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RESEARCH ARTICLE

SERUM RESISTIN LEVELS AND CARDIOVASCULAR RISK FACTORS IN CHRONIC RENAL FAILURE RAT MODEL

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Abstract

Background: Chronic kidney disease is associated with markedly increased risk for cardiovascular events and mortality. Previous studies stated the possibility that resistin may relate to different cardiovascular dysfunction in different conditions.

Aim: to investigate the relationship between serum resistin levels and cardiovascular risk factors in chronic renal failure (CRF) rat model.

Material and methods:40 healthy male albino rats weighing 150-200 gm were used and divided into two groups: control group (15 rats) and CRF-induced group (25 rats) where CRF was induced by injection of folic acid subcutaneously (300 mg in 5 ml/kg once a week) for 3 weeks.

Results:in CRF-induced group were significantly higherserum levels of resistin, urea, creatinine, glucose, insulin, total cholesterol and CRP, proteinurea, with significant elevation of mean arterial blood pressure, calculated HOMA-IR and atherogenic index than that of the control group.Serumresistin levels positively correlated with the previous parameters in the CRF-induced group. However, serum levels of HDL-cholesterol were significantly lower and negatively correlated with serum resistin levels in the CRF-induced group. In addition, in ECG, significant prolonged PR and QT intervals, lower amplitude of R-wave and higher amplitude of T-wave were detected but without correlation with serum levels of resistin in CRF group.There was significant positive correlation between atherogenic index and other parameters; serum levels of glucose, insulin, CRP, calculated HOMA-IR and mean arterial blood pressure.

Conclusion: Resistin can be considered as uremic toxin of chronic renal failure, triggering mortality through aggravation of cardiovascular risk factors in CRF.

INTRODUCTION

Resistin is a novel adipokine linked to insulin resistance and obesity in rodents ***(Hu et al., 2007).*** Resistin was found to be secreted by adipocytes and was named for the insulin resistance it induced in animal studies ***(Steppan et al., 2001; Zhang et al., 2011).*** In human, resistin is essentially expressed in macrophages from white adipose tissue, rather than in human adipocytes ***(Cohen and Horl, 2009; Teta, 2012).***

In the United States, there is a rising incidence and prevalence of kidney failure, with poor outcomes with the highest incidence rate of end stage renal disease occuring in patients older than 65 years ***(Arora and Batuman, 2012).***

Studies showed that even mild renal dysfunction is associated with an increased risk of cardiovascular disease (CVD) ***(Sarnak et al., 2003; Go et al., 2004; Yaturu et al., 2007).***

The association between renal insufficiency and CVD was first shown in patients with end-stage renal disease, whose cardiovascular mortality exceeds that of patients without renal disease by a factor 10–30 ***(Foley et al., 1998; Sarnak et al., 2005).***

Plasma levels of resistin are elevated in uremia, primarily because of a reduced renal clearance ***(Cohen and Horl, 2009; Teta, 2012;Kaynar et al.,2014; Maggio et al., 2014)***, where ***Hoet al. (2013)*** showed an inverse correlation between adipose resistin and renal function.

In humans, the relationship between resistin and coronary artery disease has been controversial ***(Hu et al., 2007; Ibrahim et al., 2012).*** Studies showed that resistin can accelerate atherosclerotic plaque progression by aggravating inflammatory conditions in the vessel wall through stimulating monocyte infiltration ***(Cho et al., 2011).*** Moreover increased plasma concentrations of resistin were associated with subsequent development of heart failure ***(Frankel et al., 2009).***

Resistin may be a risk marker for ischemic heart disease ***(Cabrera et al., 2014)*** it is significantly associated with pathogenesis of acute coronary syndrome (***Singh et al.,2014)***

Also, serum resistin levels were significantly increased butnot correlated with insulin resistancein patients presenting with acute ST segment elevation myocardial infarction ***(Ibrahim et al., 2012)***however, ***Gruzdeva et al. (2014)*** proved correlation between insulin resistanceand elevated resistin levels in myocardial infarction patients.

On the contrary, the potential role of resistin as a cardioprotective agent has not been explored. ***Gao et al. (2007)***demonstrated that pretreatment of mouse hearts with resistin protected the heart against ischaemia/reperfusion injury, as resistin can dramatically reduce apoptosis and infarct size**.**

So, resistin appears to have a potential role in CVD and may contribute to an increased atherosclerotic risk by modulating the activity of endothelial cells ***(Cohen and Horl, 2009; Teta, 2012).*** However, no clinical data regarding this issue support this hypothesis in uremic patients ***(Teta, 2012).***

Therefore, our study is designed to assess the relationship between resistin levels and cardiovascular risk factors in chronic renal failure rat model.

Material and methods:

1-Animals:

40 healthy adult male wistar albino rats weighing 150-200 gm were obtained from the animal house in faculty of veterinary medicine -Zagazig University. The animals were kept in steel wire cages (5-7/cage) in the animal house in faculty of medicine of Zagazig University under hygienic conditions.

Animals were fed standard chow and had free access to water, kept at room temperature and were maintained on a 12 h light/dark cycle. The rats were accommodated to animal house conditions for one week before the experiments going on. The experimental protocol was approved by physiology department and by local medical ethics committee in faculty of medicine of Zagazig University (Institutional Review Board, IRB).

The animals were divided into two groups: **Group (I): Control group (n=15):** 15 rats were injected with 0.3M NaHCO3 (5ml/ Kg) subcutaneously once a weekly (5 dose).**Group (II): Chronic renal failure-induced group (n =25):** rats were injected subcutaneously with folic acid at a dose of 300 mg/kg(in 5 ml) once a week(dissolved in 0.3M NaHCO3) for 5 weeks***(Nabae et al., 2006).***(7 rats died and 18 rats remained (Death rate = 28%).

Methods:

Measurement of Blood Pressure (BP)according to ***Zorniak et al.*** (***2010) and Parasuraman&Raveendran (2012)***

An overnight fasted (8–10 h) each rat was anesthetized with urethane (1200 mg/kg),and placed on a suitable rodent none electrically conductive surgical table.The skin on the ventral side of the neck is shaved and disinfected.The skin was carefully cut open(1.5–2 cm), and a slit incision was made in the platysma muscles. The trachea was identified, small incision was made on the cartilage tissue, and the tracheostomy was performed using a small piece of tracheal intubation tube**.**

One side of the carotid arterywas separated from the adjacent connective tissue, and its cephalic end was tied and the cardiac end was clamped with a bulldog clamp and cannulated using a heparinized cannula (0.5 IU/ml insaline).

The other end of the cannula connected to a three-way stopcock connected to the pressure transducer and a syringe filled with heparinized saline. Then the carotid artery cannulation site was tied with a thread without obstructing the blood flow in the carotid cannula. Then bulldog clamp was released slowly, ensuring that there was no bleeding at the cannulation site**.**

After cannulation, the animal is connected to the Power Lab (AD Instruments Pty Ltd, Australia) to record the BP. The pressure cuff of the sphygmomanometer was connected to the pressure transducer. Then, the pressure

transducer is checked by inflating to a known pressure level. The calibration between the voltage (millivolts) and the pressure (mmHg), and the results are automatically calculated by power Lab software.

