# BIOLOGICAL ASSOCIATIONS BETWEEN RESISTIN, ADIPONECTIN, VISFATIN AND GHRELIN HORMONES WITH SOME COAGULATION MARKERS

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**ABSTRACT**
**This study was aimed to investigate the biological association between resistin, adiponectin, visfatin and ghrelin hormones with some coagulation markers. The study included 130 patient and 42 healthy subjects. Serum resistin, adiponectin, visfatin, ghrelin and some other hematological and biochemical parameters were estimated. Statistical analysis showed that altered resistin, adiponectin, visfatin, and ghrelin levels were significantly and directly or indirectly through insulin resistance (IR) associated with clotting markers. From the main studied levels of adipokines, ghrelin, and clotting parameters, the study indicated high levels of serum resistin, adiponectin, visfatin and ghrelin hormones in NIDDM, ESRD, NIDDM+ESRD patients. Also, altered platelets (PLT), mean platelet volume (MPV), prothrombin time (PT), activated partial prothrombin time (aPPT), plasminogen activator inhibitor- 1 (PAI-1), and fibrinogen1 were observed. The studied adipocytokines and ghrelin concentration was correlated directly and indirectly through IR with the studied clotting parameters.**

**Keywords: Adipokines, ghrelin, NIDDM, insulin resistance, clotting abnormalities.**



## الارتباط البايولوجي بين هرمونات الريسيستين الأديبونيكتين الفيسفاتين والجريلين مع بعض علامات التخثر

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**المستخلص**
**يهدف البحث الى دراسة العلاقة البايولوجية بين هرمونات الريسيستين، الأديبونيكتين، الفيسفاتين والجريلين مع بعض علامات التخثر. شملت الدراسة 130 مريضا و 42 حالة سيطرة. تم تقدير هرمونات مصل الدم رسيستين، أديبونيكتين، فيسفاتين، جريلين وبعض المعلمات الدموية والكيمياء الحيوية الأخرى. أظهر التحليل الإحصائي أن مستويات resistin وadiponectin و visfatin و ghrelin التي تغييرت كانت بشكل كبير و ارتبطت بشكل مباشر أو غير مباشر من خلال مقاومة الأنسولين المرتبطة بعلامات التخثر. من المستويات الرئيسية التي شملتها الدراسة من معلمات dipokines، وghrelin، والتخثر، أشارت الدراسة إلى وجود مستويات عالية من هرمونات المصل resistin، وadiponectin، وvisfatin، وghrelin لدى مرضى NIDDM، وESRD، وNIDDM + ESRD. أيضا، تم تغيير MPV، PT، aPTT، الفيبرينوجين و PAI-1. تم ربط adipocytokines وتركيز جريلين بشكل مباشر وغير مباشر من خلال مقاومة الانسولين (IR) مع عوامل التخثر المدروسة.**

**الكلمات المفتاحية: هورمونات الانسجة الدهنية، الجريلين، NIDDM، مقاومة الأنسولين ،اضطرابات التخثر.**

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## INTRODUCTION

Adipose tissue is considered as the primary site for initiation and aggravation of NIDDM, other metabolic disorders like chronic kidney disease at ESRD and coagulation abnormalities. As a critical endocrine organ, adipose tissue communicates with other organs. Insulin resistance and its associated pathological conditions are one of the essential targets of public health. Recently, white adipose tissue acts as part of the endocrine system and have become an active research factor for their adipose tissue-derived markers which collectively referred to as adipokines or adipocytokines (28,19). These adipokines interact with a variety of processes in many different organs and affect various systemic phenomena. Adipokines are thought to influence systemic insulin resistance (21,28), Therefore, dysregulated adipokine production has been found to contribute to the development of many metabolic and vascular diseases by influencing many essential parameters in normal body function, such as coagulation, endothelial and other markers in the blood (29). Adiponectin, resistin, and visfatin are recently discovered adipocyte-secreted hormones, may link with insulin resistance, diabetes and chronic kidney disease (22,28,19). Ghrelin is an orexigenic hormone produced by specialized cells in the stomach known as a new endocrine pathway in the control of feeding behaviour and energy balance in the last decade (22). Some studies support the hypothesis that changes in adipokines and ghrelin levels can be considered as a risk factor of diabetes mellitus, and other metabolic disorders are developing (22,38). The physiologic regulations of adipokines and ghrelin are apparently disordered in patients with NIDDM and ESRD at treated or not with dialysis, which their levels have been repeatedly found to be changed, although, the meaning of these physiologic abnormalities is still unclear. The study aimed to evaluate Determine the potential association between the changes in resistin, adiponectin, visfatin and ghrelin hormones level in patients with ESRD, NIDDM, NIDDM+ESRD patients and controls and examine the relationship between the studied adipocytokines and ghrelin with some clotting and endothelial markers parameters.

