2.*

I. Introduction

Relaxin-2 is a two-chain peptide hormone (6 kDa) with a structure and processing similar to insulin. It is produced as a pro-hormone, containing a signal sequence and B-C-A domain configuration, and after processing by prohormone convertases, the C domain is removed and three disulphide bonds are formed between six highly conserved cysteine residues in the A (24 amino acid) and B(29 amino acid) chains (1). The mature relaxin is constituted by the A and B chains with three disulphide bonds, like insulin (2). The relaxin peptide family is encoded by seven genes in humans, which

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Received: 18 Apr 2020 | Revised: 09 May 2020 | Accepted: 12 Jun 2020

include the relaxin genes RLN1, RLN2 and RLN3, as well as the insulin-like peptide genes INSL3, INSL4, INSL5 and INSL6 (3).

Diabetic cardiomyopathy characterized by damage to the myocardium, in particular diastolic dysfunction (4), where the heart is unable to relax and undergo filling during the diastolic part of the cardiac cycle. Diabetes-induced collagen cross-linking that accumulates within the myocardium can ultimately lead to structural remodeling of the heart tissue, including cardiac fibrosis (5). Mechanisms that contribute to the phenotype of the diabetic myocardium include (but are not limited to) impairments in function of type 2 ryanodine receptors (RyR2), increased oxidative stress, activation of the renin-angiotensin-aldosterone system (RAAS), endothelin-1 upregulation, with mitochondrial dysfunction, inflammation and endoplasmic reticulum stress (6).

Relaxin has Vasodilatory effects of cardiovascular complication of diabetes through promotes flow and vasodilation in coronary arteries. An earlier study showed that relaxin lowered blood pressure, this vasodiation involves increased NO production from the endothelium (5) Via the endothelium receptor type B, is a G protein-coupled receptor (ETB receptor) which activate phosphatidylinositol-calcium second messenger system, These findings led to the clinical evaluation of relaxin as a vasodilator in patients with acute HF (heart failure) (7). This study aim to evaluate of relaxin as a biomarker for cardiovascular complication of diabetes

II. Methods

This study was designed as case–control study and done at National Diabetes Center for Research and Treatment / Mustansiriyah University. We studied 88 Iraqi subjects and divided into three groups: (29) Type 2 diabetes mellitus patients and (29) diabetic patients with CAD compared with (30) healthy person in term of non-diabetic, non-hypertensive and have no ischemic heart disease. Patients with Type 1 diabetes, gestational diabetes, chronic diabetic complication (nephropathy, retinopathy and neuropathy), type 2 diabetes taking insulin injection, malignancies were exclusion.

Serum relaxin-2 was determined by an enzyme immunoassay for quantitative in vitro diagnostic measurement using kit manufactured by Mybiosource (ELIZA kit), insulin by Demeditec (ELIZA kit) and Blood sugar profile including fasting blood sugar and HbA1c were done by Roche/Hitachi cobas c 311device.

III. Results

The mean ± SD of serum relaxin-2 (pg/ml) of type 2 diabetic (20.65±4.14) and diabetic with CAD (17.95±5.18) patients levels showed a significant decrease ($p<0.05$) in comparison to that level in control group (24.28±7.31). Meanwhile relaxin-2 level in diabetic patients with CAD demonstrate a highly significant decrease ($p<0.01$) in comparison to that level of control group. However, there is no significant differences ($p\geq0.05$) between T2DM and diabetic with CAD in compare to each other.

The results of blood sugar profile presented in (Table 1) indicated highly significant ($p < 0.01$) differences of FBS, HbA1c, HOMA-IR and HOMA- β between all studied groups. Meanwhile the insulin result indicate a significant differences ($p<0.05$) of studied groups.

Table 1: Mean±SD levels of relaxin-2 and blood sugar profile.

Parameter	Control	T2DM	Diabetic with CAD	P value
Relaxin-2 (pg/ml)	**24.28±7.31**	**20.65±4.14**	**17.95±5.18**	**0.001**
FBG (mg/dl)	**90.88±6.23**	**180.7±68.86**	**182.31±78.8**	**0.001**
HbA1C%	**5.3±0.31**	**9.906±1.91**	**9.45±2.08**	**0.001**
Insulin (µIU/ml)	**10.13±2.72**	**15.66±7.85**	**12.82±6.4**	**0.013**
HOMA-IR	**2.21±0.63**	**7.60±6.4**	**5.75±3.83**	**0.001**
HOMA-β	**144.04±47.73**	**68.82±54.77**	**55.16±43.48**	**0.001**

Table 2 show the correlation results of relaxin-2 and sugar profile where it was observed significant ($p<0.05$) correlation between serum relaxin-2 with FBS and HOMA-β in diabetic patients with CAD. While the overall analyze of all groups samples indicated highly significant negative correlation with FBS and HbA1c and a significant positive correlation with HOMA- β.