Recording ECG

Three-lead bipolar ECG was used in electrocardiography. Positive, negative, and reference electrocardiogram electrodes were placed at the left fore leg, right fore leg, and left thigh, respectively, to record electrocardiogram ***(Ordodi et al., 2005; Parasuraman and Raveendran, 2012)***.

Sampling of blood:

Blood samples were taken from the cannula after measuringBP and tracing ECG and were allowed to clot for 2 hours at room temperature before centrifuging for 20 minutes at approximately 500 rpm. The separated serum was stored at -20° C.

A- Serum analysis:

1- Resistin levels: according to ***Steppan and Lazar (2004)*** using Rat resistin ELISA kits**,**(BioVendor-Laboratorimedicina, U.S.A**.**

2-Insulin levels: according to ***Temple et al.(1992)***using INS-EASIA, KAP1251 (BioSource Europe S.A).

3-Glucoselevels:according to***Tietz (1995)***usingglucose enzymatic (GOD-PAP)-liquizyme rat Kits (Biotechnology, Egypt).

4- Cholesterol levelsaccording to ***Tietz (1995)***using total cholesterol kits estimation(BioSource Europe S.A).

5- HDL-cholesterolaccording to***Nauk et al. (1997***) by using kits for HDL-cholesterol (BioSource Europe S.A).

6- Urea levels according to ***Kaplan (1984***)using urea kits(Spinreact, S.A.U. Ctra.SantaColoma, SPAIN).

7- Creatinine levelsaccording to ***Murray et al. (1984***) using creatinine Kits (SPINREACT, S.A.U. Ctra.Santa Coloma, SPAIN).

8- c-reactive protein (CRP) levelsaccording to***Ridker et al. (1998***) usingCRP Kits (MonobindInc Lake Forest, Ca 92630, USA).

B- Estimation of protein in urinechemically by using *Microlab 300*

C- Calculation of Homeostasis model assessment of insulin resistance (HOMA-IR) according to the equationof***Sun et al., 2007*** modification on***Matthews et al***., 1989[HOMA-IR = insulin (μU/mL) x glucose (mg/dL) /405].

D- Calculation of atherogenic index(AI) according to the equation: Atherogenic index=(total cholesterol-HDL - cholesterol)/HDL-cholesterol. ***(Karthik and Ravikumar,2011)***.

E- Histopathological examinations:

The abdominal cavities of the rats were opened to remove the kidneys. The kidneys were fixed in 10 % formalin solution and embedded in paraffin. Sections were made and stained with hematoxylin and eosin (H &E) and observedmicroscopically ***(Willette et al., 2008)***. The pathologist was blinded to the treatment.

RESULTS: (table 1)

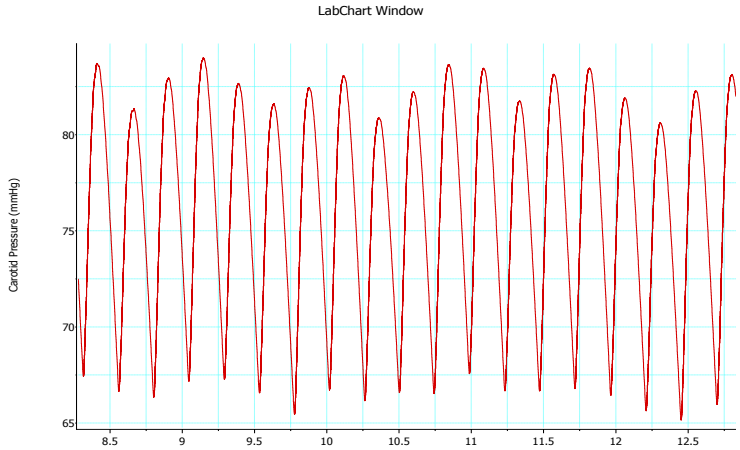
Regarding serum and urine parameters,in CRF group, there were significant high levels of serum resistin in comparison with that of control group ($P < 0.01$). These high levelswere significantly positive correlated ($P < 0.001$) with the significant higher levels of urea, creatinine, proteinuria, glucose, insulin, HOMA-IR,total cholesterol, atherogenic index and CRP($P < 0.001$). However, HDL-cholesterol levels were significantly lower than that of control group ($P < 0.05$) and negatively correlated with serum resistin levels ($P < 0.001$). In addition,while the elevated levels of AI in CRF groupsignificantly positive correlated with resistin, urea, creatinine, proteinuria,glucose, insulin,HOMA-IR, total cholesterol and CRP levels ($P < 0.001$), it correlated negatively with HDL-cholesterol.While no correlation was observed in the control group.

Regarding blood pressure, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were significantly elevated in CRF group in comparison with control group ($P<0.001$) and positively correlated with both serum resistin levels and calculated AI.

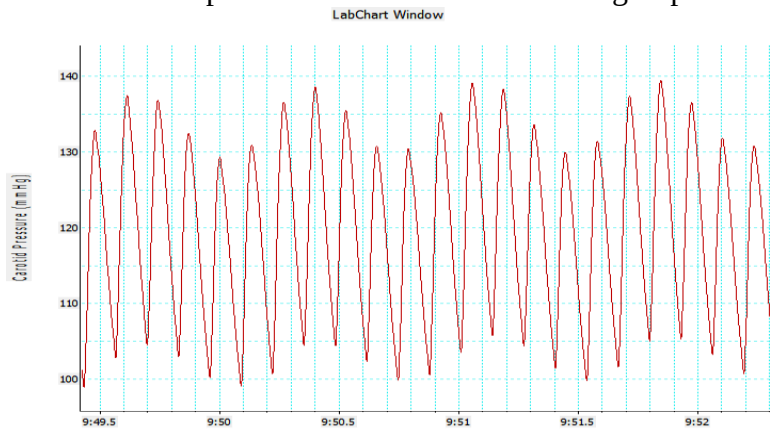
Concerning ECG, in CRF,both PR interval (sec.) and QT interval (sec.) were significantly prolonged when compared with that of control group. In addition while the amplitudes of R wavewere significantly lower,the amplitudes of T were significantly higher when compared with that of control group ($P < 0.001$). However, there were no correlations detected between any of ECG parameters with either serum resistin levels or calculated AI levels

Table 1:mean values (± SD**)** of serum measured parameters,proteinurea ,calculated HOMA-IR and AI, blood pressure and ECGin both groups.