## MATERIALS AND METHODS

This study was conducted on 172 age, and sex-matched subjects which were classified into the following groups: 130 patients and 42 healthy age and sex-matched persons. The studied population included four group subjects: Group 1 (Control Group): This group included 42 healthy people (20 males and 22 females) whose mean age range (62.60 ± 6.4 years). They were selected based on a history of no arterial hypertension, diabetes, cardiovascular, lung, renal, central nervous or endocrine system disorders. None of these subjects was under any medical treatment. Group 2 (NIDDM patients group): This group included 50 adult patients with NIDDM under medical treatment (22 males and 28 females) with ages range (60.65 ± 7.82 years). Group 3 (ESRD Patients group): 40 patients with end-stage renal disease (18 males and 22 females) under medical treatment and on hemodialysis with their mean age range (55.33 ± 6.43 years). Group 4 (NIDDM+ESRD Patients group): 40 patients with diabetic nephropathy (20 males and 20 females) under medical treatment and hemodialysis with their mean age range (53.90 ± 4.75 years). All patients and control groups were subjected to personal interview through a specially designed questionnaire form. Although we did not recruit obese patients, they had visceral fat accumulation because of the lifestyle and food quality. All the studied groups were not obese nor overweight, but they had visceral adipocyte accumulation. All the groups observed, showed average urine output, varying from oliguria to normal, even when the GFR had been very low. There was also no protein excretion in the urine samples, and statistically, when compared with the control group, we did not observe any variations. Approval of the study was obtained from Koya University/ Faculty of Science and Health-Biology Department, Academic Ethical Committee office with ethics study number (45). All patients were asked to sign an informed written consent for the acceptance of the study project. Blood samples were obtained after an overnight fasting and subjects were asked not to take their diabetes

medications for 12 hours before the visit. Samples of venous blood were collected from subjects by sterile disposable syringes from brachial vein in the morning and transferred into disposable plastic test tubes (each with 2 ml blood), one of them were collected into anticoagulant ethylene diamine tetraacetic acid (EDTA) containing cells (For estimation of plasma clotting factors, and some haematological parameters) and the remaining blood was added to biochemical gel and clot activator tubes in order to accelerate clotting for biochemical and hormonal studies. Serum and plasma were separated by the centrifugation at (1000g for 20 minutes). The separated serum was divided into several equal aliquots. One was designated for the immediate assay of biochemical parameters in the serum. The other serum and plasma aliquots were stored at freezing point -84 Cº (Sony, Ultra-low, Japan) C ° for subsequent assay. Hemolysed samples were thrown away during the study, and repetitious freezing and thawing were avoided. Some anthropometric, hematological, biochemical and hormonal evaluations were done. The main parameters included: Blood pressure measurement, Serum glycated haemoglobin (HbA1c), fasting blood glucose(FBS), renal function tests (serum urea and creatinine) were determined by using the biochemical KENZA analyzer diagnostic kit (4 KENZA 240TX /Hitachi-USA) with a full automated biochemical analyzer, French. Insulin resistance (IR) was calculated by homeostatic model assessment of insulin resistance (HOMA-IR) formula. Estimated glomerular filtration rate (eGFR ) was calculated by applying the Cockcroft-Gault equation. Platelet count (PLT in 109/L) and mean platelet volume (MPV in fL) were analyzed by coulter counter machine (Coulter counter/ Hitachi 211Q/ Japan). Plasma levels of PT and aPTT and fibrinogen were determined by fully automated immunoanalyzer (Cobas e 411 Roche Diagnostics, HITACHI, Japan) which based on the ECL technology. Serum levels of resistin, adiponectin, visfatin, ghrelin, PAI-1 and fasting insulin were measured using an enzyme linked Immunoassay method kits using ELISA technique.

**Statistical analysis**: All values are presented as mean values ± standard error (Mean ± SE). Statistical analyses were performed using one-way analysis of variance (ANOVA) by using Graphpad prism (Version 8). Person's Correlation coefficient (r) was also used to find the association between the studied adipokines and the mentioned parameters. Differences between NIDDM, ESRD and NIDDM+ESRD subjects compared to control subjects are shown with star sign (*P<0.05, **P<0.01, ***P<0.001), differences between NIDDM+ESRD with NIDDM and ESRD subjects are shown with hash sign (#P< 0.05, # #P<0.01, # # #P<0.001), while differences between NIDDM and ESRD subjects are shown with cross sign (+ P< 0.05, ++ P<0.01, +++ P<0.001).

## RESULTS AND DISCUSSION

**1. Serum levels of resistin, adiponectin, visfatin and ghrelin in patients when compared with control group**: The results in Table 1. show a significant increases in resistin level in NIDDM, ESRD, NIDDM+ ESRD when compared to controls at the level (P<0.001). Resistin level in NIDDM+ ESRD group was significantly higher than in ESRD group at level (P<0.05) and NIDDM group at level (p<0.001) with no differences between NIDDM and ESRD group. Serum adiponectin was significantly (P<0.001) increased in all groups when compared with the control subjects. Adiponectin was significantly (P<0.001) highest in NIDDM+ESRD when compared with both ESRD and NIDDM groups. Adiponectin level in ESRD was significantly (P<0.001) highest when compared with NIDDM (Table 1). Patients with NIDDM, ESRD and NIDDM+ESRD patients had significantly higher level (P<0.001) of visfatin when compared with control subjects (Table 1). Ghrelin level was significantly lowest in NIDDM group when compared with control at (P<0.05), while the level was elevated at (P<0.001) in both ESRD and NIDDM+ESRD groups when compared with controls. Also, a significant (P<0.001) increases in ghrelin was shown in NIDDM+ESRD when compared with NIDDM group with no significant differences with ESRD. Ghrelin level in ESRD was

significantly (P<0.001) highest when compared with NIDDM (Table1).

