Resistin, inflammatory biomarkers and insulin resistance in chronic kidney disease

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ABSTRACT

In the present study, the role of decreased renal function on resistin was explored. The possible links with inflammation and the insulin resistance present in patients with chronic kidney disease (CKD) were investigated. Post-transplantation changes in these factors and relations were also examined. The study included 83 subjects; 67 patients suffering from chronic kidney diseases and 16 healthy subjects. Participants were classified into the following groups: Group I: 16 chronic kidney disease patients on conservative treatment (9 males and 7 females, mean age 42.75 ± 11.7 years). Group II: 26 dialysis patients (13 males and 13 females, mean age 43.8 ± 14.6 years). Group III: 25 post kidney transplantation patients (13 males, 12 females, mean age 44.2 ± 8.2 years). Group IV: 16 healthy, age and sex matched subjects served as control group (8 males and 8 females, mean age 43.50±9.2 years). Estimated glomerular filtration rate (eGFR) was calculated by Modification of Diet in Renal Disease (MDRD) formula. Insulin resistance was estimated using the homeostasis model assessment for insulin resistance (HOMA-IR) index. Serum levels of resistin, hs CRP and IL6 were estimated by ELISA technique. Results showed that circulating resistin levels were significantly higher in patient groups compared to the control group. They decreased significantly post-transplantation, yet still higher than normal subjects. These levels showed significantly negative correlation with eGFR. However, resistin levels correlated significantly positive with inflammatory biomarkers (IL6 and hs CRP) in the studied groups. On the other hand, there was no significant correlation between resistin and insulin resistance in any group. ***In conclusion:*** *Resistin levels correlate with renal function and inflammation in CKD patients. However, it is not a likely mediator of insulin resistance in those patients. Renal function is an important factor to take into account in clinical studies relating insulin sensitivity to inflammatory biomarkers in CKD.*

Keywords: *chronic kidney disease; glomerular filtration rate; resistin; insulin resistance; inflammation.*

INTRODUCTION

The recent discovery of resistin, a 12.5-kDa cysteine-rich protein secreted mainly by adipocytes and apparently inhibiting insulin action in vitro,[1–3] has generated much interest. Resistin, like adiponectin, circulates in serum in at least two distinct dimeric assembly forms that appear to have

different levels of bioactivity.[4] Administration of recombinant resistin to mice impairs glucose tolerance and decreases the action of insulin, whereas an increase in insulin sensitivity is noted when the animals are treated with resistin-neutralizing antibodies.[1]

Although several studies[1,5] implicate resistin as an important regulator of glucose levels in mice, the role of resistin in human syndromes of insulin resistance, such as uremia, is far from clear.[1,6–8] Indeed, the few studies[9–11] that have so far been performed in non-renal patients have been unable to find a significant relationship between serum glucose levels or markers of insulin resistance and circulating resistin or resistin expression by subcutaneous adipocytes. Similar results were observed in a small study of 30 CKD patients by Kielstein et al.[6]

Insulin resistance is the central pathophysiological process of the metabolic syndrome,[1] a well-established and major risk factor for the development of cardiovascular disease.[12,13] Chronic kidney disease (CKD) of any etiology is associated with insulin resistance of primarily peripheral tissues resulting in varying degrees of hyperinsulinemia and glucose intolerance.[14,15] Decreased response to insulin is manifest already in mild renal dysfunction[16] and progresses with declining glomerular filtration rate (GFR),[17] only to improve slightly at the initiation of renal replacement therapy.[17]

The proposed link(s) between declining renal function and insulin resistance appear to act mainly in peripheral tissues,[14] but the exact mechanisms have so far not been clarified,[18] and a variety of possible etiologies are proposed. Recent studies have implicated acidosis,[16] the effects of chronic systemic inflammation,[19] changes in body composition[19,20] and accumulation of free fatty acids[21] as well as uremic carbamoylation of signaling proteins[11] as possible mechanisms.

The present work aimed at studying levels of resistin in CKD patients. It also aimed at investigating the relationship between levels of resistin, eGFR, inflammatory activity and insulin resistance syndrome present in those patients.

SUBJECTS & METHODS

Subjects:

Subjects enrolled in the present study were classified into 4 groups (total 83 subjects).

