

# The Role of Resistin in Patients with Primary Fibromyalgia

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## Summary:

**Background:** Fibromyalgia syndrome (FMS) is a common rheumatologic syndrome with multiple manifestations and associated with many diseases, it characterized by chronic wide spread muscular pain and tenderness. Resistin is an adipokine discovered in 2001 and considered as a link between obesity and type 2 diabetes by antagonizing and resisting the action of insulin as its name encompasses; resistin (resist insulin). It is secreted mainly from adipose tissue in mice and from white blood cells besides the adipose tissue in humans. Research revealed that resistin has a role in some inflammatory diseases like Rheumatoid Arthritis (RA).

**Objective:** The objective of this study is to measure Resistin concentration and to evaluate its role in the pathogenesis of primary FMS.

**Patients and methods:** Fifty patients with primary FMS were included in this study (37 females and 13 males) the age range of (17-65) years (Mean  $\pm$  SD) (40.13  $\pm$  12.0) years, and thirty healthy individuals volunteers (21 females and 9 males), whose age and sex matching with FMS patients, age ranging (18 - 63) years, (Mean  $\pm$  SD) (36.1  $\pm$  10.0) years. Resistin concentration was measured in sera of patients and controls by ELISA kit. Anthropometric measurements like body mass index (BMI) and waist circumference (WCr) were taken, besides other features like sleep disturbance, emotional distress, and fatigue were reported.

**Results:** Resistin concentration was higher in FMS patients than controls (2.15 $\pm$ 0.9) ng/ml vs. (1.57 $\pm$ 0.6) ng/ml. This elevation was highly significant statistically (p=0.003). Other measurements in patients group like BMI, WCr were (28.39 $\pm$ 5.0) Kg/m<sup>2</sup> and (100.34 $\pm$ 13.21) cm respectively. These values were highly significant when compared to their control group (p=0.002) and (p=0.008) respectively. Serum resistin level was positively correlated with both waist circumference (r=0.411, p=0.003) and age (r=0.405, p=0.004). Waist circumference was positively correlated with age (r=0.604, p=0.000). Clinical features like sleep disturbance, emotional distress, and fatigue showed highly significant difference between the two groups. No significant differences were reported with respect to age and sex.

**Conclusion:** The result of the current study suggests that Resistin might have a role in the pathogenesis of FMS.

**Keywords:** Resistin, Fibromyalgia.

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## Introduction:

According to the criteria of the American College of Rheumatology (ACR), fibromyalgia (FMS) is characterized by chronic widespread pain in all 4 quadrants of the body at least 3 months duration associated with tender points and associated with constitutional symptoms of fatigue, aching, and non restorative sleep(1). The etiology of FMS remains elusive. Resistin is an adipokine, a member of secretory protein family known as resistin like molecules (RELMs) (2), the family is characterized by highly conserved cysteines – rich C terminus in which the spacing of cysteines is invariant, four members of this family are found in mice which these are (resistin, RELM $\alpha$ , RELM $\beta$ , and RELM $\gamma$ ), only two counterparts were found in human (resistin and RELM $\beta$ ) (3). Resistin is 114 amino acid peptide with a molecular weight of (12.5 kDa) secreted as disulfide-link homodimer(4). Many hormones and molecules can regulate resistin gene expression, such as Thiozolidindiones (TZDs), insulin, glucose, glucocorticoid, growth hormone and others (5,6).

Although resistin was firstly postulated to contribute to insulin resistance more evidence indicated that it may also be involved in inflammatory process, Some pro-inflammatory agents, such as (tumor necrosis factor- $\alpha$ ), (interleukin-6) and lipopolysaccharide (LPS), can regulate resistin gene expression in human peripheral blood mononuclear cells *in vivo* and *in vitro* potentially mediated via the integration of nuclear factor kappa – light chain – enhancer of activated B cells (NF- $\kappa$ B) signaling pathway (7).