**Table 1. Hormonal test for resistin, adiponectin, visfatin, and ghrelin of the studied patient populations when compared with control group (Mean ± S.E).**

| Parameters | Control N=20 | NIDDM N=24 | ESRD N=23 | NIDDM+ESRD N=23 |
|---|---|---|---|---|
| Resistin (ng/ml) | 7.689 ± 0.539 | 32.590 ± 0.974 *** ### | 34.920 ± 0.823 *** # | 38.350 ± 0.914 *** |
| Adiponectin (ng/ml) | 6.213 ± 0.501 | 10.290± 0.866 *** ### +++ | 22.910 ± 0.756 *** ### | 17.520 ± 0.548 *** |
| Visfatin (ng/ml) | 7.054 ± 0.232 | 10.120 ± 0.168 *** | 9.963 ± 0.190 *** | 10.550 ± 0.157 *** |
| Ghrelin (ng/ml) | 4.717 ± 0.127 | 3.879 ± 0.185 * ### +++ | 9.446 ± 0.31 *** | 7.121 ± 0.182 *** |

**2. Effect of resistin, adiponectin, visfatin and ghrelin on some biochemical and anthropometric parameters in control, NIDDM, ESRD and NIDDM+ESRD subjects**

Some laboratory data from the total study group (n = 172) were selected and shows in Table 2. It was observed significant differences in some parameters in all studied ages. There was no statistically significant difference among studied and control groups as regards age and sex in all studied ages. The study revealed no significant differences in weight of NIDDM, when compared with control. Whereas, there was significant decrease in weight of ESRD and NIDDM+ESRD subjects when compared with control group at (P<0.001). Moreover, weight had significantly decreased in ESRD and NIDDM+ESRD patients when compared with NIDDM at (P<0.001). There was no significant change in BMI in NIDDM, when compared with control. BMI showed significant decrease in ESRD and NIDDM+ESRD subjects when compared with control at (P<0.001). Furthermore, BMI was significantly decrease in both ESRD and NIDDM+ESRD subjects when compared with NIDDM at (P<0.001). Waist circumference in NIDDM group showed no significant differences when compared with control. While slightly significant differences at (P<0.05) was found in waist circumference in ESRD and NIDDM+ESRD subjects when compared with control at (P<0.05) and waist circumference in NIDDM+ESRD subjects when compared with NIDDM at (P<0.05). Results of the current study in Table 2 show significant (p<0.05) elevation in MAP of NIDDM group when compared with control. However, in ESRD and NIDDM+ESRD subjects MAP was increased significantly at the level (P<0.001) when compared with the control subjects. MAP increased slightly (P<0.05) in ESRD when compared with NIDDM groups. Statistical evaluation showed that SBP were markedly elevated in NIDDM, ESRD and NIDDM+ESRD subjects at (P<0.01), (P<0.01), (P<0.001) when compared with the control subjects. There was significant increase (P<0.001) in SBP of NIDDM+ESRD group when compared with NIDDM and ESRD groups at (P<0.01), (P<0.01) respectively. DBP of ESRD and NIDDM+ESRD groups showed slightly increase (P<0.05) when compared with control. Results in Table 2 show that HOMA-IR significantly elevated in NIDDM, ESRD and NIDDM+ESRD subjects when compared with control at (P<0.001), (P<0.05) and (P<0.001) respectively. HOMA-IR was significantly (P<0.001) highest in NIDDM+ESRD when compared with both ESRD and NIDDM groups. Also, HOMA-IR of NIDDM was significantly (P<0.001) high when compared with ESRD (P<0.001). Statistical analysis revealed that serum insulin levels were markedly elevated (P<0.001) in all groups when compared with the control subjects. There was significant increase (P<0.001) in serum insulin of NIDDM+ESRD group when compared with ESRD group. while serum insulin level in ESRD was significantly (P<0.001) lowest when compared with NIDDM. Serum level of FBS was significantly (P<0.001) increased in all groups when compared with the control subjects. FBS was significantly (P<0.001) elevated in

NIDDM+ESRD when compared with both ESRD and NIDDM groups. FBS level in ESRD was significantly (P<0.001) lowest when compared with NIDDM. Statistical analysis revealed significant elevation in HbA1c % at (P<0.001) in NIDDM and NIDDM+ESRD groups when compared with the control subjects. There was significant increases (P<0.001) in HbA1c % in NIDDM+ESRD when compared with ESRD group. Also HbA1c level was significantly (P<0.001) high in NIDDM when compared with ESRD. Renal function test showed a highly decline in GFR, elevation in serum creatinine and urea level in ESRD and NIDDM+ESRD patients (P<0.001) when compared to control subjects. While, no significant changes observed between NIDDM and control. Significant differences was found in eGFR in NIDDM when compared with ESRD and NIDDM+ESRD group as observed in (Table 2).