Group I (Conservative Group): 16 chronic kidney disease patients attending out-patient Nephrology Clinic, Kasr Al Aini Hospital, for follow up of their chronic renal impairment (9 males and 7 females, aged 42.75± 11.7 years).

Group II (Dialysis Group): 26 dialysis patients affiliated to Kasr Al Aini Center for Dialysis (13 males and 13 females, aged 43.8±14.6 years).

Group III (Post-transplantation Group): 25 post kidney transplantation patients attending follow up in Transplant Clinic of Kasr Al Aini (13 males, 12 females, aged 44.2 ± 8.2 years). Post-transplantation duration was 2.0±0.1 years.

Group IV (Control Group): 16 healthy, age and sex matched subjects (doctors, nurses and patient relatives)

served as control group for comparative analysis of biochemical and metabolic parameters. (8 males and 8 females, aged 43.50±9.2 years). The control subjects were submitted to a similar protocol as the patient groups.

An informed consent was taken from all participants. The study was performed during the period from January 2007 to July 2007.The causes of CKD were chronic glomerulonephritis in 28 patients, polycystic kidney disease in 18 patients and other, or unknown etiology in 21 patients.

The majority of patients were on antihypertensive medications (angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin II receptor antagonists, n=25; β blockers, n=30; calcium-channel blockers, n=33) and other commonly used drugs in CKD, such as phosphate and potassium binders, diuretics, erythropoiesis-stimulating agents, iron substitution and vitamin B, C, and D supplementation.

Exclusion criteria:

1- Recent surgery
2- Patients with current or recent (within last two weeks) overt infection e.g. upper respiratory tract infection, urinary tract infection, gastroenteritis.
3- Patients with current or recent (within last two weeks) inflammatory process e.g. gouty arthritis, rheumatoid arthritis.
4- Patients with known malignancy.
5- Diabetic patients.
6- Patients having Body Mass Index (BMI) ≥ 30.

Sample Collection:

After overnight fast, venous blood was collected into three tubes:

i) One tube containing fluoride for estimation of plasma glucose. [22] Plasma was separated by centrifugation at 3000 rpm for 15 minutes.
ii) The second tube containing EDTA for separation of plasma and estimation of glycosylated hemoglobin (HbA1c) by the kit provided by Stanbio, Italy [23]. Insulin was estimated in plasma by RIA technique using kit provided by Linco Research Inc., Missouri, USA [24]. Insulin resistance was estimated using the homeostasis model assessment for insulin resistance (HOMA-IR) index [i.e. fasting plasma glucose (mmol/L) x fasting plasma insulin (μU/mL)/22.5]. [25]
iii) The third was plain tube for separation of serum. Sera were aliquoted and stored at -80°C until analysis was carried out.

Serum creatinine[26], cholesterol[27] and triglycerides[28], were determined using commercially available kits.

eGFR has been calculated by MDRD formula[29] using a soft ware program provided freely from St George's University of London.

$$\mathbf{eGFR = 175 \times (S_{CR} \times 0.0113)^{-1.154} \times (age)^{-0.203} \times (0.742\ [if\ female])}$$

where MDRD = Modification of Diet in Renal Disease, eGFR = estimated glomerular filtration rate (mL/min/1.73 m^2), S_{CR} = serum creatinine concentration (μmol/L), and age is expressed in years.

Determination of serum Resistin[30]:

Levels of resistin were determined using Human Resistin ELISA kit provided by Biovendor GmbH (Germany).

Determination of serum IL6[31] and hs CRP[32]: was carried out by ELISA technique using kits provided by DiaMed EuroGen (Belgium) for hs CRP and by Biosource International Inc., Camarillo, California, USA for IL6.

Statistical analysis:

All analyses were performed using the Statistical Package for Social Sciences (SPSS) software. Numerical data were expressed as mean ± SD. Comparisons were performed by analysis of variance "ANOVA" on ranks, Scheffe's test was used as a post-hoc test. Correlations were tested by spearman's test. Comparisons and correlations were considered statistically significant when $P<0.05$.[33]

RESULTS

Table 1: Demographic and laboratory data in the studied groups.