Table 2: Pearson correlation analysis of relaxin-2(pg/ml) with sugar profile in studied groups.

parameters	T2DM (r)	Diabetic with CAD (r)	All groups (r)
FBS(mg/dl)	**-0.303**	**-0.439***	**-0.409****
HbA1C %	**-0.363**	**-0.168**	**-0.389****
Insulin (µIU/ml)	**0.116**	**-0.042**	**-0.097**
HOMA-IR	**-0.016**	**-0.296**	**-0.21**
HOMA- β	**0.094**	**0.402***	**0.300***

***p<0.05, **p<0.01, No asterisk p≥0.05**

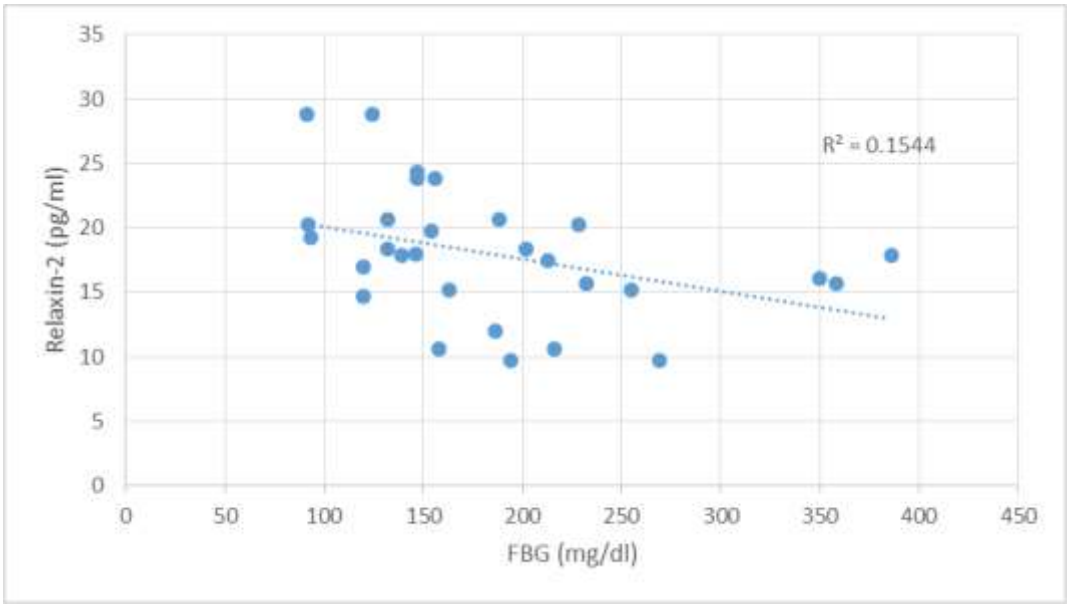

Figure 1: correlation between serum relaxin-2 and FBS in diabetic patients with CAD.