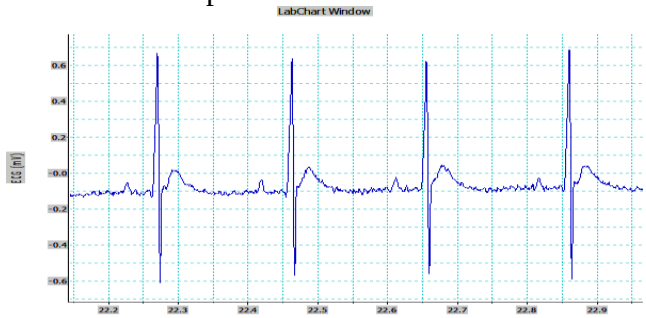
parameters	Control (group I) (n =15)		Chronic renal failure group (group II) (n =18)			
	mean ± SD	r	mean ± SD	P value	r1	r2
Serum Resistin (mg/L)	0.982 ± 0.22		1.262±0.284	< 0.01		0.969 P <0.001
SerumUrea(mg/dL)	25±5.81	0.200 NS	70.8±5.64	<0.001	0.909 P<0.001	0.924 P <0.001
SerumCreatinine(mg/dL)	0.55±0.15	-0.197 NS	2.31±0.448	<0.001	0.935 P<0.001	0.912 P <0.001
proteinuria(gm/dL)	0.58 ± 0.10	0.036 NS	1.49± 0.273	< 0.001	0.973 P<0.001	0.926 P <0.001
Serum glucose(mg/dL)	87.2±9.99	-0.367 NS	183.8±26.49	<0.001	0.900 P<0.001	0.876 P <0.001
serum insulin(MIU/L)	17.47±2.45	-0.199 NS	25.46±4.804	<0.001	0.915 P<0.001	0.933 P <0.001
HOMA-IR	3.68±0.8	-0.323 NS	11.48±3.5	<0.001	0.972 P<0.001	0.964 P <0.001
Serum total cholesterol(mg/dL)	104.3±6.9	0.819 <0.001	154.83±8.2	<0.001	0.981 P<0.001	0.980 P <0.001
Serum HDL-cholesterol(mg/dL)	58.5 ±7.86	0.244 NS	51.9 ±8.13	<0.05	-0.916 P<0.001	-0.979 P <0.001
atherogenic index(AI)	0.817± 0.28	-0.36 NS	2.067±0.6	<0.001	0.969 <0.001	
Serum CRP(Ug/mL)	0.802±0.22	0.222 NS	1.257 ± 0.272	< 0.001	0.876 <0.001	0.855 P <0.001
systolic blood pressure(mmHg)	92±12.63	-0.472 NS	127±14.14	<0.001	0.894 <0.001	0.891 P<0.001
diastolic blood pressure(mmHg)	57±9.23	-0.567 < 0.05	92±9.58	<0.001	0.821 <0.001	0.801 P <0.001
mean arterial blood pressure(mmHg)	75 ± 10.6	-0.527 <0.05	109±11.4	< 0.001	0.9 <0.001	0.890 P <0.001
PR interval(sec.)	0.1±0.014	-0.363 NS	0.22±0.04	<0.001	0.152 NS	0.223 NS
QT interval(sec.)	0.068±0.01	0.354 NS	0.08±0.0160.016	<0.01	-0.188 NS	0.278 NS
R amplitude(mV)	0.7 ±0.12	-0.112 NS	0.5 ±0.15	<0.001	0.087 NS	0.112 NS
T amplitude(mV)	0.1 ±0.02	0.102 NS	0.18 ±0.03	<0.001	0.278 NS	0.207 NS



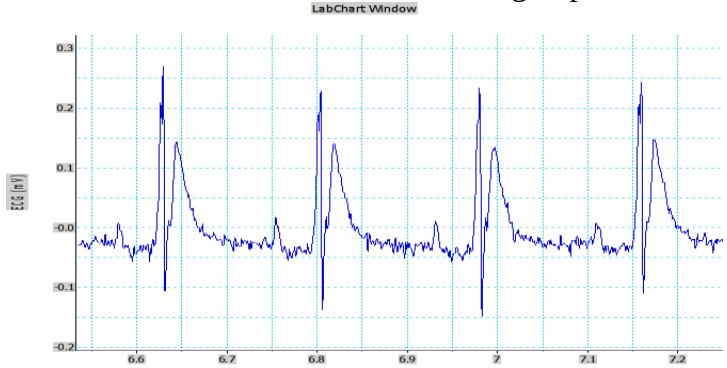
Trace 1: blood pressure of rat from the control group



Trace 2: blood pressure of rat from the CRF induced group.



Trace 3: ECG of a rat from the control group.



Trace 4: ECG of a rat from the CRF-induced group.

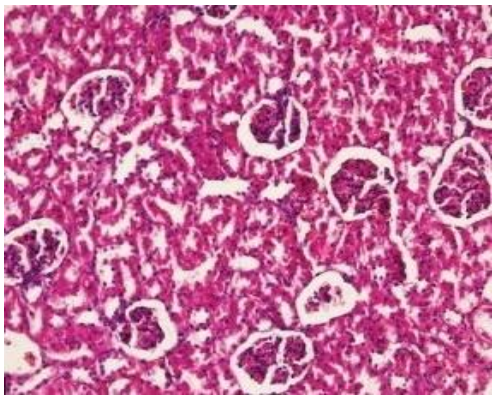


Figure 1: Photomicrograph of normal renal tissueformed of normal renal tubules and glomeruliseparated by scanty interstitial tissue. (Hematoxylin& Eosin x400).

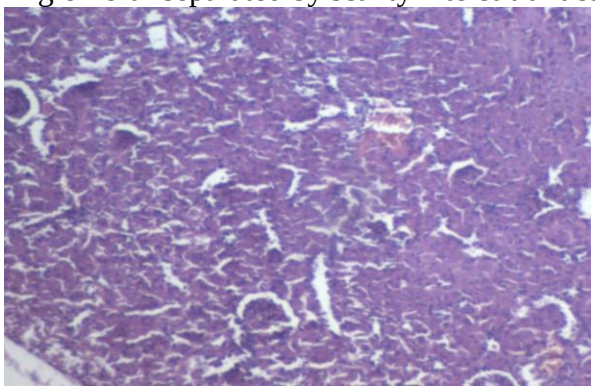


Figure 2:Photomicrograph of renal tissue after treatment with folic acid regimen showing areas of fibrosis between the renal tubules and glomeruli.(Hematoxylin& Eosin x400).

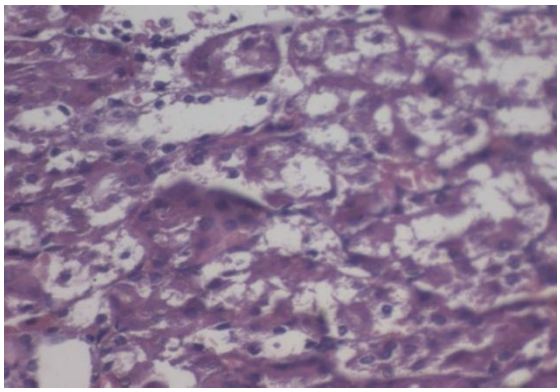


Figure 3: Photomicrograph of renal tissue after treatment with folic acid regimen showing sloughing and degeneration of the renal tubular epithelial cells with picnotic nuclei. (Hematoxylin& Eosin x400).

DISCUSSION

In this study, the usage of folic acid to induce renal failure guided by ***Ku (2005)***who proved that chronic large doses of folic acid may interfere with sleep patterns and cause malaise, irritability, anorexia, nausea, bloating, flatulence, bad taste, lower seizure threshold in epileptics and progression of neurologic injury in pernicious anemia, but no cardiovascular disorders were detected**.**

CRF is proved by the elevated levels of urea and creatinine in serum samples and by the high levels of proteinuria. Also, histopathological examination of kidneys showed areas of fibrosis between the renal tubules and

glomeruli in addition to sloughing and degeneration of the renal tubular epithelial cells with picnotic nuclei. These results supported by ***Tsutsumi et al. (2004)***histological examination of the kidney of animals treated weekly with folic acid for five weeks revealed focal interstitial inflammatory lesions with scattered tubular atrophy.