	Conservative group n= 16	**Dialysis Group n=26**	**Post-transplant-ation Group n= 25**	**Control Group n= 16**
Age (Years)	42.75± 11.7(a)	43.8 ± 14.6(a)	44.2 ± 8.2(a)	43.50±9.2(a)
M/F	9/7	13/13	13/12	8/8
BMI (Kg/m^2)	25.9±2.9(a)	24.7±5.0(a)	26.1± 3.7(a)	26.8±2.1(a)
Creatinine (µmol/L)	338.3±72.01(d)	1030.1±63.4(c)	187.8±36.8(b)	86.7±12.02(a)
eGFR ($mL/min/1.73m^2$)	23.7±15(c)	ND	54.6±19.8(b)	90±13(a)
FPG (mmol/L)	5.7±0.26(a)	5.8±1.41(a)	5.5±0.8(a)	5.16±0.9(a)
FPI(µIU/mL)	20.28±3.72(b)	22.98±2.9(b)	13.55±3.03(a)	11.62±1.64(a)
HOMA-IR	5.3±0.7(c)	5.86±1.2(c)	3.82±0.51(b)	2.7±0.34(a)
Hb A1c (%)	4.58±1.73(a)	5.03±1.07(a)	4.87±0.67(a)	4.4±0.23(a)
TC (mg/dL)	235.2±14.1(b)	236.2±11.6(b)	200.9±11.3(a)	194.5±12.4(a)
TAG(mg/dL)	111.4±15.6(a)	110.1±39.3(a)	116.2±22.4(a)	107.5±18.8(a)

Levels are expressed as means ±SD.
M/F: Male/Female; BMI: body mass index; eGFR: estimated glomerular filtration rate; ND: not detected; FPG: fasting plasma glucose; FPI: fasting plasma insulin; HOMA-IR: homeostasis model assessment for insulin resistance; HbA1c: glycated hemoglobin A1c; TC: total cholesterol; TAG: triacyl glycerol.
Same letters (a,b,c,d) under each group indicate a non-significant difference among groups.
Different letters (a,b,c,d) under each group indicate significant difference among groups.

Table 1 shows demographic data, serum creatinine, eGFR, fasting plasma glucose (FPG), fasting plasma insulin (FPI), insulin resistance (HOMA-IR) and HbA1c% in the studied groups. All groups were matched regarding age, sex and BMI. Creatinine was significantly higher in dialysis group than other groups (P<0.001). eGFR was significantly higher in pos-transplantation group than conservative group (P<0.001).However, it was still significantly lower than control group (P<0.001) . As dialysis patients were anuric, no GFR was estimated in that group. As regards markers of glucose metabolism, FPI and HOMA-IR were significantly higher in dialysis group and conservative group than other groups (P<0.001). There was no statistically significant difference in FPG and HbA1c among groups. Total cholesterol was significantly higher in dialysis group and conservative group than control and post-transplantation groups (P<0.01).There was no statistically significant difference in TAG among groups.

Table 2: Levels of resistin, IL6 and hsCRP in the studied groups

	Conservative group n= 16	**Dialysis Group n=26**	**Post-transplantation Group n= 25**	**Control Group n= 16**
Resistin (ng/mL)	23.6±1.38(d)	40.59±2.2(c)	17.02±5.15(b)	8.13±0.82(a)
IL6 (pg/mL)	6.86±2.19(c)	14.83±6.81(b)	4.14±2.22(a)	3.38±2.3(a)
hs CRP (μg/mL)	4.1±1.0(b)	6.8±2.01(c)	3.5±1.1(b)	1.2±0.7(a)

Values are means ±SD.
hs CRP: high sensitive C reactive protein.
Same letters (a,b,c,d) under each group indicate a non-significant difference among groups.
Different letters (a,b,c,d) under each group indicate significant difference among groups.

Table (2) shows the levels of resistin, IL6 and hs CRP in the studied groups. All were significantly higher in dialysis group than other groups (P<0.001). Resistin and hs CRP decreased significantly after transplantation but still were significantly higher than control group (P<0.001). However, there was no significant difference in IL6 between post-transplantation and control groups.

