Glucagon-like Peptide-1 Levels and Related Parameters in Rheumatoid Arthritis Patients Prone to Atherosclerosis

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Abstract

The study aimed to estimate the role of glucagon-like peptide-1 (GLP-1) and visfatin as a novel pro inflammatory marker in Rheumatoid Arthritis (RA) according to the activity scores of disease to assess the possibility of introducing glucagon-like peptide-1 and visfatin in the diagnosis and monitoring of RA patients and to found the correlation of visfatin level with GLP-1 and AIP in patients prone to atherosclerosis ,fifty healthy individuals as control group (G_1) and fifty rheumatoid arthritis (RA) patients (G_2) were enrolled in this study with middle age ranged (30 – 40) years and BMI ≥24 kg/m^2. ESR ,RF, lipid profile, CRP,insulin, visfatin and GLP-1were determined. Results in table (1) revealed highly significant increase in ESR,RF,TC,TG,LDL,VLDL and AIP level in rheumatoid arthritis (G_2) comparing to (G_1) while significant decrease noticed in (G_2) group comparing to (G_1). Results in table(2) showed highly significant increase in insulin ,CRP, visfatin and GLP-1 level Results in table(3) illustrated correlation relation data and results revealed highly significant ,were r=0.035 for GLP-1 with visfatin for (G_1), and highly significant , r= -0.089 for (G_2) as shown in figure(1-A) and(1-B), the result also highly significant were r= -0.183 for GLP-1 with CRP for control group and significant ,r= 0.043 for GLP-1 with CRP for RA group as shown in figure(2-A) and(2-B), and significant, r= -0.056 for GLP-1with AIP for G_1 and no significant, were r= 0.042 for GLP-1 with AIP for G_2 as shown in figure (3-A)and (3-B). conclusion that summarized from this study is glucagon-like peptide-1 and visfatin plays a role in RA pathogenesis that can be considered marker in RA . and may be used as a drug in future for RA patients.

Keyword:GLP-1, Rheumatoid Arthritis, Atherosclerosis.

Abbreviation: Rheumatoid arthritis (RA), ESR (erythrocyte sedimentation rate), RF(rheumatoid factor), CRP (C-reactive protein)

Introduction

Glucagon-like peptide-1 (GLP-1) is a member of the pro-glucagon incretin family involved in the control of zest and satiety ,GLP-1 acts during GLP-1 receptor (GLP-1R), a 463 amino-acid member of the G protein-coupled receptor (GPCR) super family [1]. Bioactive GLP-1 found in two equipotent molecular forms: GLP-$^{17–37}$ and GLP-$^{17–36}$ amide. GLP-1 is rapidly split by DP IV, which results in the production of largely inactive molecular GLP-$^{19-36}$ amide and GLP-$^{17-37}$ forms. In the cardiovascular system, incretins have been recently facilities for the increase of endogenous antioxidant defenses, repression of cardiomyocyte apoptosis, attenuation of endothelial inflammation and dysfunction[2]. In this brief review, we will summarize recent progress about the important role of GLP-1 in myocardial protection and signaling pathway. [3]. In pacing-induced heart failure case, the stimulation of GLP signaling by GLP-1 has also been demonstrated to improve cardiac performance in conscious dogs with dilated cardiomyopathy [4].

Recently, a significant number of studies have indicated useful effects of GLP-1 on cardiovascular function, which gave justification for the use of GLP-1 in the treatment of cardiovascular diseases. [3].

Infusions of GLP-1 have also been shown to promote post-prandial lipaemic excursions [5]., an distinct risk factor in the development of atherosclerotic cardiovascular disease. GLP-1 receptors are expressed on cardiac tissue, so, it is possible that the hormone, or its synthetic analogues, may directly mediate a range of cardiac functions. Recent research include the investigation of GLP-1 involvement in myocardial metabolism, coronary blood flow, pre-/post-ischemic conditioning, left ventricular (LV) remodeling and LV performance. Studies including animal and human have suggested that GLP-1 agonists may have effects on myocardial metabolism, and this may be translated into possible therapeutic benefit on cardiac function. In addition, an animal study suggested that GLP-1 may have effects on coronary blood flow and protect against ischemia and reperfusion injury [6].