**3. Effect of resistin, adiponectin, visfatin and ghrelin on some coagulation parameters in control, NIDDM, ESRD and NIDDM+ESRD subjects**

Results in Table 3 show that PLT count was markedly decreased in NIDDM, ESRD and NIDDM+ESRD subjects at (P<0.001), when compared with the control subjects. There was significant increase (P<0.001) in PLT count of NIDDM group when compared with NIDDM+ESRD groups at (P<0.001). Furthermore, PLT count of NIDDM group was showed slightly elevation, when compared with ESRD group at (P<0.05). MPV was markedly increased in NIDDM (P<0.001), ESRD (P<0.001) and NIDDM+ESRD subjects at (P<0.001) when compared with the control subjects. MPV was significantly decreased (P<0.01) in NIDDM when compared with NIDDM+ESRD group. PT was markedly increased in NIDDM, ESRD and NIDDM+ESRD subjects at (P<0.001) when compared with the control subjects. There was significant decreases (P<0.01) in PT of NIDDM, ESRD groups when compared with NIDDM+ESRD group. Level of aPPT was markedly increased in NIDDM, ESRD and NIDDM+ESRD subjects at (P<0.001) when compared with the control subjects. There was significant decreases (P<0.001) in aPPT of NIDDM, ESRD groups when compared with NIDDM+ESRD group. In addition, aPPT of NIDDM group showed slightly decreases when compared with ESRD group at (P<0.05). PAI-1 level was markedly increased in NIDDM, ESRD and NIDDM+ESRD subjects at (P<0.001) when compared with the control subjects. There was significant decrease (P<0.001) in PAI-1 level of NIDDM, ESRD groups when compared with NIDDM+ESRD group. Fibrinogen was markedly elevated in NIDDM, ESRD and NIDDM+ESRD subjects at (P<0.001) when compared with the control subjects. Fibrinogen was markedly decreased in NIDDM subjects at (P<0.001) when compared with the NIDDM+ESRD group. Fibrinogen of ESRD group showed significant elevation when compared with NIDDM group at (P<0.001).

**Table 2. Mean values (Mean ± S.E) of some anthropometric and assayed biochemical parameters for control subjects and patients in NIDDM, ESRD and diabetic nephropathy groups**

| Parameters | Control N=42 | NIDDM N=50 | ESRD N=40 | NIDDM+ESRD N=40 |
|---|---|---|---|---|
| Age (year) | 61.120±1.245 | 61.360±1.655 | 61.190±1.148 | 60.810±1.392 |
| Weight (Kg) | 73.660 ±1.114 | 73.880 ±0.998 ### +++ | 62.880 ±1.468 *** | 59.634±1.074 *** |
| BMI (Kg/$m_2$) | 26.730±0. 034 | 26.180±0.560 ### +++ | 23.180±0.489 *** | 21.780±0.345 *** |
| Waist circumference (cm) | 82.180± 0.808 | 82.930±0.760 ≠ | 79.590 ± 1.236 * | 78.640± 1.113 * |
| MAP (Mean, mmHg) | 97.030 ± 1.164 | 104.500 ± 1.130 * # | 107.100 ± 1.392 *** | 111.500 ± 2.655 *** |
| SBP (Mean, mmHg) | 118.8 ± 1.777 | 132.6 ± 2.520 ** ## | 134.400 ± 1.801 ** # | 146.800 ± 4.082 *** |
| DBP(Mean, mmHg) | 86.140 ± 1.280 | 89.400 ± 1.007 | 93.490 ± 1.849 * | 93.830 ± 2.555 * |
| insulin (pmol/L) | 14.160 ± 1.524 | 40.040±1.919 *** +++ | 26.750±1.307 *** ### | 45.900 ± 2.043 *** |
| FBS (mg/dl) | 104.000±3.013 | 313.600±12.790 *** ### +++ | 123.300±3.110 *** ### | 264.100 ±7.451 *** |
| HOMA-IR | 0.6121±0.054 | 4.831±0.281 *** ### +++ | 1.496±0.067 * ### | 7.344±0.290 *** |
| HbA1C (%) | 5.000±0.100 | 7.354±0.090 *** +++ | 5.063±0.087 ### | 7.100±0.130 *** |
| Urea (mg/dl) | 37.220±1.338 | 41.240±1.811 ### +++ | 92.560±7.765 *** | 97.050±3.932 *** |
| Creatinine (mg/dl) | 0.996±0.037 | 1.404±0.097 ### +++ | 7.365±0.444 *** | 7.517±0.624 *** |
| eGFR (ml/min) | 89.500±4.417 | 80.000±1.912 ### +++ | 15.810±1.817 *** | 14.710±1.632 *** |