In the present study, serum resistin levels was significantly higher in CRF-induced group than that of control group.This result comes in agreement with ***Teta (2012)*** who stated anaccumulation of adipokinesinrenal clearance, as their molecular weights usually middleand large. Moreover, serum resistin levels were two times higher in patients with advanced chronic kidney disease (CKD)***Marouga et al. (2013)***due to decreased filtration ***(Malyszko et al.,2007; Nehus et al., 2012; Maggio et al.,2014)***

However, decreased clearance might not be the only cause of elevated resistin levels, where CKD has been recognized as a state of chronic inflammation ***(Stenvinkel et al., 2005; Silverstein, 2009),*** and many data suggest that resistin is involved in inflammatory processes. Resistin stimulates production of IL-6 and TNF-α ***(Bokarewa et al., 2005; Cho et al., 2011),*** Furthermore,***Axelsson et al.(2006)*** showed a significant independent association of resistin with IL-6 in adults with CKD.

The relation between resistin and CRF is evidenced in this study by the positive correlation between serum resistin levels and serum levels of urea and creatinine and proteinuria in the CRF-induced group. This comes in line with ***Nehus et al. (2012)*** who have demonstrated that serum resistin level increases with progressively declining kidney function in children with CKD.

As regards glucose metabolic parameters, our study showed that in CRF-induced group, serum levels of insulin and glucose and calculated HOMA-IR were significantly higher when compared to that of control group, these results were supported by***Cheng et al. (2012)***and***Maggio et al. (2014).***Moreover,serumresistin levels were positive correlation with serum glucose, serum insulin and calculated HOMA-IR levels in the CRF-induced group which wasn't detected in the control group. These results are supported by ***Steppan et al. (2004) and Gharibeh et al. (2010)***who proved a significant correlation between resistin level and insulin resistance.

Moreover, ***Noureldeen et al., 2014***reported increased insulin resistanceindiabetic patients associated with increased resistin and TNF-α. The positive correlation found between serum resistin levels and glucose metabolic parameters can be explained by the evidence that resistin inhibits insulin-dependent glucose transport and mediates increased blood glucose level and hepatic glucose production ***(Moon et al., 2003; Pravenec et al., 2003).***In addition, resistin suppresses phosphorylation and glycogen synthase kinase 3(GSK3) in a dose dependent manner***(Zhou et al., 2007)*** and an upregulation of suppressors of cytokine signaling, which interferes with the activation of insulin-receptor substrate ***(Barnes and Miner, 2009).***

In contrast,resistin is notlinkedto insulin resistance in Type II diabetes (TIIDM)(***Nagaev and Smith, 2001)*** or CKD patients (***Axelsson et al., 2006).***

Concerning serum levels of total cholesterol in this study, they weresignificantly higher in CRF-induced group compared to that of control group where there was positive correlation between serum resistin levels and serum levels of total cholesterol in the CRF-induced group.

On the other hand, serum levels of high-density lipoprotein (HDL-cholesterol) were significantly lower in CRF-induced group than that of control group and it was negatively correlated with serum resistin levels.

These results come in agreement with ***Nehus et al. (2012)*** who found that elevated serum resistin level was significantly associated with high triglycerides and low HDL-cholesterol in children with CKD. Moreover, ***Raman et al. (2013)*** revealed that increased expression of resistin is seen in lipid-rich atheromatous plaques compared to lipid-poor fibrotic plaques.

In ***2013***, ***Balla et al.*** stated that dyslipidemia in CKD is caused in part by damage of the glomerular filtration barrier resulting in proteinuria and compensatory up regulation of hepatic protein synthesis, which includes lipoproteins. Also ***Vaziri (2013)*** showed that end stage renal diseases results in down-regulation of apolipoprotein-A1 and lecithin-cholesterol acyl-transferase in the liver, reduction of plasma HDL, and impaired antioxidant, anti-inflammatory and reverse cholesterol transport capacities of HDL.

Zohng et al.(2014) implied that inflammation promoted renal lipid accumulation and foam cell formation by disrupting cellular cholesterol homeostasis as inflammation increased cellular cholesterol uptake and synthesis via up-regulating the expression of low-density lipoprotein receptor and 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

And accordingly, we found that atherogenic index (AI) was significantly higher in CRF-induced group than that of control group, where there was also a positive correlation between serum resistin levels and AI in CRF-induced group which was not detected in control group.

As regards blood pressure, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in CRF-induced group than that of control group and they were positively correlated with serum resistin levels in CRF-induced group.

This comes in agreement with ***Zhang et al. (2010)*** who suggested that higher plasma resistin levels are independently associated with an increased risk for incident hypertension among women without diabetes.

A cross-sectional studies of patients with diabetes revealed that serum resistin levels were higher and associated with both Systolic BP and Diastolic BP in patients with hypertension compared with non-hypertensive patients***(Sabbatini et al., 2014;Takata et al., 2008).***However,***Asgary et al. (2014)*** reported that in patients with metabolic syndromethere were no significant correlation between resistin levels and both Systolic BP and Diastolic BP.

Resistin is primarily involved in the inflammatory process by up-regulating IL-6 and TNF-α ***(Bokarewa et al., 2005;*****Kunnari et al. 2006)**,increasing cardiovascular risk, unstable angina, poor prognosis in coronary artery disease **(*Lubos et al. 2007;Norata et al. 2007*).**resistin exerts direct effects by inducing endothelin 1 release ***(Verma et al., 2003)*** and increasing the expression of adhesion molecules such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 ***(Verma et al., 2003; Kawanami et al., 2004; Mattu and Randeva, 2013)***. This pro-inflammatory role is also supported by its proportional relation to the severity of the sclerotic lesion in animal models of atherosclerosis (***Lago et al. 2007;Mattu and Randeva,2013*****).**Furthermore, in isolated coronary artery rings, resistin can induce endothelialdysfunction ***(Dick et al. 2006)***. All these processes can induce inflammation within the vascular wall and lead to vascular remodeling and injury.

Moreover, at the functional level, resistin has been shown to reduce endothelium-dependent and independent vasorelaxation, possibly by increasing superoxide radical production and by decreasing endothelial nitric oxide synthase expression in endothelial cells ***(Kougias et al., 2005)***.

In addition, ***Vaziri (2013)*** found that in end stage renal diseases, there is impaired clearance leads to accumulation of proinflammatory and atherogenic chylomicron and VLDL remnants, formation of small dense LDL, hypertriglyceridemia, these events contribute to systemic inflammation, accelerated atherosclerosis, cachexia, and impaired exercise capacity.

Dyslipidemia is known to impair endothelium-dependent vasodilatation ***(Attman and Samuelsson, 2009)***. Dyslipidaemia, along with insulinaemia and glycaemia, is one of the most significant IR risk factors in the acute and early recovery phases of myocardial infarction (***Gruzdeva et al.,2014****).*

On ECG tracing, we found that there were significant prolongation in both PR interval and QT interval in the CRF-induced group when compared to that of the control group. Moreover, the amplitude of T wave was significantly higher in the CRF-induced group than that of the control group.