Table 3: Correlations for markers of glucose metabolism and inflammatory biomarkers with serum resistin levels

	Conservative group n= 16 Serum resistin (ng/mL) **(r)**	**Dialysis Group n=26 Serum resistin** (ng/mL) **(r)**	**Post-transplantation Group n= 25 Serum resistin** (ng/mL) **(r)**	**Control Group n= 16 Serum resistin** (ng/mL) **(r)**
Markers of glucose metabolism:				
-FPG(mmol/L)	0.06	0.06	0.05	0.11
-FPI(µIU/mL)	0.131	0.231	0.41	0.31
-HOMA-IR	0.048	0.14	0.48	0.43
-Hb A1c(%)	0.129	0.32	0. 29	0.24
Markers of inflammation:				
-IL6 (pg/mL)	0.7**	0.81***	0.63**	0.61**
-hs CRP (µg/mL)	0.83***	0.66***	0.55**	0.5*

** = P< 0.05*
*** = P< 0.01*
****= P< 0.001*

Table 3 shows correlations between serum resistin and markers of glucose metabolism and inflammatory biomarkers. There was significant correlation between serum levels of resistin and markers of inflammation, i.e. hs CRP and IL6. However, there was no significant correlation with any of markers of glucose metabolism, i.e. FPG, FPI, HOMA-IR and Hb A1c.

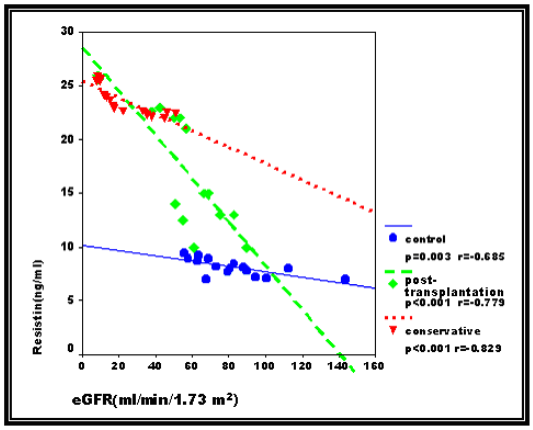

Figure 1 : Correlation between eGFR and Resistin

Figure 1 shows that there was significant negative correlation between serum resistin and eGFR in conservative group ($r=-0.829$, $p<0.001$), post-transplantation group ($r=-0.779$, $p<0.001$) and control group ($r = -0.685$, $P<0.01$).

DISCUSSION

The present study demonstrated that circulating serum resistin levels, like other adipokines such as leptin and adiponectin [34,35] were markedly elevated in patients with renal function impairment. Several factors might contribute to elevated circulating resistin levels in CKD. First, a strong impact of GFR on circulating fasting serum levels of resistin was demonstrated .Thus, the current data confirm the association previously reported by Kielstein et al.[6] in a cohort of CKD patients.

As resistin is a 12.5 kDa protein, it could be hypothesized that this small protein will have similar renal clearance characteristics as β_2-microglobulin (13.7 kDa), which has been extensively studied.[36] If this is true, it might be expected that resistin secretion through the kidneys is the major pathway of elimination, and current dialysis techniques will only partially be able to remove excess resistin from the circulation. Clearly, in future clinical studies evaluating circulating resistin levels, renal function must be taken into account.

Another major finding of the present study is the association between serum levels of resistin and various biomarkers of inflammation, confirming studies in patients without renal function impairment.[37–40] Recently, it has become apparent that CKD is a state of chronic inflammation that is associated with significant increases in serum proinflammatory cytokine levels already at moderate levels of renal function impairment. Although fat mass is likely an important source of both resistin and several proinflammatory cytokines,[9] other links between inflammation and resistin are also likely present.

First, in cultured human vascular endothelial cells, resistin was able to induce expression of adhesion molecules. Furthermore, resistin mRNA is abundant in human primary acute leukemia cells and in myeloid cell lines,[7] indicating a hitherto unidentified biological function of resistin in leukocytes. Indeed, Patel et al.[40] found that resistin is more expressed in bone marrow than in adipose tissue. Moreover, in vitro studies have demonstrated resistin mRNA expression in peripheral blood monocytes, with increased levels after stimulation by IL-1, IL-6, and TNF-α, as well as with lipopoly-saccharides.[41,42] Finally, Reilly et al.[43] have demonstrated that serum resistin levels were correlated with markers of inflammation and predict coronary atherosclerosis in humans independently of CRP.