**Table 3. Mean ± S.E of some coagulation tests in control, NIDDM, ESRD and NIDDM+ESRD subjects**

| Parameters | Control N=42 | NIDDM N=50 | ESRD N=40 | NIDDM+ESRD N=40 |
|---|---|---|---|---|
| PLT (mg/dL) | 219.500 ± 10.580 | 153.900 ± 3.349 *** ### + | 131.900 ± 4.791 *** | 110.800 ± 2.248 *** |
| MPV (fL) | 8.140 ± 0.180 | 9.120 ± 0.1240 * * ## | 9.668 ± 0.223 *** | 9.919 ± 0.252 *** |
| PT (mg/dL) | 13.290±0.397 | 15.960±0.168 *** ## | 15.900±0.329 *** ## | 17.340 ±0.268 *** |
| aPPT (mg/dL) | 35.690 ± 0.779 | 44.040 ± 0.405 *** ### + | 46.640 ± 0.467 *** ### | 51.260 ± 0.798 *** |
| PAI-1 (ng/ml) | 13.300 ± 0.327 | 25.900± 0.669 *** ### | 26.540 ± 0.627 *** ### | 29.860 ± 0.493 *** |
| Fibrinogen (mg/dL) | 170.800±6.058 | 315.800±7.364 *** ### +++ | 351.200±4.716 *** | 350.400±4.788 *** |

**4.a. Relationships between serum resistin, adiponectin, visfatin, ghrelin with fibrinogen, PAI-1 and other clotting dependent parameters in control with NIDDM subjects**

Correlation analysis in NIDDM (Table 4) shows that concentration of resistin positively correlated with PAI-1 level (r=0.797, p=0.001), insulin (r=0.720, p=0.001), FBS (r=0.402, p=0.004), HOMA-IR (r=0.410, p=0.001), HbA1c (r=0.458, p=0.001). Whereas the relationship between resistin concentration with Plt, MPV, PT, aPTT and fibrinogen was none significant. Concentration of adiponectin positively correlated with PAI-1 level (r=0.434, p=0.001), insulin (r=0.421, p=0.002), FBS (r=0.340, p=0.01), HOMA-IR (r=0.558, p=0.001), HbA1c (r=0.291, p=0.03). However, the findings from the current study showed that adiponectin concentration none significantly correlated with Plt, MPV, PT, aPTT and fibrinogen. Visfatin level was found to correlate in a positive and significant way with PAI-1 level (r=0.439, p=0.001), insulin (r=0.657, p=0.001), FBS (r=0.533, p=0.001), HOMA-IR (r=0.416, p=0.003), HbA1c (r=0.526, p=0.001). Nevertheless, the relationship between visfatin

concentration and Plt, MPV, PT, aPTT and fibrinogen was none significant. Statistical correlation analysis showed that concentration of ghrelin positively correlated with PAI-1 levels (r=0.418, p=0.001). While ghrelin was correlated in significant and negative direction with insulin (r=-0.657, p=0.001), FBS (r=-0.390, p=0.006), HOMA-IR (r=-0.437, p=0.001), HbA1c (r=-0.440, p=0.001). The relationship between ghrelin concentration with Plt, MPV, PT, aPTT and fibrinogen was none significant.

**Table 4. Relationships between serum resistin, adiponectin, visfatin, ghrelin with fibrinogen and other clotting parameters in control with NIDDM subjects**

| Parameters | | Resistin | Adiponectin | Visfatin | Ghrelin |
|---|---|---|---|---|---|
| PLT | r | -0.002 | -0.149 | -0.027 | -0.224 |
| | P | N.S | N.S | N.S | N.S |
| MPV | r | 0.179 | 0.185 | 0.176 | 0.184 |
| | p | N.S | N.S | N.S | N.S |
| PT | r | 0.098 | 0.019 | 0.165 | 0.068 |
| | p | N.S | N.S | N.S | N.S |
| aPTT | r | 0.171 | 0.151 | 0.039 | 0.132 |
| | p | N.S | N.S | N.S | N.S |
| Fibrinogen | r | 0.205 | 0.123 | 0.125 | 0.094 |
| | p | N.S | N.S | N.S | N.S |
| PAI-1 | r | 0.797 | 0.434 | 0.439 | 0.418 |
| | p | 0.001 | 0.001 | 0.001 | 0.001 |
| HOMA-IR | r | 0.410 | 0.558 | 0.416 | -0.437 |
| | p | 0.001 | 0.001 | 0.003 | 0.001 |
| Insulin | r | 0.720 | 0.421 | 0.657 | -0.606 |
| | p | 0.001 | 0.002 | 0.001 | 0.001 |
| FBS | r | 0.402 | 0.340 | 0.533 | -0.390 |
| | p | 0.004 | 0.01 | 0.001 | 0.006 |
| HbA1c | r | 0.458 | 0.290 | 0.526 | -0.440 |
| | p | 0.001 | 0.03 | 0.001 | 0.001 |

**4.b. Relationships between serum resistin, adiponectin, visfatin, ghrelin with fibrinogen, PAI-1 and other clotting dependent parameters in control with ESRD subjects**