However, these ECG changes were not correlated with serum resistin levels. So, theses ECG changes may be due to electrolyte disturbances found in CRF ***(Mahaldar, 2012).***It was found that CRF is frequently complicated by elevations in serum potassium, phosphate, and magnesium ***(Duerksen and Papineau, 1998),***this hyperkalemia will lead to ECG changes such as high peaked T waves, prolongation of PQ interval, lowering of P wave amplitude, widening of QRS complexes and bradycardia***(Berkova et al., 2012)***.

Concerning C-reactive protein (CRP), our study showed that its serum levels were significantly higher in CRF-induced group than that of the control group.

This comes in agreement with ***Panichi et al., 2001*** who showed that CRP and IL-6 were related with renal function. Also ***Abraham et al., 2009*** stated that a high degree of inflammation and malnutrition exists in predialysis patients as seen by high CRP values and low serum albumin levels and that synergism of these factors could contribute to atherosclerosis in CKD apart from the classic risk factors.

In addition, our study demonstrated a positive correlation between serum levels of resistin and CRP in the CRF-induced group which was not detected in the control group, which comes in line withother studieswhichrevealed a positive correlation between serum resistin and CRP levels in non-diabetic, typeII diabetic subjectsand elderly, non-diabetic patients with CKD **(*McTerna et al., 2003*;*Al-Daghri et al., 2005;marouga et. al,2013*).**

These data suggest a potential role for resistin as a marker associated with inflammation in both TIIDM and coronary heart disease ***(Cabrera et al 2014*).** Moreover some studies have shown pro-inflammatory cytokines to be important inducers of CRP, such as IL-6and TNF-α***(Maachi et al., 2004)***, and resistin may also play a role as an inducer of CRP***(Al-Daghri et al.,2005)***.

Moreover, ***Yaturu et al., 2007*** suggested a role for resistin as a possible marker of inflammation in subjects with CKD by the increased plasma levels of resistin and CRP in association with TNF-α.

Regarding the relationship between AI and glucose metabolic parameters, we found that there were positive correlations between AI and each of serum levels of glucose and insulin and calculated HOMA-IR.

These results come in agreement with ***Fan, 2006*** who stated that insulin resistant states have been strongly associated with subclinical and clinical cardiovascular disease (CVD) and all-cause mortality

Tison et al., 2011 showed that HOMA-IR has a positive and graded association with extra coronary calcification, which may reflect a generalized process of atherosclerosis ***(Allison et al., 2006; Demer et al., 2008)***.

Moreover, hyperinsulinemia may play a role in the lipid disturbance and associated cardiovascular risk ***(Legro et al.,2001; Orio et al., 2008; Roa Barrios et al., 2009; El-Manzy et al., 2010)***.

This comes in line with another study suggesting that insulinresistance is independently associated with subclinical atherosclerosis in patients with TIIDM ***(Park et al., 2009)*** which comes in consistent with other findings from ***Watarai et al., 1999*** and ***Cardellini et al., 2007*** who showed that insulin sensitivity was associated with increasing carotid intima/media thickness in patients with TIIDM and in non-diabetic normotensive offspring of TIIDM patients.

Many ***(Rajala et al., 2002; Bonora et al., 2007; Cardellini et al., 2007)*** but not all ***(Ishizaka et al., 2003; Larsson et al., 2003; Rutter et al., 2005)*** of previous studies have reported an independent association between insulin resistance and either clinical or subclinical CVD.**li et al.,(2013)**stated that insulin resistance is an independent predictor of CV morbidity and mortality in a cohort of non-diabetic patients.

It is evidenced that chronic low-grade inflammation is a hallmark of the obese state***(Yudkin et al., 2000, Bays et al., 2004),***insulin resistance/TIIDM ***(Festa et al., 2000; Hoekstra et al., 2005)*** and the early stages of atherogenesis***(Festa et al., 2000)***, pointing to mechanisms inducing a low-grade systemic inflammation as a putative link that connects adipose tissue dysfunction and the metabolic and vascular pathologies.

While regarding the relationship between AI and serum levels of CRP, our study showed a positive correlation between them in the CRF-induced group. This was explained in 2011 by***Ibrahim et al.*** who showed the role of early accumulation of CRP in the phenomena of atherosclerotic lesion formation.

First, CRP may act as a chemo-attractant for blood monocytes in vivo. Second, CRP is known to inhibit neutrophil chemotaxis and the binding of neutrophils to endothelial cells ***(Torzewski et al.,2000).*** Third, CRP has been shown to exert direct adverse effects on the vascular endothelium by reducing nitric-oxide release and increasing endothelin-1 production, as well as by inducing expression of endothelial adhesion molecules ***(Schmitz and Hombach, 2010).***

In conclusion: Resistin can be considered as uremic toxin of chronic renal failure. Resistin aggravates cardiovascular risk factors in CRF.

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REFERENCES

Abraham G, Sundaram V, Mathew M, Leslie N, Sathiah V*:* C-Reactive protein, a valuable predictive marker in chronic kidney disease. Saudi J Kidney Dis Transpl., 20(5):811-5, ***2009.***

Allison MA, Cheung P, Criqui MH, Langer RD, Wright CM: Mitral and aortic annular calcification are highly associated with systemic calcified atherosclerosis. *Circulation* ,113(6):861–6, ***2006.***

Al-Daghri N, Chetty R, McTernan P.G, Al-Rubean K, Al-Attas O, Jones AF, Kumar S *:* Serum resistin is associated with C-reactive protein and LDL- cholesterol in type 2 diabetes and coronary artery disease in a Saudi population. *Obes Res*, **11**(8)**:**997-1001, ***2005.***

Arora P and Batuman V: Chronic Kidney Disease:http://emedicine.medscape .com/ article/238798 overview, 2012.

Asgary S, SamsamShariat SZ, Ghorbani, A, Keshvari M, Sahebkar A, Sarrafzadegan N:relationship between serum resistin concentrations with metabolic syndrome and its components in an Iranian population. *Diabetes MetabSyndr, **2014** [Epub ahead of print]***.**

Attman PO, and Samuelsson O: Dyslipidemia of kidney disease. CurrOpinLipidol, 20(4):293-299, ***2009.***

Axelsson J, Bergsten A, Qureshi AR, Heimburger O, Barany P: Elevated resistin levels in chronic kidney disease are associated with decreased glomerular filtration rate and inflammation, but not with insulin resistance. *Kidney Int*., 69(3): 596–604, ***2006.***

Balla S, Nusair MB, Alpert MA*:* Risk factors for atherosclerosis in patients with chronic kidney disease: recognition and management. *Current Opinion in Pharmacology*, 13(2):192-9, ***2013.***

Barnes KM and Miner JL *:* Role of resistin in insulin sensitivity in rodents and humans. *Curr.ProteinPept. Sci*., 10(1): 96–107, ***2009.***

Bays H, Mandarino L, De FronzoRA: Role of the adipocyte, free fatty acids, and ectopic fat in the pathogenesis of type 2 diabetes mellitus: peroxisomal proliferators activated receptor agonists provide a rational therapeutic approach. *J ClinEndocrinolMetab*, 89(2):463-78, ***2004.***

Berkova M, Berka Z, Topinkova E*:* Life threatening hyperkalemia with ECG changes and rhythm disturbance in elderly patients. Two case reports. *European Geriatric Medicine*, 3S: S9/3–S143, Volume 3, (1): S93, ***2012.***

Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A: Resistin, an adipokine with potent proinflammatory properties. *Immunol*., 174(9): 5789–5795, ***2005.***

Bonora E, Kiechl S, Willeit J: Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in Caucasian subjects from the general population:theBruneckstudy.*Diabetes Care*, 30(2): 318–24, ***2007.***

Cabrera DA, Almeida GD, González HA, Juan A, SJ, Brito DB, Domínguez CS, Marcelino RI, Aguirre JA, Rodríguez P MC*:* The association of resistin with coronary disease in the general population. *J AtherosclerThromb*, 21(3):273-81, ***2014***

Cardellini M, Marini MA, Frontoni S*:* Carotid artery intima-media thickness is associated with insulin-mediated glucose disposal in nondiabetic normotensive offspring of type 2 diabetic patients. *Am J PhysiolEndocrinolMetab*, 292(2): E347–352, ***2007.***

Cheng HT, Huang JW, Chiang CK, Yen CJ, Hung KY, Wu KD: Metabolic syndrome and insulin resistance as risk factors for development of chronic kidney disease and rapid decline in renal function in elderly. *J of ClinEndocrinMetabo.*, 97(4):1268–1276, ***2012***

Cho Y, Lee SE, Lee HC, Hur J, Lee S, Youn SW, Lee J, Lee HJ, Lee TK, Park J, Oh BH, Park YB*:* Adipokineresistin is a key Player to modulate monocytes, endothelial cells, and smooth muscle cells, leading to progression of atherosclerosis in rabbit carotid artery . *Am. Coll. Cardiol*.,57(1): 99–109, ***2011.***

Cohen G and Horl WH*:*Resistin as a cardiovascular and atherosclerotic risk factor and uremic toxin. *Semin Dial*., 22(4): 373-377, ***2009.***

Demer LL and Tintut Y: Vascular calcification: pathobiology of a multifaceted disease. *Circulation*, 117(22): 2938–48, ***2008.***

Dick GM, Katz PS, Farias M, Morris M, James J, Knudson JD, Tune JD: Resistin impairs endothelium-dependent dilation to bradykinin, but not acetylcholine, in the coronary circulation. *Am J Physio. Heart and CircPhysio.*, 291(6) H2997–H3002, ***2006.***

Duerksen DR and Papineau N*:* Electrolyte abnormalities in patients with chronic renal failure receiving parenteral nutrition. *J Parenter Enteral Nutr*, 22(2):102-4, ***1998.***

El-Mazny A, Abou-Salem N, El-Sherbiny W, El-Mazny A*:* Insulin resistance, dyslipidemia, and metabolic syndrome in women with polycystic ovary syndrome. *International Journal of Gynecology and Obstetrics*, 109(3): 239–241, ***2010.***

Fan AZ: Metabolic syndrome and progression of atherosclerosis among middleaged US adults. *J AtherosclerThromb.*, 13(1):46–54, ***2006.***

Festa A, D'AgostinoJr R, Howard G, Mykkanen L, Tracy RP, HaffnerSM: Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study. *Circulation*,102(1): 42-7, ***2000.***

Frankel DS, Vasan RS, D'AgostinoSr RB, Benjamin EJ, Levy D, Wang TJ.*:* Resistin, adiponectin, and risk of heart failure the Framingham offspring study. *J Am CollCardiol*, 53(9):754–62, ***2009***.

Foley RN, Parfrey PS, Sarnak MJ: Epidemiology of cardiovascular disease in chronic renal disease. *J Am SocNephrol*, 9 (12): S16–23, ***1998.***

Gao J, Chang Chua C, Chen Z, Wang H, Xu X, Hamdy RC, Izumo S, Chua BHL: Resistin, an adipocytokine, offers protection against acute myocardial infarction. *J Mol Cell Cardiol*, 43(5): 601–9, ***2007.***

Gharibeh MY, Al Tawallbeh GM, Abboud MM, Radaideh A, Alhader AA, Khabour OF*:* Correlation of plasma resistin with obesity and insulin resistance in type 2 diabetic patients. *Diabetes & Metabolism*, 36**n° 6P1**: 443–449, ***2010.***

Go AS, Chertow GM, Fan D, McCulloch CE Hsu CY*:* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J, 351(13): 1296–305, ***2004***.

Gruzdeva O, Uchasova E, Belik E, Dyleva Y, Shurygina E, Barbarash O*:*Lipid, adipokine and ghrelin levels in myocardial infarction patients with insulin resistance**.***BMCCardiovasc Disord*,14,7doi: 10.1186/1471-2261-14-7., ***2014.***

Ho KJ, Xue H, Mauro CR, Nguyen B, Yu P, Ming Tao M, Seidman MA, Brunelli SM, Ozaki CK: Impact of uremia on human adipose tissue phenotype. Journal of Surgical Research, 179(1): 175-182, ***2013.***

Hoekstra T, Geleijnse JM, Schouten EG, Kok FJ, Kluft C: Relationship of C-reactive protein with components of the metabolic syndrome in normal-weight and overweight elderly. *NutrMetabCardiovasc Dis*, 15(4): 270-8, ***2005.***

Hu WL, Qiao SB, Hou Q, Yuan JS: Plasmaresistin is increased in patients with unstable angina. *Chin Med J (Engl)*. 120(10): 871-875, ***2007.***

Ibrahim AE, EL-Yassin HD, AL-Janabi HS*:* The impact of inflammation on Resistin, IL-6 and CRP in Acute Myocardial Infarction Patients. *Fac Med Baghdad*, 53, No.2, 216-220 ,***2011.***

Ibrahim HH, Korah TE, Badr EAE, ElshafieMK: Serumresistin in acute myocardial infarction patients with and without diabetes mellitus. *The Egyptian Heart Journal*, 64(1): 27–33, ***2012.***

Ishizaka N, Ishizaka Y, Takahashi E*:* Association between insulin resistance and carotid arteriosclerosis in subjectswith normal fasting glucose and normal glucose tolerance. *ArterioscIerThromVascBiol*, 23(2):295–301, ***2003.***

Karthik D and Ravikumar S: A Study on the Protective Effect of Cynodondactylon Leaves Extract in Diabetic Rats. *Biomed Environ Sci*, 24(2): 190 - 199, ***2011***

Kaplan A. Urea. Kaplan A et al. ClinChemThe C.V. Mosby Co. St Louis. Toronto. Princeton**;** 1257-1260 and 437 and 418,***1984***

Kaynar K, Kural BV, Ulusoy S, Cansiz M, Akcan B, Misir N, Kaya N*:*Is there any interaction of resistin and adiponectin levels with protein-energy wasting among patients with chronic kidney disease. *Hemodial Int*.18(1):153-62,***2014.***

Kawanami D, Maemura K, Takeda N, Harada T, Nojiri T, Imai Y, Utsunomiya K, Nagai R*:* Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: A new insight into adipocytokine-endothelial cell interactions. *BiochemBiophys Res Commun*, 314(2): 415–419, ***2004.***

Kougias P, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C*:* Adipocyte-derived cytokine resistin causes endothelial dysfunction of porcine coronary arteries. *J VascSurg*, 41(4): 691–698, ***2005.***

Ku D*:* Folic acid. Encyclopedia of Toxicology (Second Edition): 384-349,***2005.***

Kunnari A, Ukkola O, Paivansalo M, Kesaniemi YA*:* High plasma resistin level is associated with enhanced highly sensitive C-reactive protein and leukocytes. J ClinEndocrinolMetab., 91(7): 2755–2760,***2006***.