The Rheumatoid Arthritis (RA) is a chronic autoimmune disease identified by synovial inflammation, cartilage damage, and bone erosion, [7].

Visfatin, known as nicotinamide phosphoribosyltransferase (Nampt), was originally described as a cytokine involved in early B-cell development and was later renamed visfatin since it is secreted mainly by visceral fat [8].

A proinflammatory action of visfatin was described to be mediated by the insulin signaling pathway through Protein Kinase B (PKB) phosphorylation [9].. Studies reported the up regulation of visfatin inactivated RA-SFs in response to proinflammatory stimuli in RA synovium: Visfatin was expressed in the lining layer, aggregates of lymphoid, and vessels interstitial . [10].

Study demonstrated that heart failure led to death in RA patients [11],which accelerated atherosclerosis than the other subjects [12].

Inflammatory processes resemble to the other chronic inflammatory diseases, like atherosclerosis[13]. Expression of proinflammatory cytokines and mediators influences of atherosclerosis. Aclot formation to thrombus development responsible for myocardial infarction[14].

The study aimed to estimate the role of glucagon-like peptide-1 and visfatin as a novel pro inflammatory marker in rheumatoid arthritis patients according to the active scores of disease to assess the possibility of introducing visfatin in the diagnosis and monitoring of RA patients and to found the correlation of visfatin level with glucagon-like peptide-1 and AIP in rheumatoid arthritis patients prone to atherosclerosis.

Materials and Methods

Blood collected from fifty healthy individuals as control group (G_1) and fifty rheumatoid arthritis (RA) patients (G_2) were enrolled in this study with middle aged ranged (30 – 40) years and BMI ≥24 kg/m^2. ESR was determined in blood using the westergren method. Three milliliters of blood was allowed to clot, and was centrifuged 1 h ,.the serum collected was stored until analysis (TC, TG, HDL) were determine according to the procedure of the hospital laboratory. LDL – C and VLDL were calculated from Friedewald equation: [LDL-c(mg/dl)= TC - (HDL-c+ VLDL-c)] ,VLDL-c (mg/dl)=TG/5[15] AIP was calculated according to the following equation (log TG/HDL). Visfatin, was measured by (ELISA) Kit (Phoenix Pharmaceuticals Inc., Burlingame, California, United states) [8]. Serum CRP was assessed by turbidimetry quantitative method [16].Rheumatoid factor (RF) was assessed by turbidimetry quantitative method [17]. Insulin and GLP-1were determined by using a ready kit based on ELISA technique[18].

The results were expressed as mean ± SD. Differences between the groups were assassed by student's T-test which P-value of < 0.05 and < 0.0001 considered as significant and highly significant differences ,respectively .Correlation relation was estimated for GLP-1 with visfatin ,CRP and AIP.

Results and Discussion:

Table(1)represented levels of ESR,RF,TC,TG,HDL,LDL,VLDL for patients and control groups, results in table (1) revealed highly significant increase in ESR,RF,TC,TG,LDL,VLDL and AIP level in G_2 comparing to G_1 while significant decreased noticed in HDL levels in G_2 comparing to G_1.

Several immune cells and soluble mediators play important role in the pathogenesis of atherosclerosis in RA. [19] ,such as visfatin that is an adipokine synthesis visceral white adipose tissue [4] and represents an additional link between adipose tissue and inflammation[20]

Jian et al. [21] and Nalesnik et al. [22], who observed that ESR levels in RA patients was increase more than control group..

Rheumatoid Factor (RF) is considered as a nonspecific marker of RA in addition to collagen vascular disease [23]. These data were in agreement with those of Novikov et al. [24], who noticed that RA linked the presence of RF. The results were in agreement with those of [Khalifa and Abdelfattah] [25] and [Hui et al]. [26], who showed that the elevation found in RF in RA group when comparing to non RA group.