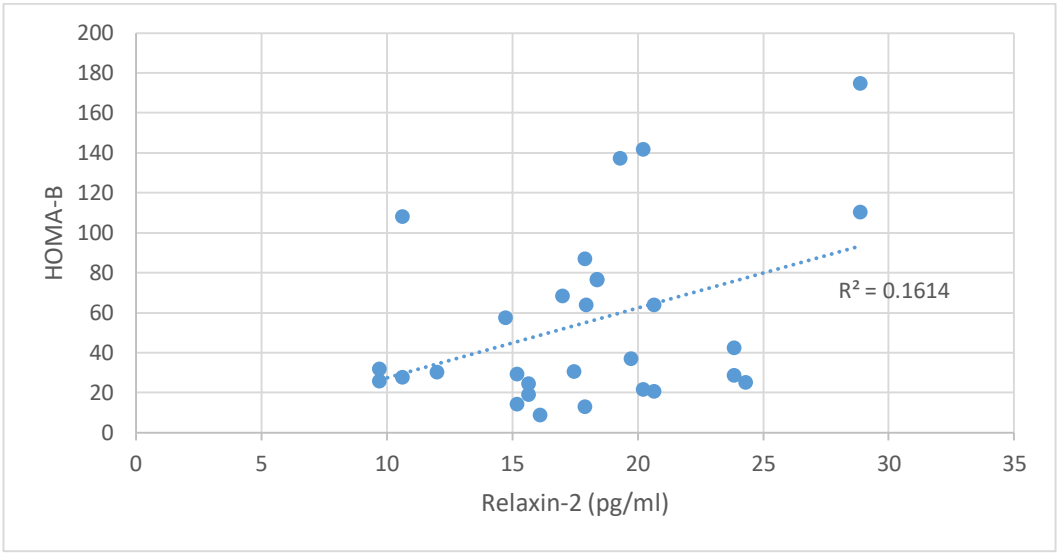

Figure 2: the correlation between serum elaxin-2 and HOMA-B in diabetic patients with CAD.

Received: 18 Apr 2020 | Revised: 09 May 2020 | Accepted: 12 Jun 2020

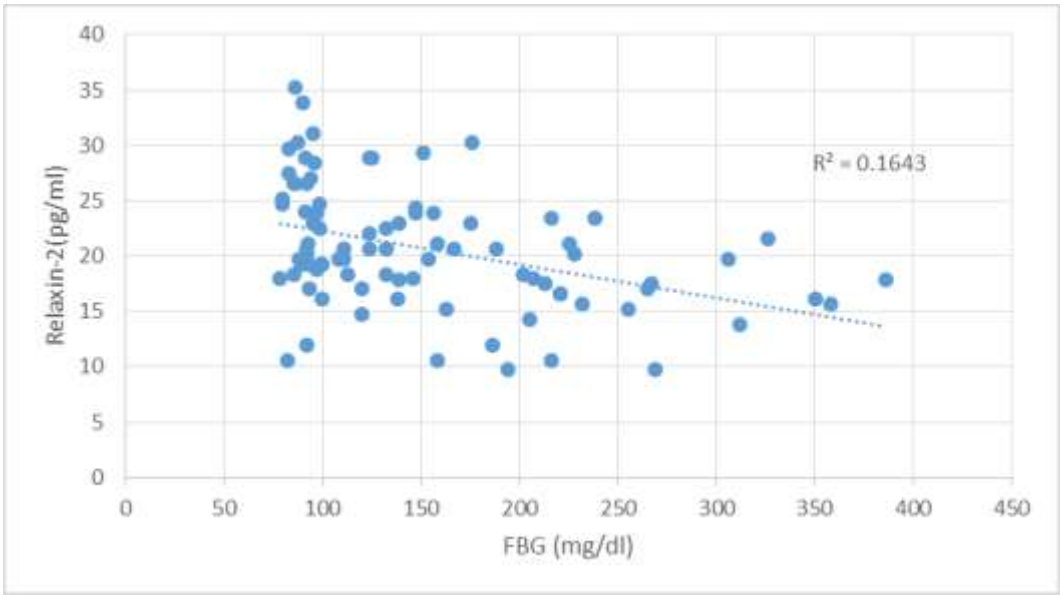

Figure 3: correlation between serum relaxin-2 with FBS in all samples (control, T2DM and diabetic patients with CAD groups).