Since the discovery of resistin in 2001,[1–3] the putative association between resistin and insulin resistance has attracted a lot of interest. In mice, resistin mRNA and protein levels declined in parallel with glucose and insulin during fasting and were restored after refeeding[5] and adipose resistin expression and serum resistin increase in response to

hyperinsulinemia and further in response to hyperglycemia. [5] In obese mice, circulating resistin levels were significantly elevated and positively correlated with insulin, glucose and lipids,[44] and mice lacking the resistin gene exhibited low blood glucose levels after fasting due to reduced hepatic glucose production. Interestingly, a recent study by Muse et al.[45] suggested that this effect was mainly due to modulation of hepatic insulin resistance.

Although resistin seems to be strongly associated with insulin resistance in mice models, several recent studies have questioned the hypothesis that resistin is a significant determinant of insulin resistance in humans. First, Janke et al.[9] found low levels of resistin expression in subcutaneous adipocytes and no correlation with insulin resistance. Similarly, Heilbronn et al.[10] found that serum resistin concentrations did not differ among non-obese, obese and obese diabetic subjects, nor were they significantly correlated with glucose metabolism during a hyperinsulinemic glucose clamp across the groups. Finally, when comparing three different immunoassays for resistin, Pfützner et al.[11] found no correlation between fasting serum levels of resistin and any of the measured parameters of insulin resistance or with blood lipids in patients with type II diabetes mellitus. In the present study no significant correlation between fasting serum resistin levels and marker of insulin resistance (HOMA-IR) was found.

The present results agree with those of Kielstein et al.[6] who found no relationship between serum levels of resistin and markers of glucose metabolism, despite markedly elevated resistin levels in CKD patients with IgA nephropathy. A number of recent reports suggest that increased levels of the acute-phase inflammatory markers, such as CRP, were related to insulin resistance[46,47] and the chronic low-grade inflammation present in the metabolic syndrome has been suggested to play an important role in the development of this complication.[48] Indeed, a recent report by Arkan et al.[46] demonstrated that liver cells play an important role in modulating hepatic insulin resistance, whereas myeloid cells may play a central role in the development of systemic insulin resistance. The reason(s) for that is far from clear, but likely does not involve circulating resistin levels, which were also not correlated with HOMA-IR. Clearly, as mild to moderate renal function impairment is a common phenomenon in patients with diabetes mellitus and the metabolic syndrome, future clinical studies investigating a possible direct link between inflammation biomarkers and insulin resistance should take GFR into account.

Some shortcomings of the present study should be addressed. First, it should be pointed out that this is a post hoc analysis of CKD patients with mostly advanced renal impairment. Clearly, this may limit the value of the study, and further studies on patients with mild renal impairment are needed. Second, although HOMA-IR has been reported to be a valid surrogate marker also in this patient group,[49] it may not

accurately reflect insulin resistance. However, it has been postulated that resistin is mainly active in modulating hepatic insulin resistance,[45] making use of the euglycemic clamp technique potentially also problematic as it is known to measure mainly peripheral insulin resistance.[50] Another point of criticism might be that we do not know if resistin levels in the present study represent active resistin or if an accumulation of inactive resistin metabolites accounts for the major part of the increased plasma resistin concentration observed in CKD. Also, circulating resistin levels may not accurately reflect local resistin action at the tissue level.

Finally, the use of antihypertensive medications has been reported to influence insulin sensitivity. Thus, while β-blockers appear to decrease insulin sensitivity, most (but not all) ACE inhibitors (ACEI) and calcium blockers appear to improve it.[51] As the majority of these patients were taking more than one class of drugs, it might be thought that this confounder is of minor importance and will not unduly affect the reported results. Indeed, no significant differences were found in HOMA-IR between patients taking ACEI and those not taking ACEI (not presented data).

In summary, the present data support the hypothesis that inflammation is associated with hyper-resistinemia. As no significant relationship was found between serum resistin levels and insulin resistance, resistin is not a likely mediator of insulin resistance in patients with renal disease. Renal function is an important factor to take into account in clinical studies relating insulin sensitivity to inflammatory biomarkers in CKD.