Correlational analysis in ESRD shows in Table 5 that resistin concentration positively related with PAI-1 level (r=0.864, p=0.001), insulin (r=0.657, p=0.001), FBS (r=0.478, p=0.001), HOMA-IR (r=0.355, p=0.01), HbA1c (r=0.395, p=0.005). Whereas the relationship between resistin concentration with Plt, MPV, PT, aPTT and fibrinogen was not significant. Concentration of adiponectin positively correlated with PAI-1 level (r=0.822, p=0.001), insulin (r=0.691, p=0.001), FBS (r=0.500, p=0.001), HOMA-IR (r=0.642, p=0.001), HbA1c (r=0.417, p=0.003). Whereas, the data from the current study showed that adiponectin concentration non significantly correlated with Plt, MPV, PT, aPTT and fibrinogen. Visfatin level was found to correlate positively and significantly with PAI-1 level (r=0.805, p=0.001), insulin (r=0.428, p=0.002), FBS (r=0.525, p=0.001), HOMA-IR (r=0.407, p=0.004), HbA1c (r=0.325, p=0.02). However, the relationship between visfatin concentration and Plt, MPV, PT, aPTT and fibrinogen was not significant. Pearson's correlation analysis concentration of ghrelin positively correlated with PAI-1 levels (r=0.806, p=0.001), insulin (r=0.607, p=0.001), FBS (r=0.429, p=0.002), HOMA-IR (r=0.285, p=0.04), HbA1c (r=0.319, p=0.02). Whereas the relationship between ghrelin concentration with Plt, MPV, PT, aPTT and fibrinogen was not significant.

**Table 5. Relationships between serum resistin, adiponectin, visfatin, ghrelin with fibrinogen and other clotting parameters in control with ESRD subjects**

| Parameters | | Resistin | Adiponectin | Visfatin | Ghrelin |
|---|---|---|---|---|---|
| PLT | r | -0.165 | -0.152 | -0.315 | -0.164 |
| | p | N.S | N.S | N.S | N.S |
| MPV | r | 0.171 | 0.229 | 0.205 | 0.154 |
| | p | N.S | N.S | N.S | N.S |
| PT | r | 0.163 | 0.156 | 0.168 | 0.167 |
| | p | N.S | N.S | N.S | N.S |
| aPTT | r | 0.209 | 0.259 | 0.222 | 0.212 |
| | p | N.S | N.S | N.S | N.S |
| Fibrinogen | r | 0.241 | 0.233 | 0.231 | 0.232 |
| | p | N.S | N.S | N.S | N.S |
| PAI-1 | r | 0.864 | 0.822 | 0.805 | 0.806 |
| | p | 0.001 | 0.001 | 0.001 | 0.001 |
| HOMA-IR | r | 0.355 | 0.642 | 0.407 | 0.285 |
| | p | 0.013 | 0.001 | 0.004 | 0.048 |
| Insulin | r | 0.657 | 0.691 | 0.428 | 0.607 |
| | p | 0.001 | 0.001 | 0.002 | 0.001 |
| FBS | r | 0.478 | 0.500 | 0.525 | 0.429 |
| | p | 0.001 | 0.001 | 0.001 | 0.002 |
| HbA1c | r | 0.395 | 0.417 | 0.325 | 0.319 |
| | p | 0.005 | 0.003 | 0.023 | 0.027 |

**4.c. Relationships between serum resistin, adiponectin, visfatin, ghrelin with fibrinogen, PAI-1 and other clotting dependent parameters in control with NIDDM+ESRD subjects**: It reveals from the Table 6 that correlation analysis in NIDDM+ESRD with control groups showed that concentration of resistin correlated positively with PAI-1 level (r=0.905, p=0.001). Whereas the relationship between resistin concentration with Plt, MPV, PT, aPTT and fibrinogen was none significant. Concentration of adiponectin positively correlated with PAI-1 level (r=0.888, p=0.001). However, the findings from the current study showed that adiponectin concentration none significantly correlated with Plt, MPV, PT, aPTT and fibrinogen. Visfatin level was found to correlate in a positive and significant way with PAI-1 level (r=0.835, p=0.001). Nevertheless, the correlation between visfatin concentration and Plt, MPV, PT, aPTT and fibrinogen was not significant. Pearson's correlation analysis concentration of ghrelin positively correlated with PAI-1 levels (r=0.755, p=0.001). Whereas no relationship was found between between ghrelin concentration with Plt, MPV, PT, aPTT and fibrinogen. Pearson correlation analysis in control with NIDDM+ESRD which presented that a significant and positive correlation was observed between resistin concentrations with insulin (r=0.879, p=0.001), FBS (r=0.463, p=0.001), HOMA-IR (r=0.399, p=0.005), HbA1c (r=0.504, p=0.001). Adiponectin concentration in pearson analysis showed that it was positively correlated with insulin (r=0.831, p=0.001), FBS (r=0.439, p=0.001), HOMA-IR (r=0.470, p=0.001), HbA1c (r=0.498, p=0.001). Visfatin level positively correlated with each of the insulin (r=0.779, p=0.001), FBS (r=0.534, p=0.001), HOMA-IR (r=0.457, p=0.001), HbA1c (r=0.525, p=0.001). positive and significant relation was found between ghrelin with each of the insulin (r=0.703, p=0.001), FBS (r=0.505, p=0.001), HOMA-IR (r=0.361, p=0.01), HbA1c (r=0.420, p=0.002).