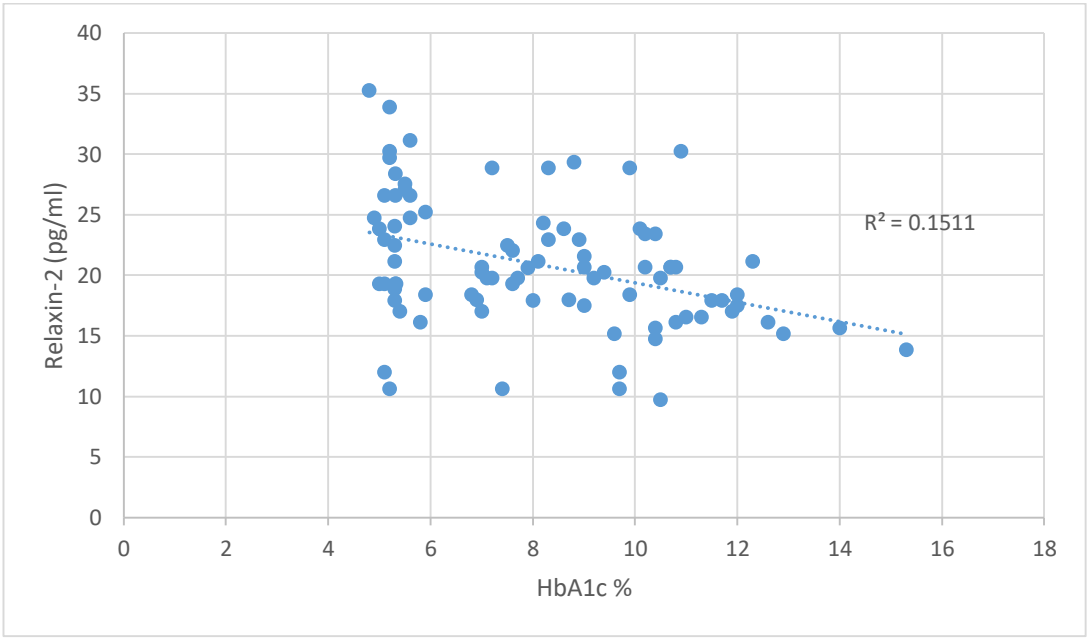

Figure 4: correlation between serum relaxin-2 with HbA1c in all samples (control, T2DM and diabetic patients with CAD groups).

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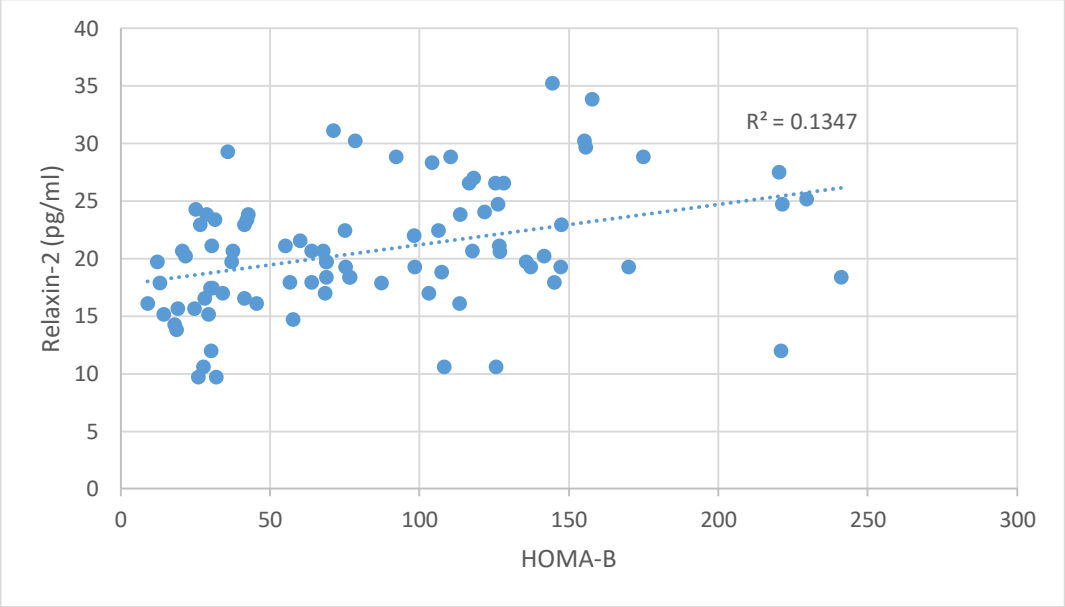

Figure 5: correlation between serum relaxin-2 with HOMA- β in all samples (control, T2DM and diabetic patients with CAD groups).

IV. Discussion

It is well known that T2DM patients have a high risk of developing cardiovascular disease, cardiovascular complication is associated with significant cardiac morbidity and mortality (4). Endothelial dysfunction is a pivotal event in atherogenesis and cardiovascular disease that can be identified in the clinical research setting by evaluating blood flow and vascular reactivity and by measuring various plasma markers of endothelial activation, coagulation/fibrinolysis, and inflammation. Obesity, insulin resistance, and endothelial dysfunction closely coexist throughout the natural history of type 2 diabetes (8).