Lipid disorder have important role in atherosclerosis, a process which is accelerated by dysfunction characterizing RA. The elevation in changed endothelial cells in RA patients allow the entry of LDL, which is possess in the intima, oxidized with subsequent recruitment of circulating leukocytes within atherosclerotic plaques[27] Also, lowers in HDL levels may accelerate atherosclerosis lead to the exerting atheroprotective functions.[28]

Other study, demonstrated that TC and LDL increase together in RA patients with low levels of HDL. [29] An elevation in the TC/HDL ratio, which display an atherogenic index, is a signification marker for heart disease[30]

In this study, the RA patients had an atherogenic index, indicate a higher risk of atherosclerosis. Thus, it can be inference that the role of dyslipidaemia in the pathogenesis of subclinical atherosclerosis in RA patients should be seen in the context of other operating mechanisms[19]. Moreover, it is potential that other fractions of specific lipoprotein particles as (VLDL) and HDL may play a important role in atherogenesis in RA[31].

Atherogenesis is accelerated in RA patients[13] .and elevation mortality from acute cardiovascular events[32].

Results in table (2) showed highly significant increase in insulin ,CRP, visfatin and GLP-1 levels.

Both GLP-1(7-36) amide and the GLP-1 receptor agonist, exendin-4 are shown to increase heart rate and blood pressure in both anesthetized and conscious restrained rats, although the mechanisms are controversial [33]. In vitro studies have failed to show any effects of GLP-1 on cardiac myocyte contractility. Very recently, promising clinical data from Shannon's lab showed that GLP-1 infusion improved regional and global function in patients with acute myocardial ischemia and severe systolic dysfunction after successful primary angioplasty [34]. Several animal studies and analyses in humans have demonstrated a potential cardioprotective effect of GLP-1 RAs[35] .There is evidence that the GLP-1 protective effect on myocardium may be particularly important in ischemic conditions and may also attenuate other factors causing premature atherosclerosis. [36]

Other study demonstrated When GLP-1 was infused into isolated mouse hearts, cGMP production markedly increased compared with non treated hearts, suggesting a role for this signaling pathway in GLP-1 activity. If the signaling mechanisms observed in pancreatic cells are stimulated by GLP-1 in vascular and cardiac cells, vascular tone, muscle contractility, cell growth/differentiation, extracellular matrix remodeling, and apoptosis may be affected. [37].

Determination of CRP and ESR ,which used as a marker of inflammation disease have significant role in RA [38].

These results are in agreement with those of Al-mesryet al. [39], who found that CRP is a protein produced in response to tissue injury, infection, and inflammation.

Another study revealed that increase visfatin levels in RA patients as a result of alteration in the gene encoding visfatin may be due to the RA triggering factors: a condition that causes elevation in its production autonomously independent of disease activity. [40] Another study demonstrated that visfatin have a critical role in atherogenesis and destabilization of plaque [41]

Results in table (3) illustrated correlation relation data and T-test for GLP-1 with visfatin ,CRP and AIP for G_2 and G_1 groups .

Results revealed highly significant ,were r=0.035 for GLP-1 with visfatin for G_1 and highly significant , r=-0.089 for G_2 as shown in figure(1-A) and(1-B) .

The result also highly significant , r= -0.183 for GLP-1 with CRP for G_1 and significant , r= 0.043 for GLP-1 with CRP for G_2 as shown in figure(2-A) and (2-B). and significant, r= -0.056 for GLP-1 with AIP for G_1 and no significant, were r= 0.042 for GLP-1 with AIP for G_2 as shown in figure (3-A)and (3-B).

Gonzalez-Gay et al. [40] and Senolt et al. [42], illustrated that visfatin levels did not correlate with BMI, age, and duration of disease in patients with active RA when company with control subjects which indicate that adipocytokine production in RA patients due to the processes of disease part of the inflammation systemic and destruction of bone led to suggested a role visfatin in the pathogenesis of RA.

The current study also found that there was a positive correlation between visfatin and both CRP and ESR in RA patients. These observation are in agreement with other study reported that visfatin was correlated with (CRP and ESR) ,study seen that visfatin has a catabolic function in cartilage and may play significant role in the pathophysiology of arthritis. There is proof for an important function of innate immunity in the pathogenesis of RA [12]. although a study by Luk et al. [43] showed that visfatin considered as a novel mediator of in nateimmunity, which led to improved that visfatin is involved in activity of proinflammatory, innateimmunity, and cartilage-catabolic functions in the processes of RA [44].

The conclusion could be drown from this studyGLP-1 and visfatin plays a role in the pathogenesis of RA and can be considered as a marker in RA, and may be used as a drug in future for RA patients.