Larsson H, Berglund G, Ahren B*:* Insulin sensitivity, insulin secretion, and glucose tolerance versus intima-media thickness in nondiabetic postmenopausal women. J ClinEndocrinolMetab, 88(10):4791–7, ***2003.***

Lago F, Dieguez C, Gomez-Reino J, Gualillo O: The emerging role of adipokines as mediators of inflammation and immune responses. *Cytokine and Growth Factor Reviews*. 18 :313–325, ***2007.***

Legro RS, Kunselman AR, Dunaif A: Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. *Am J Med.*,111(8):607–13, ***2001.***

Li Y, Zhang L, Gu Y, Hao C, Zhu T: Insulin resistance as a predictor of cardiovascular disease in patients on peritoneal dialysis. *Perit Dial Int*., 33(4):411-8, ***2013***.

Lubos E, Messow CM, Schnabel R, Rupprecht HJ, Espinola-Klein C, Bickel C, Lackner KJ, Tiret L*:*Resistin, acute coronary syndrome and prognosis results from the AtheroGene study. *Atherosclerosis*193(1):121-8, ***2007.***

Maachi M, Pieroni L, Bruckert E, Jardel C, Fellahi S, Hainque B, Bastard JP*:* Systemic low-grade inflammation is related to both circulating and adipose tissue TNF alpha, leptin and IL-6 levels in obese women. Int J ObesRelatMetabDisord, 28(8):993-7,***2004.***

McTernan P, Fisher FM : Resistin and type 2 diabetes: regulation of resistin expression by insulin and rosiglitazone and the effects of recombinant resistin on lipid and glucose metabolism in human differentiated adipocytes.JClinEndocrinolMetab,, 88 (12)**:** 6098-106, ***2003.***

MahaldarAR: Acid base and fluid electrolyte disturbances in Chronic Kidney Disease, clinical queries, *nephrology* 1 (4): 295-299, ***2012.***

Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Turner RC:. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, 28(7):412-9, **1985**

Maggio MC, Montaperto D, Maringhini S, Corrado C, Gucciardino E, Corsello G*:*Adiponectin, resistin and leptin in paediatric chronic renal failure: correlation with auxological and endocrine profiles .*J Nephrol*, 27(3):275-9,***2014.***

Malyszko J, Malyszko JS, Kozminski P, Pawlak K, Mysliwiec M: Elevated resistin is related to inflammation and residual renal function in haemo- dialysed patients. *Nephrology (Carlton)*, 12(3):246-53,***2007.***

Marouga A, Dalamaga M, Kastania AN, Antonakos G, Thrasyvoulides A, Kontelia G, Dimas C, Vlahakos DV*:* Correlates of serum resistin in elderly, non-diabetic patients with chronic kidney disease. *clin. lab*, 59(10):1121-1128, ***2013***.

Mattu HS and Randeva HS: Role of adipokines in cardiovascular disease. *J Endocrinol*. 216(1):T17-36, ***2013***

Moon B, Kwan JJ, Duddy N, Sweeney G, Begum N*:* Resistin inhibits glucose uptake in L6 cells independently of changes in insulin signaling and GLUT4 translocation, Am. J. Physiol. Endocrinol.Metab., 285(1):E106-15, ***2003.***

Murray RL, Creatinine, Kaplan A: Clinical Chemistry. The C.V. Mosby Co. St.Louis. Toronto. Princeton, p 1261-1266 and 418,***1984.***

Nabae K, Doi Y, Takahashi S, Ichihara T, Toda C, Ueda K, Okamoto Y, Shirai T: Toxicity of di(2-ethylhexyl)phthalate and di(2-ethylhexyl)adipate under conditions of renal dysfunction induced with folic acid in rats: Enhancement of male reproductive toxicity of DEHP is associated with an increase of the mono-derivative. Reproductive Toxicology, 22(3): 411–417, ***2006.***

Nagaev I and Smith U: Insulin Resistance and Type 2 Diabetes Are Not Related to Resistin Expression in Human Fat Cells or Skeletal Muscle. *BiochandBiophyl Res Comm.*, 285(2): 561–564 , ***2001***

Nauk M, Marz W, Jarausch J: Multicenter evaluation of homogenous assay for HDL-Cholesterol without sample pretreatment. *Clin Chem*,43(9):1622-1629, ***1997.***

Nehus E, Furth S, Warady B, Mitsnefes M: Correlates of resistin in children with chronic kidney disease: the chronic kidney disease in children. J *pediatrics*: 161(2):276-80, ***2012.***

Norata GD, Ongari M, Garlaschelli K, Raselli S, Grigore L &Catapano AL: Plasma resistin levels correlate with determinants of the metabolic syndrome. European *Journal of Endocrinology*, 156(2): 279–284,***2007.***

Noureldeen AF, Qusti SY, Al-Seeni MN, Bagais MH*:* Maternal leptin, adiponectin, resistin, visfatin and tumor necrosis factor-alpha in normal and gestational diabetes. *Indian J ClinBiochem*., 29(4):462-70,***2014***

Ordodi VL, Mic FA, Mic AA, Toma O, Sandesc D, Paunescu V: A simple device for invasive measurement of arterial blood pressure and ECG in the anesthesized rat. *Timisoara Med J*, 55 No3 :235-237, ***2005.***

Orio F, Vuolo L, Palomba S, Lombardi G, Colao A*:* Metabolic and cardiovascular consequences of polycystic ovary syndrome. *Minerva Ginecol*,60 (1):39–51, ***2008.***

Panichi V, Migliori M, De Pietro S, Taccola D, Norpoth M, Metelli MR, Palla R*:* C reactive protein in patients with chronic renal diseases, *Ren Fail*., 23(3-4):551-62, ***2001***.

Parasuraman S and Raveendran R: Measurement of invasive blood pressure in rats. *Journal of pharmacololgy&pharmacotherapeutics*, 3(2):172-177, ***2012.***

Park SW, Kim SK, Cho YW, Kim DJ, Song YD, Choi YJ, Cho MA, Lee EJ, Huh KB*:* Insulin resistance and carotid atherosclerosis in patients with type 2 diabetes. *Atherosclerosis*, 205(1):309–313, ***2009.***

Pravenec M, Kazdova L, Landa V, Zidek V, Mlejnek P, Jansa P, Qi N, Kurtz TW *:* Transgenic and recombinant resistin impair skeletal muscle glucose metabolism in the spontaneously hypertensive rat. *J. Biol. Chem.*, 278(46): 45209–45215, ***2003.***

Raman PK, Purushothaman M, Kang S, Chemaly E, Hajjar R, Moreno P*:* Increased expression of adipokine-resistin expression in lipid-rich atheromatous plaques when compared to lipid poor- fibrotic plaques in human atherosclerosis-implication in accelerated at herosclerotic lesion progression. *Vascular medicine*, 61(10): E2035, ***2013.***