NF- $\kappa$ B is a protein complex that controls the transcription of DNA and is found in almost all cell types and involved in cellular response to stimuli such as stress, cytokines, free radicals, oxidized LDL-C, and bacterial or viral antigens and play a key role in regulating the immune response to infection (8). Some researchers investigated the role of resistin in inflammation related diseases such as Rheumatoid Arthritis and found that the Synovial fluid from patient with (RA) showed significantly higher level of resistin compared with control samples and resistin level in RA synovial fluid was positively correlated with synovial leukocyte count

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and IL-6 level(9) ,resistin found to be accumulated in inflamed joints of RA patient (10).In the present study a trail was made to investigate the role of resistin in patients with primary FMS and its association with the pathogenesis of the syndrome and if there is association between circulating resistin and body mass index , waist circumference ,age and gender in FMS.

#### Patients and methods:

**Subjects:** The study has included 50 patients with primary FMS (37 females and 13 males) the age range of (17-65) years (Mean  $\pm$  SD) (40.13  $\pm$  12.0) years. The clinical diagnosis of these patients was confirmed by Consultant Rheumatologists of the Baghdad Teaching Hospital according to the ACR 1990 criteria for the diagnosis of FMS. Patients with primary fibromyalgia were included in this study. Thirty healthy individuals volunteers (21 females and 9 males), whose age and sex matching with FMS patients, age ranging (18 - 63) years, (Mean  $\pm$  SD) (36.1  $\pm$ 10.0) years.They had no musculoskeletal complaints or lower back pain and did not seek any medical help for pain. A pre- tested questionnaire was designed to obtain information from both patients and control group about past medical and drug history. Inclusion criteria:- Known cases of FMS approved by clinical, laboratory, and radiological diagnosis. Patients on medical treatments that never affect the laboratory tests. Exclusion Criteria: Diabetes mellitus (DM) ,Rheumatoid arthritis (RA),Systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), Osteoarthritis (OA),Sleep apnea ,Patients on steroid therapy, Chronic renal failure, Chronic liver disease, Previous breast surgery, Inflammatory systemic disease or infection, Serious cardiopulmonary, vascular or other internal medical condition. Medication that may influence with the results (e.g. local corticosteroids, biological agents). **Blood collection:** After overnight fasting venous blood samples (10 ml ) were aspirated from each patient and control at 9.00 am - 12.00 pm using disposable plastic syringes . Seven ml of the blood samples were allowed to clot in plane tubes at room temperature for (20-30) minutes. Sera were separated by centrifugation at 3000 rpm for 10 minutes. For each sample, the serum was transferred into plastic plane tubes and kept frozen at (-20°C) until the time of assay. The rest 3 ml blood samples were collected in EDTA tubes for ESR, PCV, and WBC tested by routine work to exclude inflammatory reasons. **Methods:** Serum resistin was determined by DRG ELISA kit, USA which is solid phase enzyme- linked immunosorbent assay based on the sandwich principle .Kit used was from International Inc-USA. Pain was measured using Visual Analogue Scale (VAS).

**Statistical analysis:** To compare the significant of the difference in the means values at any two patients and controls, SPSS (social process statistical system) was used. Student t-test was applied (P < 0.05) was considered statistically significant, and the

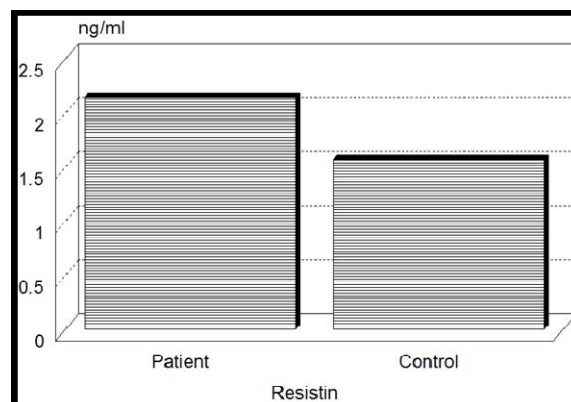
correlation coefficient (r) test is used to describe the association between different parameters studied

#### Results:

As shown in table-1, there was significantly high concentration of Resistin in patients with FMS than healthy controls (p=0.003). Patients and controls were age, sex match (p=0.124), (p=0.698) respectively. There was a statistically significant difference in BMI and WCr between patients and controls (p=0.002), (p=0.008) respectively.