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Table (1) ESR, RF,TC,TG,HDL,LDL,VLDL levels in G_1 and G_2:

Groups / Parameters	Mean± SEM G_2	Mean± SEM G_1	T-Test G_1 vs G_2
ESR(mm/h)	42.35 ± 5.52	12.34±2.28	<0.0001
RF(IU/ml)	135.52 ± 9.14	33.89±9.5	<0.0001
T C (mg/dl)	264.73 ± 32.87	110.85±14.11	<0.0001
TG(mg/dl)	245.14±35.5	98.77±28.6	<0.001
HDL	32.74±3.65	42.64±3.96	<0.001
LDL	178.24±37.87	58.19±18.9	<0.001
VLDL	42.14±5.03	25.42±1.57	<0.0001
AIP	0.874±0. 98	0.36±0.85	<0.001

*(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,(CRP, C-reactive protein; ESR).

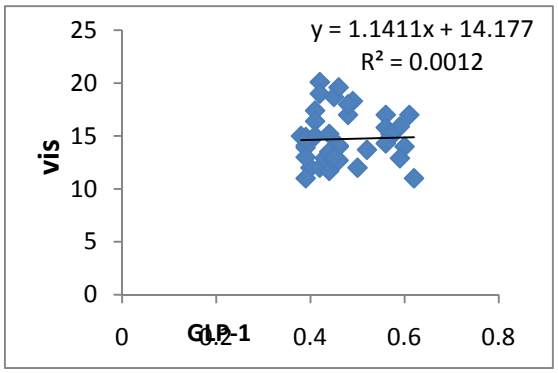
Table (2) GLP-1,CRP, Visfatin, Insulin levels for studied groups

Group variables	Mean± SEM G_1	Mean± SEM G_2	T-Test G_1 vs G_2
GLP-1	2.24±1.48	0.46±0,07	<0.05
CRP(mg/dl)	4.96±0.82	1.76±0.48	<0.0001
visfatin (ng/ml)	63.3±6.5	12.71±1.7	<0.0001
Insulin(IU/ml)	15.44±2.43	3.92±0.60	<0.0001

*(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

Table (3) correlation coefficient and p-value between GLP-1 levels and visfatin.CRP and AIP. for studied groups.

Groups / Parameters	G_2		G_1	
	r.value	p-value	r.value	p-value
GLP-1with Vis	-0.089	<0.0001	0.035	<0.0001
GLP1withCRP	0.043	<0.0001	-0.183	<0.0001
GLP-1withAIP	-0.042	0.02	-0.056	<0.05



A B

Figure (1) Correlation between GLP-1 and visfatin in G_1(A),G_2(B)

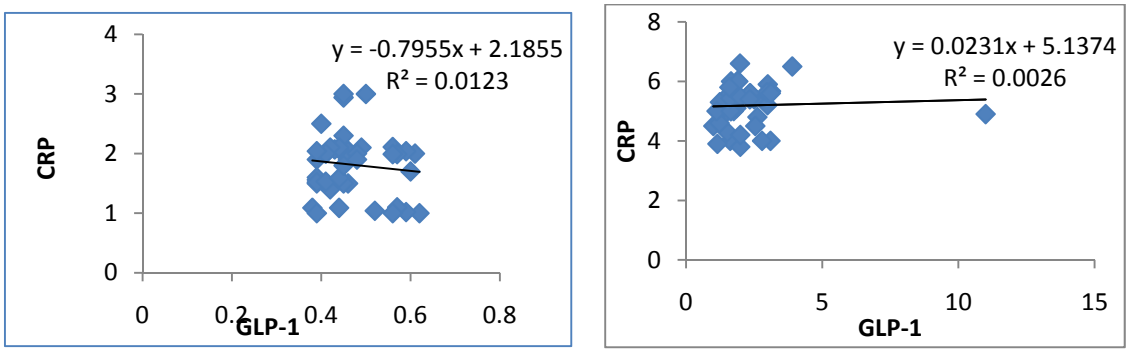
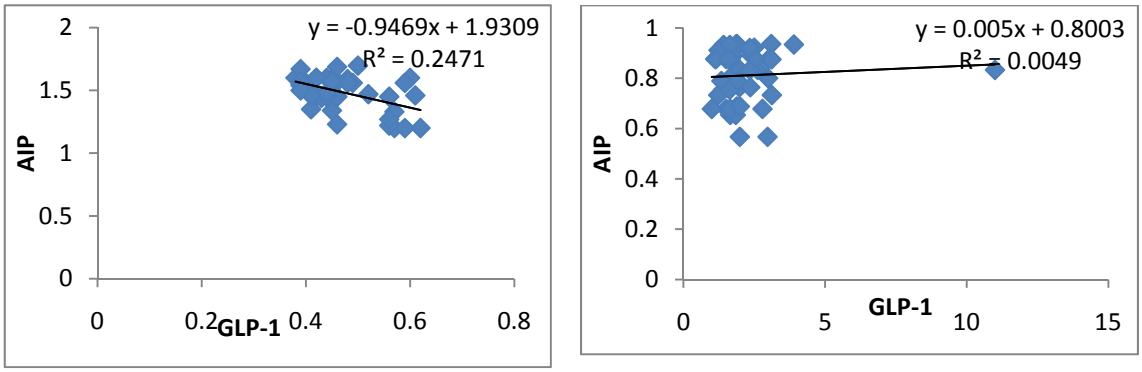