**5. Indirect relationships between serum resistin, adiponectin, visfatin, ghrelin through HOMA_IR with fibrinogen and other clotting parameters**: The results in Tables 4, 5 and 6, show that serum resistin, adiponectin, visfatin, ghrelin associated strongly with HOMA_IR in all

groups with control. Interestingly, HOMA-IR in NIDDM with control which is set out in Table 7 was observed a negative correlation with PLT (r=-0.544, p=0.001) ,while, positively correlated with MPV, PT, aPTT, fibrinogen levels and PaI-1 at (r= 0.414, p=0.001), (r=0.580, p=0.001), (r=0.638,

**Table 6. Relationships between serum resistin, adiponectin, visfatin, ghrelin with fibrinogen and other clotting parameters in control with NIDDM+ESRD subjects**

| Parameters | | Resistin | Adiponectin | Visfatin | ghrelin |
|---|---|---|---|---|---|
| PLT | r | -0.048 | -0.124 | -0.035 | -0.074 |
| | p | N.S | N.S | N.S | N.S |
| MPV | r | 0.180 | 0.186 | 0.216 | 0.224 |
| | p | N.S | N.S | N.S | N.S |
| PT | r | 0.137 | 0.072 | 0.207 | 0.032 |
| | p | N.S | N.S | N.S | N.S |
| aPTT | r | 0.253 | 0.211 | 0.241 | 0.165 |
| | p | N.S | N.S | N.S | N.S |
| Fibrinogen | r | 0.168 | 0.181 | 0.167 | 0.213 |
| | p | N.S | N.S | N.S | N.S |
| PAI-1 | r | 0.905 | 0.888 | 0.835 | 0.755 |
| | p | 0.001 | 0.001 | 0.001 | 0.001 |
| HOMA-IR | r | 0.355 | 0.642 | 0.407 | 0.285 |
| | p | 0.013 | 0.001 | 0.004 | 0.048 |
| Insulin | r | 0.657 | 0.691 | 0.428 | 0.607 |
| | p | 0.001 | 0.001 | 0.002 | 0.001 |
| FBS | r | 0.478 | 0.500 | 0.525 | 0.429 |
| | p | 0.001 | 0.001 | 0.001 | 0.002 |
| HbA1c | r | 0.395 | 0.417 | 0.325 | 0.319 |
| | p | 0.005 | 0.003 | 0.023 | 0.027 |

p=0.001), (r=0.503, p=0.001) and (r=0.835, p=0.001) respectively. On average, HOMA_IR in ESRD with control were shown to have a negative association with Plt (r= -0.544, p=0.001), while positively associated with MPV, PT, aPTT, fibrinogen levels and PaI-1 at (r= 0.366, p=0.01), (r=0.580, p=0.001), (r=0.603, p=0.001), (r=0.357, p=0.004) and (r=0.380, p=0.001) respectively. The results of the correlation analysis on HOMA_IR in NIDDM+ESRD with control groups were observed to have negative relation with Plt (r= -0.621, p=0.001), while positively related with MPV, PT, aPTT, fibrinogen levels and PaI-1 at (r= 0.504, p=0.001), (r=0.669, p=0.001), (r=0.759, p=0.001), (r=0.475, p=0.004) and (r=0.621, p=0.001) respectively. Several factors may contribute to elevated circulating resistin levels. Cytokine suppressor signaling up-regulation may elevate circulating resistin which interferes with the activation of insulin receptor substrate (IRS-1) by affecting insulin signaling and stimulation of expression of phosphatase and tensin homolog deleted on chromosome ten, which dephosphorylates 3-phosphorylated phosphoinositide. Several studies support a positive correlation between insulin resistance and elevated serum resistin in humans. This may be due to the expression of resistin in human hepatocytes which induces insulin resistance suggesting the role of resistin in the pathogenesis of human NIDDM (18,13). In ESRD and NIDDM+ESRD, the main expected cause is due to the impaired resistin secretion through the kidney and its association with low GFR since dialysis technique will only partially be able to eliminate excess resistin from the circulation (2,9).

**Table 7. Indirect relationships between serum resistin, adiponectin, visfatin, ghrelin through HOMA_IR with fibrinogen and other clotting parameters**

| Parameters | | HOMA-IR (NIDDM with control) | HOMA-IR (ESRD with control) | HOMA-IR (NIDDM+ESRD with control) |
|---|---|---|---|---|
| PLT | r | -0.544 | -0.374 | -0.621 |
| | p | 0.001 | 0.001 | 0.001 |
| MPV | r | 0.414 | 0.366 | 0.504 |
| | p | 0.001 | 0.01 | 0.001 |
| PT | r | 0.580 | 0.580 | 0.669 |
| | p | 0.001 | 0.001 | 0.001 |
| aPTT | r | 0.638 | 0.603 | 0.759 |
| | p | 0.001 | 0.001 | 0.001 |
| Fibrinogen | r | 0.503 | 0.357 | 0.475 |
| | p | 0.001 | 0.004 | 0.001 |
| PAI-1 | r | 0.835 | 0.380 | 0.621 |
| | p | 0.001 | 0.001 | 0.001 |