REFERENCES

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

2- **Holcomb IN, Kabakoff RC, Chan B, Baker TW, Gurney A, Henzel W, Nelson C, Lowman HB, Wright BD, Skelton NJ, Frantz GD, Tumas DB, Peale FV Jr, Shelton DL and Hébert CC (2000):** FIZZ1, a novel cysteine-rich secreted protein associated with pulmonary inflammation, defines a new gene family. EMBO J; 19: 4046–4055.

3- **Kim KH, Lee K, Moon YS, Sul HS (2001):** A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte differentiation. J Biol Chem; 276: 11252–11256.

4- **Patel SD, Rajala MW, Rossetti L and Shapiro L (2004):** Disulfide-dependent multimeric assembly of resistin family hormones. Science; 304: 1154–1158.

5- **Rajala MW, Qi Y, Patel HR, Takahashi N, Banerjee R, Pajvani UB, Sinha MK, Gingerich RL, Scherer PE and Ahima RS (2004):** Regulation of resistin expression and circulating levels in obesity, diabetes, and fasting. Diabetes; 53:1671–1679.

6- **Kielstein JT, Becker B, Graf S, Brabant G, Haller H, Fliser D (2003):** Increased resistin blood levels are not associated with insulin resistance in patients with renal disease. Am J Kidney Dis; 42: 62–66.

7- **Yang RZ, Huang Q, Xu A, McLenithan JC, Eisen JA, Shuldiner AR, Alkan S and Gong DW (2003):** Comparative studies of resistin expression and phylogenomics in human and mouse. Biochem Biophys Res Commun; 310: 927–935.

8- **Shuldiner AR, Yang R, Gong DW (2001):** Resistin, obesity and insulin resistance – the emerging role of the adipocyte as an endocrine organ. N Engl J Med; 345: 1345–1346.

9- **Janke J, Engeli S, Gorzelniak K, Luft FC and Sharma AM (2002):** Resistin gene expression in human adipocytes is not related to insulin resistance. Obes Res; 10: 1–5.

10- **Heilbronn LK, Rood J, Janderova L, Albu JB, Kelley DE, Ravussin E, Smith SR (2004):** Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. J Clin Endocrinol Metab ; 89:1844–1848.

11- **Pfützner A, Langenfeld M, Kunt T, Löbig M and Forst T (2003):** Evaluation of human resistin assays with serum from patients with type 2 diabetes and different

12- degrees of insulin resistance. Clin Lab; 49: 571–576.

13- **Eckel RH, Grundy SM, Zimmet PZ (2005):** The metabolic syndrome. Lancet; 365: 1415.

14- **Jadhav S, Petrie J, Ferrell W, Cobbe S and Sattar N (1997):** Insulin resistance as a contributor to myocardial ischaemia independent of obstructive coronary atheroma: a role for insulin sensitisation? Heart; 90: 1379.

15- **Alvestrand A (1997):** Carbohydrate and insulin metabolism in renal failure. Kidney Int Suppl ; 62: S48–S52.

16- **DeFronzo RA, Alvestrand A, Smith D, Hendler R, Hendler E, Wahren J (1981):** Insulin resistance in uremia. J Clin Invest; 67: 563–568.

17- **Kobayashi S, Maesato K, Moriya H, Ohtake T and Ikeda T (2005):** Insulin resistance in patients with chronic kidney disease. Am J Kidney Dis; 45: 275.

18- **Govaerts P (1952):** Physio-pathology of glucose excretion by the human kidney. BMJ; 2: 175–179.

19- **Rigalleau V and Gin H (2005):** Carbohydrate metabolism in uraemia. Curr Opin Clin Nutr Metab Care; 8: 463–469.

20- **Axelsson J, Heimburger O, Lindholm B and Stenvinkel P (2005):** Adipose tissue and its relation to inflammation: the role of adipokines. J Ren Nutr; 15:131–136.

21- **Axelsson J, Rashid Qureshi A, Suliman ME, Honda H, Pecoits-Filho R, Heimbürger O, Lindholm B, Cederholm T and Stenvinkel P (2004):** Truncal fat

mass as a contributor to inflammation in end-stage renal disease. Am J Clin Nutr; 80: 1222–1229.

22- **Vaziri ND and Liang K (1996):** Down-regulation of tissue lipoprotein lipase expression in experimental chronic renal failure. Kidney Int; 50: 1928–1935.