Figure (2) Correlation between GLP-1 and CRP in G_1(A),G_2(B)



A B

Figure (3) Correlation between GLP-1 and CRP in G_1(A),G_2(B)

مستويات الكلوكاكون شبيه الببتايد-1 والمعاملات ذات الصلة في مرضى التهاب المفاصل الرثوي المعرضين للإصابة بتصلب الشرايين

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الخلاصة

تهدف هذه الدراسه الى تحديد دور الفزفاتين كداله اساسيه للالتهابات المتواليه في مرضى التهاب المفاصل الرثوي وفقا لدرجات نشاط المرض لتقييم امكانيه استخدام الفزفاتين في تشخيص ومراقبه مرضى التهاب المفاصل الرثوي وايجاد معاملات الارتباط لمستوى الفزفاتين مع AIP, GLP-1 في المرضى العرضين للاصابه بتصلب الشرايين,تم جمع نماذج الدم من خمسين شخصا من الاصحاء ظاهريا G_1 وخمسين شخصا من مرضى التهاب المفاصل الرثوي G_2 بلغت متوسط اعمارهم(30-40) سنه بكتله جسميه 24≤ كغم/م^2.تم قياس مستويات RF,CRP,GLP-1,ESR ومستويات الدهون,الانسولين,الفزفاتين.النتائج في الجدول (1) تظهر زياده معنويه عاليه في مستويات RF,TC,TG,LDL,VLDL,AIP,ESR في المجموعه G_2 مفارنه بالمجموعه الظابطه G_1 اما نتائج الجدول الثاني(2) تظهر زياده معنويه عاليه في مستويات الانسولين ,الفزفاتين CRP,GLP-1, ويوضح الجدول الثالث بيانات العلاقات الارتباطيه واظهرت النتائج معامل ارتباط معنوي 0.035 لل GLP-1 مع الفزفاتين للمجموعه G_1 ومعامل ارتباط معنوي-0.089 للمجموعه G_2 كما موضح بالشكل (1-A), (1-B),كما اظهرت النتائج ومعامل ارتباط معنوي0.183- لل GLP-1مع CRP للمجموعه G_1 ومعامل ارتباط معنوي 0.043 لمجموعه المرضى كما موضح بالشكل (2-A), (2 -B)
اما معامل ارتباط GLP-1 مع AIP بالنسبه للمجموعه الظابطه كانت معنويه 0.056-وغير معنويه 0.042- لمجموعه المرضى كما موضح بالشكل (3-A), (3 -B) , ونستنتج من هذه الدراسه ان الفزفاتين يلعب دورا فعالا في الحالات المرضيه من التهاب المفاصل الرثوي وعلاقته ببقيه المعاملات التي تعتبر مؤشرات للاصابه بالجلطه القلبيه ويعتبر مؤشر مرضي قوي لل RA ويمكن ان يستخدم مستقبلا كعلاج لمرض RA.

الكلمات المفتاحيه:GLP-1, التهاب المفاصل الرثوي, تصلب الشرايين.