Raajala U, Laakso M, Paivansalo M, Pelkonen O, Suramo I, Keinanen- Kiukaanniemi S*:* Low insulin sensitivity measured by both quantitative insulin sensitivity check index and homeostasis model assessment method as a risk factor of increased intima-media thickness of the carotid artery. J ClinEndocrinolMetab, 87:5092–7, ***2002.***

Ridker PM, Rifai N, Pfeffer MA, Sacks F M, Moye LA., Goldman S, Flaker GC, Braunwald E: Inflammation, Pravastatin and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Circulation, 98(9): 839- 844, ***1998.***

Roa Barrios, M, Arata-Bellabarba G, Valeri L, Velázquez-Maldonado E: Relationship between the triglyceride/high-density lipoprotein-cholesterol ratio, insulin resistance index and cardiometabolic risk factors in women with polycystic ovary syndrome. *EndocrinolNutr*, 56(2):59–65, ***2009.***

Rutter MK, Meigs JB, Sullivan LM, D'Agostino B, Wilson PW: Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham offspring study. *Diabetes*, 54(11):3252–7, ***2005.***

Sabbatini AR, Faria AP, Barbaro NR, Gordo WM, Modolo RG, Pinho C, Moreno, H*:* Deregulation of adipokines related to target organ damage on resistant hypertension. *J Hum Hypertens*. *28(6):388-92,****2014.***

Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW*:* Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation,108(17):2154–2169,***2003.***

Sarnak MJ, Greene T, Wang X: The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. *Ann Intern Med*., 142(5):342–51, ***2005.***

Schmitz G and Hombach *V:* Biomarkers in Heart Failure. *Engl J Med* , 358(20):2148-2159, ***2010.***

Silverstein DM: Inflammation in chronic kidney disease: role in the pro- gression of renal and cardiovascular disease. *PediatrNephrol* , 24(8): 1445-52, ***2009.***

Stenvinkel P, Ketteler M, Johnson RJ, Lindholm B, Pecoits-Filho R, Riella M*:* IL-10, IL-6, and TNF-a: central factors in the altered cytokine network of uremia: the good, the bad, and the ugly. *Kidney Int* , 67(4):1216-33, ***2005***.

Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Patel HR, Ahima RS, Lazar MA*:* The hormone resistin links obesity to diabetes, *Nature*, 409(6818) : 307–312, ***2001***.

Steppan CM and Lazar MA*:* The current biology of resistin. *J. Intern. Med*., 255(4): 439–447, ***2004.***

Singh P, MG, Rajappa M, Balachander J, Kadhiravan T*:*Adiponectin-resistin index and its strong association with acute coronary syndrome in South Indian men. 63(11):961-8, ***2014***

Sun G, Bishop J, Khallili S, Vasdev S, Gill V, Pace D: Serum visfatin concentrations are positively correlated with serum triacylglycerols and down-regulated by overfeeding in healthy young men. *Am J ClinNutr*, 85(2): 399-404, ***2007.***

Takata Y, Osawa H, Kurata M, Kurokawa M, Yamauchi J, Okura T, Higaki J, Makino H*:*Hyperresistinemia is associated with coexistence of hypertension and type 2 diabetes. *Hypertension*, 51(2): 534–539, ***2008*.**

Temple RC, Clark PM, Hales CN: Measurement of insulin secretion in type II diabetes: problems and pitfalls. *Diabetic medicine*, 9(6): 503-512, ***1992.***

Teta D: Adipokines as uremic toxins. *Journal of Renal Nutrition*, 22, (1): 81-85,***2012.***

Tietz NW, Clinical guide to laboratory tests. W.B. Saunders, Co., Philadelphia, 509-512, ***1995***.

Tison GH, Blaha MJ, Budoff MJ, Katz R, Rivera JJ, Bertoni AG, Blumenthal RS, Eng J, Tracy R*:* The relationship of insulin resistance and extracoronary calcification in the multi-ethnic study of atherosclerosis. *Atherosclerosis*, 218 (2): 507–510, ***2011.***

Torzewski M, Rist C, Mortensen RF, Thomas P, Zwaka TP, Magda Bienek M, Jan Torzewski J :C-reactive protein in the arterial intima role of C-reactive protein receptor–dependent monocyte recruitment in atherogenesis. arteriosclerThrombVasc Biol.,20(9):2094-2099, ***2000.***

Tsutsumi T, Ichihara T, Kawabe M, Yoshino H, Asamoto M, Suzuki S, Shirai T: Renal toxicity induced by folic acid is associated with the enhancement of male reproductive toxicity of di(*n*-butyl) phthalate in rats. *Reproductive Toxicology*, 18(1): 35–42, ***2004***.

Vaziri ND: Altered lipid metabolism and serum lipids in kidney disease and kidney failure. *Nutritional management of renal disease: 3rd chapter (Third Edition)* p31–48, ***2013.***

Verma S, Li SH, Wang CH, Fedak PW, Li RK, Weisel RD, Mickle DA: Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. *Circulation*, 108(6): 736–740, ***2003.***

Watarai T, Yamasaki Y, Ikeda M: Insulin resistance contributes to carotid arterial wall thickness in patients with non-insulin-dependent-diabetes mellitus. *Endocr J* ,46(5):629–38, ***1999.***

Willette R, Bao W, Nerurkar S, Yue TL, Doe CP, Stankus G, Turner GH, Ju H, Thomas H, Sulpizio A: Systemic activation of the transient receptor potential V4 channel causes endothelial failure and circulatory collapse: part 2. *J. Pharmacol. Exp. Ther.*, 326(2): 443-452,**2008.**

Yaturu S, Reddy RD, Rains J, Jain SK*:* Plasma and urine levels of resistin and adiponectin in chronic kidney disease. *Cytokine*, 37(1) :1–5, ***2007.***

Yudkin JS, Kumari M, Humphries SE, Mohamed-Alı V*:* Inflammation, obesity, stress and coronary hearth disease: is interleukin-6 a link? *Atherosclerosis*, 148 (2) :209-14***, 2000.***

Zhang L, Curhan GC, Forman JP: Plasmaresistin levels associate with risk for hypertension among non diabetic women. *Nephrol*., 21(7): 1185-1191***, 2010.***

Zhang MH, Beeya NA, Schiller NB, WhooleyMA: Association of resistin with heart failure and mortality in patients with stable coronary heart disease. *Journal of Cardiac Failure*,17(1) :24-30, ***2011.***

Zhou L, Sella H, Eckardta K, Yangb Z, Eckel J*:* Conditioned medium obtained from in vitro differentiated adipocytes and resistin induce insulin resistance in human hepatocytes . *FEBS Letters*, 581 (22): 4303–4308, ***2007.***

Zhong S, Zhao L, Li Q, Yang P, Varghese Z, Moorhead JF, Ruan XZ*:* Inflammatory stress exacerbated mesangial foam cell formation and renal injury via disrupting cellular cholesterol homeostasis**.** ***2014***Epub ahead of print] *DOI:10.1007/s10753-014-0058-0.*

Zorniak M, Mitrega K, Bialka S, Porc M, Krzeminski TF: *Comparison of thiopental, urethane, and pentobarbital in the study of experimental cardiology in rats in vivo. J CardiovascPharmacol*, 56 (1):38-44, ***2010.***