According to our investigations, we hypothesized that increased levels of resistin due to decreased GFR and hyperglycemia might be one factor behind the insulin resistance syndrome present in diabetic nephropathy patients. In this study, the main cause for high adiponectin level in serum of diabetic nephropathy could be due to either high biodegradation and elimination of adiponectin in the kidneys, or overproduction in adiponectin in adipose tissues by amelioration of glomerular hypertrophy through activation of adenosine 5'-monophosphate-activated protein kinase by adiponectin receptors type I (AdipoR1) and activation of peroxisome proliferator-activated receptor (PPAR)-α signalling pathway by adiponectin receptors type II (AdipoR2) (39). The suggestion of our study is confirmed by the study of Mohammad et al., (24), who demonstrated that adiponectin makes its effects on other organs via AdipoR1 and AdipoR2, both have been identified in NIDDM and chronic kidney disease patients confirming our study (24). High visfatin level could be due to the fact that it demonstrates insulin upregulation for visfatin protein expression. Some studies on isolated human adipocytes observed that insulin-stimulated the release of various pathogenic adipocytokines (10,26). Confirming our current study demonstrated that insulin significantly increased visfatin protein expression. Several studies have clearly shown that the sensitivity to the action of insulin with respect to glucose metabolism is markedly impaired in ESRD. Mechanisms might be contributed to insulin resistance in ESRD including defects at the post-receptor level of insulin action in muscle, adipose, and liver tissues (30). The result of high visfatin in ESRD group was in agreement with the results obtained by (2,11). From this study, it could be suggesting aware of the relation between visfatin levels and decrease in eGFR (32,8). Also, the differences in serum visfatin level in ESRD patients can be attributable to the cardiovascular events (20) which found association between hyper visfatinaemia and endothelial dysfunction in ESRD (37,23,20). In NIDDM, ghrelin roles in insulin sensitivity is complex. Indeed, some previous studies demonstrated that only obesity was associated with an imbalance in the levels of ghrelin (17). On the other hand, Zhang et al., (40) have shown that administration of ghrelin to non-obese diabetic mice increased their insulin sensitivity by increasing the mRNA levels of GLUT4 (40,3). Regarding ghrelin in the present study, it was significantly higher in ESRD and NIDDM+ESRD patients compared to NIDDM and healthy individuals. Conflicting reasons for circulating ghrelin levels in ESRD have been presented. Some observational studies have reported that high ghrelin levels are associated with insulin resistance, while others correlated it to low eGFR and kidney dysfunction. The better possible explanation for the high ghrelin level in these patients group supposes a competition between the factors that increase ghrelin level, hyperinsulinemia and the high percentage of insulin resistance in diabetic nephropathy patients may support this explanation (1). A significant positive correlation was seen between serum levels of adipokines with insulin, HbA1c, FBS and HOMA-IR. This shows that the increase in adipokines, insulin, HOMA-IR level causes an increase in the oxidative stress markers was identified as an ideal marker to assess the oxidative stress and clotting factors dysfunction (34). These results are novel markers to evaluate the

complication in ESRD patients and the severity of the chronic renal failure, which could be correlated with the oxidative stress status and levels of adipokines, and HOMA-IR (4). The most striking result to emerge from the study is that serum resistin, adiponectin, visfatin, and ghrelin associated indirectly through HOMA_IR with fibrinogen and other clotting parameters. The size and volume of circulating platelets were found to be changed in patients with high adipokine levels which described to predict its relation with diabetes mellitus, and other chronic diseases (7,31). It is clear that high MPV could reflect increased platelet turnover. Several studies observed maturation and release of megakaryocytes by specific adipokines (31,35). Some other recent researches indicated changed platelet count, MPV, and thrombotic risk which could be directly related with insulin resistance, as a consequence for high adipokines in the blood (25,5). Insulin resistance due to the high adipokines in NIDDM could be associated with elevated hepatic fibrinogen production in response to insulin suggesting hepatic dysregulation which was in consistence with studies where done by (24,27). From the present study in correlation with previous investigations, we suggest that high coagulatory markers due to hyperglycemia, insulin resistance and the consequent oxidative stress could be gave rise to increased their pathway which contributes to platelet aggregation via glycoprotein IIb/IIa and promotes formation of fibrin which contributes to plasma viscosity (33). In ESRD and NIDDM+ESRD groups, fibrinogen and other coagulation marker levels were increased, Which also observed by (6) in nephrotic and hemodialysis patients, suggesting specific mechanisms acting in these divergent patient groups affect fibrinogen metabolism. Low eGFR and high levels of coagulatory factors are a large number of damaged renal units, resulting in the loss of normal excretory function and a reduction in the removal of procoagulant substances (12). Plasma insulin levels and HOMA-IR index tended to be higher in patients on dialysis implying that intensive glucose loading during dialysis process has effect on insulin resistance and fibrinogen level (16). It is important to notice that, in spite of the absence of direct evidence for either of these factors, the occurrence of an indirect effect of these factors cannot completely be excluded. Studies of (15) were in line with our results. They confirmed that PAI-1 deficiency attenuates diabetic nephropathy, and disruption of the PAI-1 gene markedly attenuates thrombosis and fibrosis in mice. Therefore, inhibition of PAI-1 gene expression by gene knockout technology might exert critical renal and insulin protective effects. Altogether, these data strongly support the notion that disturbance in endothelial and coagulation biomarkers are markedly affected by IR and adipose tissue markers (14,36).

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