23- **Trinder P (1969):** Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann Clin Biochem; 6:24-27

1. **23-Danilova LA and Lopatina NI (1986):** Colorimetric method of determining glycosylated hemoglobins. Lab. Delo; 5: 282-283.

24- **Heding LG (1972):** Determination of total serum insulin (IRI) in insulin treated diabetic patients. Diabetologia; 8:260-266

25- **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, and Turner RC (1985):** Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia; 28:412 -419.

26- **Heinegard D and Tiderstorm K (1973):** Determination of serum creatinine by a direct colorimetric method. Clin.Chim. Acta; 43:305.

27- **Wahlefeld AW (1974):** Triglyceride determination after enzymatic hydrolysis. In: Methods of enzymatic analysis; HU Berger ed., 2nd English ed (translated from 3rd German ed.),Verlag Chemie Weinheim and Academic Press, Inc.NY and London . Vol. 4,pp1813-1835.

28- **Flegg HM (1973):** An investigation for the determination of serum cholesterol by an enzymatic method. Ann.Clin. Biochem; 10:79-84.

29- **Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW and Chronic Kidney Disease Epidemiology Collaboration (2006):**Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. Ann Intern Med; 145: 247-254.

30- **Bokarewa M, Nagaev I, Dahlberg L, Smith U and Tarkowski A (2005):** Resistin, an adipokine with potent proinflammatory properties. J Immunol; 174: 5789- 95.

31- **Ledur A, Fitting C, David B, Hamberger C, Cavaillon JM (1995):** Variable estimates of cytokine levels produced by commercial ELISA kits: results using international cytokine standards. J Immunol Methods; 186: 548-553.

32- **Mitra B and Panja M (2005):** High sensitive CRP: a novel biochemical marker and its role in coronary atherosclerosis. J Assoc Physicians India; 53: 25-32.

33- **Saunders D and Trapp G (2001):** Basic and clinical Biostatistics; 3rd edition, Connecticut, Appleton and Lang .

34- **Nordfors L, Lonnqvist F, Heimburger O,Danielsson A,**

Schalling M and Stenvinkel P (1998): Low leptin gene expression and hyperleptinemia in chronic renal failure. Kidney Int ; 54: 1267–1275.

35- **Stenvinkel P, Marchlewska A, Pecoits-Filho R, Heimbürger O, Zhang Z, Hoff C, Holmes C, Axelsson J, Arvidsson S, Schalling M, Barany P, Lindholm B and Nordfors L (2004):** Adiponectin in renal disease: relationship to phenotype and genetic variation in the gene encoding adiponectin. Kidney Int ; 65: 274–281.

36- **Karlsson FA, Groth T and Sege K (1980):** Turnover in humans of beta 2-microglobulin: the constant chain of HLA-antigens. Eur J Clin Invest; 10: 293–300.

37- **Kaser S, Kaser A, Sandhofer A, Ebenbichler CF, Tilg H and Patsch JR (2003):** Resistin messenger-RNA expression is increased by proinflammatory cytokines in vitro. Biochem Biophys Res Commun; 309: 286–290.

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

39- **Lehrke M, Reilly MP, Millington SC, Iqbal N, Rader DJ and Lazar MA (2004):** An inflammatory cascade leading to hyper resistinemia in humans. Plos Med; 1: e45.

40- **Patel L, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, Plumpton C, Macphee CH and Smith SA (2003):** Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem Biophys Res Commun 300: 472–476.

41- **Pecoits-Filho R, Heimburger O, Barany P Suliman M, Fehrman-Ekholm I, Lindholm B and Stenvinkel P. (2003)** Associations between circulating inflammatory markers and residual renal function in CRF patients. Am J Kidney Dis; 41: 1212–1218.

42- **Landray MJ, Wheeler DC, Lip GY Newman DJ, Blann AD, McGlynn FJ, Ball S, Townend JN and Baigent C (2004):** Inflammation, endothelial dysfunction, and platelet activation in patients with chronic kidney disease: the chronic renal impairment in Birmingham (CRIB) study. Am J Kidney Dis; 43: 244–253.

43- **Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA and Rader DJ (2005):** Resistin is an inflammatory marker of atherosclerosis in humans. Circulation; 111: 932–939.