Insulin resistance and persistent hyperinsulinemia are found in a variety of medical condition including dyslipidemia and hypertention and it has established as a precursor and acts as a strong factor linking T2DM with CVD (9), the results in this study indicate a significant increase of FBS, HbA1c, serum insulin and HOMA-IR of T2DM group and diabetic with CAD group in comparison to that in control group due to decreased glucose utilization and increased hepatic glucose production result in hyperglycemia. Glucose uptake via glucose transporter (GLUT)-4, which is insulin dependent, is reduced leading to decreased glucose availability in the myocardium, so, fatty acid (FA) uptake is increased leading to lipid accumulation in the form of triglyceride (TG) resulting in cell damage (10). These findings are agreement with Y. Huang, et al, concluded impaired fasting glucose, or raised HbA1c, was associated with an increased risk of cardiovascular disease (11), D. S.H. Bell, reported that the prevalence of diabetic cardiomyopathy in the type 2 diabetic patient is higher than was previously believed, and diabetic cardiomyopathy is due to diastolic dysfunction caused by myocardial fibrosis, which occurs in response to hyperglycemia (12). M. P Srinivasan, et al, establishes the important role of IR in the pathogenesis of diabetic vascular disease, IR as measured by HOMA might aid in predicting the severity

of CAD (13). Also the results in agreement with E.Bonora, et al, indicated that insulin resistance, as estimated by HOMA-IR, was a strong predictor of CVD in type 2 diabetes (14). Masahiro Yamazoe, et al, reported that IR and fasting insulin predicted CAC progression, whereas fasting glucose and HbA1c did not, IR may play important roles not only in atherogenesis but also in advanced plaque progression through promoting apoptosis of endothelial cells, macrophages, and vascular smooth muscle cells (15) this findings disagreement with results showed in Table (1) in concerning with FBS and HbA1c not predicted.

Also indicate a highly significant decrease of HOMA- β in (T2DM) group and (diabetic with CAD) group in comparison to that in control group. This finding was agree with previous studied Steven M Haffner, et al, who's reported that HOMA provides a useful model to assess β-cell function through its low HOMA β-cell function in T2DM (16). Decreases of β-cell function determined by HOMA- β were it is lower value (17). Hyperglycemia can impair β-cell function, causing a worsening metabolic state, poorly functioning, de-differentiated β cells and loss of β cell mass from apoptosis (18). Numbers of studies in Asian population have demonstrated the dominant role of β-cell dysfunction in the pathogenesis of T2DM (19), and increased insulin requirements imposed by insulin resistance, and toxicities from hyperglycemia and elevated free fatty acids (20), The accumulation of long-chain fatty acid-CoA, potentially resulting in many deleterious effects on β-cell function and viability (21).

The results of serum Relaxin-2 in (T2DM) and (diabetic with CAD) groups showed a significant decrease in comparison to that results in (control) group. These finding agreements with XiaohuiZhang, et al, who has concluded that the plasma levels of relaxin-2 in diabetes patients were lower than in controls (22). Also results of relaxin agreement with J. M. V. Raleigh, et al, and H. Hooi Ng, et al, studies who's showed that relaxin may offer a promising role in the prevention or treatment of diabetes-related cardiovascular complications, Although pre-clinical studies suggest a potential promising role for relaxin to protect against diabetes-associated cardiovascular complications, due to low value of serum relaxin-2 in T2DM (23) (5). The peptide hormone relaxin act as vasodilation through inhibit or reduce the vasoconstriction effects of angiotensin-II (AngII) (24), anti-fibrotic, angiogenic and anti-apoptotic (25). Relaxin-2 also acts on neutrophils by increasing the expression of iNOS protein and the release of NO, because iNOS is known to yield high amounts of NO, as high NO concentrations are deemed able to inhibit neutrophil function, so it is considered as anti-inflammatory factor (26). Relaxin-2 has important impact on the cardiovascular pathophysiology, it seems clear that relaxin is a new potential candidate as a therapeutic agent to treat/prevent cardiometabolic diseases, so that it has clear effects on vascular function, has positive chronotropic and inotropic effects in the heart, and prevents ischemia/reperfusion injury and atrial fibrillation (27). In our study indicated that serum RLX-2 was positively associated with parameter of islet β-cell function and negatively associated with the levels of fasting glucose and HbA1c. This finding in agreement with (28).

V. CONCLUSIONS

In this study concluded there was a negative correlation between relaxin-2 and FBS in diabetic patients with CAD. Further studies are required to confirm and expand these findings.

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