44- **Banerjee RR, Rangwala SM, Shapiro JS, Rich AS, Rhoades B, Qi Y, Wang J, Rajala MW, Pocai A, Scherer PE, Steppan CM, Ahima RS, Obici S, Rossetti L and Lazar MA. (2004):** Regulation of fasted

blood glucose by resistin. Science ; 303: 1195–1198.

45- **Muse ED, Obici S, Bhanot S, Monia BP, McKay RA, Rajala MW, Scherer PE and Rossetti L (2004):** Role of resistin in diet-induced hepatic insulin resistance. J Clin Invest; 114: 232–239.

46- **Arkan MC, Hevener AL, Greten FR Maeda S, Li ZW, Long JM, Wynshaw-Boris A, Poli G, Olefsky J and Karin M (2005):** IKK-[beta] links inflammation to obesity-induced insulin resistance. Nat Med; 11: 191- 198.

47- **Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J and Shoelson SE (2005):** Local and systemic insulin resistance resulting from hepatic activation of IKK-[beta] and NF-[kappa]B. Nat Med; 11: 183-190.

48- **Sjoholm A and Nystrom T (2005):** Endothelial inflammation in insulin resistance. Lancet; 365: 610- 612.

49- **Kanauchi M, Akai Y and Hashimoto T (2002):** Validation of simple indices to assess insulin sensitivity and pancreatic beta-cell function in patients with renal dysfunction. Nephron; 92: 713-715.

50- **Tripathy D, Almgren P, Tuomi T and Groop L (2004):** Contribution of insulin-stimulated glucose uptake and basal hepatic insulin sensitivity to surrogate measures of insulin sensitivity. Diabetes Care; 27: 2204–2210.

51- **Mediratta S, Fozailoff A and Frishman WH (1995):** Insulin resistance in systemic hyper-tension: pharmaco-therapeutic implications. J Clin Pharmacol; 35: 943–956.

الريزستين، دلالات الالتهاب و مقاومة الانسولين في أمراض الكلي المزمنة

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تهدف الدراسة الحالية الى البحث عن تأثير أمراض الكلي علي مستويات الريزستين وأيضا العلاقة بين الالتهاب و مقاومة الانسولين و هذا البروتين كما تهدف الى دراسة تأثير زراعة الكلي علي هذه المستويات.
وقد شمل البحث ٨٣ شخصا، ٦٧ مريضا و ١٦ من الأصحاء كمجموعة ضابطة.
وتم تقسيم مجموعات البحث إلى :
المجموعة الأولى:تضم ١٦ مريضا علي علاج تحفظي.
المجموعة الثانية: تضم ٢٦ مريضاعلي غسيل دموى.
المجموعة الثالثة:تضم ٢٥مريضا أجريت لهم زراعة الكلي.
المجموعة الرابعة: تضم ١٦ شخصا من الأصحاء متماثلين من حيث العمر و الجنس مع المجموعات الثلاثة السابقة كمجموعة ضابطة.
وقد تم حساب معدل ترشيح البول و مقاومة الانسولين كما تم قياس مستويات الريزستين و انترلوكين ٦ و البروتين المتفاعل ج شديد الحساسية بواسطة تقنية" الايليزا" في مصل جميع المرضي و الأصحاء المشاركين في الدراسة.
وأظهرت نتائج البحث ارتفاع مستويات الريزستين في مرضي الكلي مقارنة بالأصحاء ، و انخفاض هذه المستويات بعد أجراء زراعة الكلي ولكنها مازالت أعلي من المجموعة الضابطة كذلك ارتباط مستويات الريزستين بعلاقة سلبية ذات دلالة احصائية مع معدل ترشيح البول و بعلاقة طردية ذات دلالة احصائية مع دلالات الالتهاب مثل انترلوكين ٦ و البروتين المتفاعل ج شديد الحساسية.
و من ناحية أخري، لم توجد علاقة ذات دلالة احصائية بين مستويات الريزستين و مقاومة الانسولين في أي من المجموعات.
واستخلصت الدراسة أرتفاع مستويات الريزستين في مرضي الكلي و أن حالة الكلي الوظيفية يجب أن تؤخذ في الاعتبار عند دراسة الحساسية للانسولين و دلالات الالتهاب في هؤلاء المرضي.