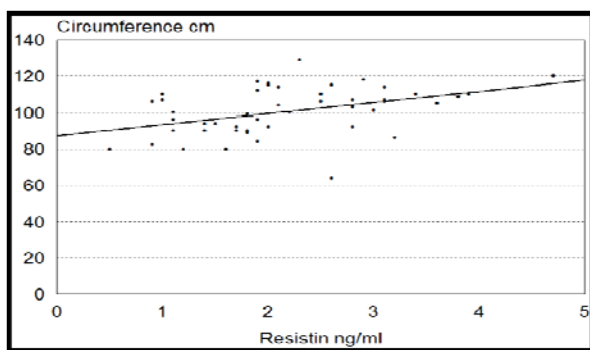
**Table(1):- shows all mean values of the parameters measured for patients and control group, (Mean $\pm$  SD) values for age ,BMI, resistin ,WCr , in FMS group (n=50), and control group (n=30) .**

Characteristic	FMS patients n=50 Mean $\pm$ SD	HC n =30 Mean $\pm$ SD	P- value	Sig
Resistin (ng/ml)	2.15 $\pm$ 0.90	1.57 $\pm$ 0.60	0.003	HS
BMI ( Kg/m <sup>2</sup> )	28.39 $\pm$ 5.0	25.14 $\pm$ 3.19	0.002	HS
WCr (cm)	100.34 $\pm$ 13.21	92.63 $\pm$ 10.76	0.008	HS
Age (year)	40.18 $\pm$ 12.08	36.10 $\pm$ 10.02	0.124	NS

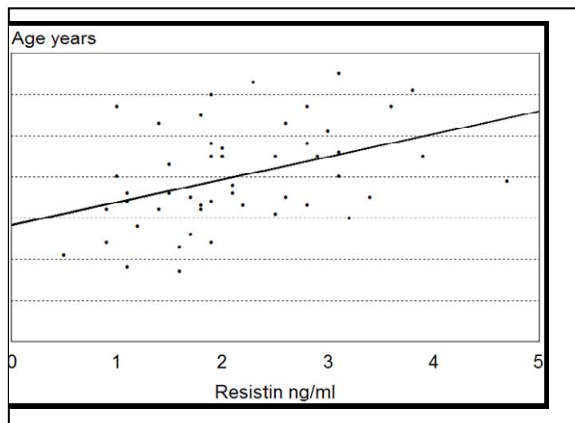


**Figure (1):- mean value for serum Resistin level in FMS patients and control group**

Serum resistin level was positively correlated with both WCr ( r = 0.411 ) , ( p = 0.003 ) , figure (2) and age ( r = 0.405 , p =0.004 ) figure (3) .Waist circumference was positively correlated with age in this study ( r = 0.604 ) ,( p < 0.000 ) figure (4). In this study there is significant positive correlation between BMI (Kg/m<sup>2</sup>) and age (year),(r=0.397) ,(p=0.004) , figure (5).

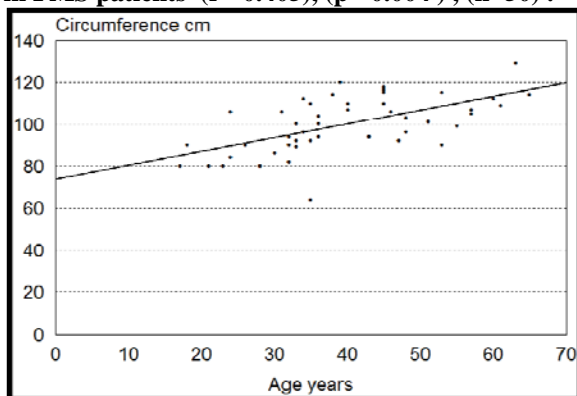


**Figure (2) correlation between serum resistin and WCr in FMS patients( $r = 0.411$ ), ( $p = 0.003$ ),**

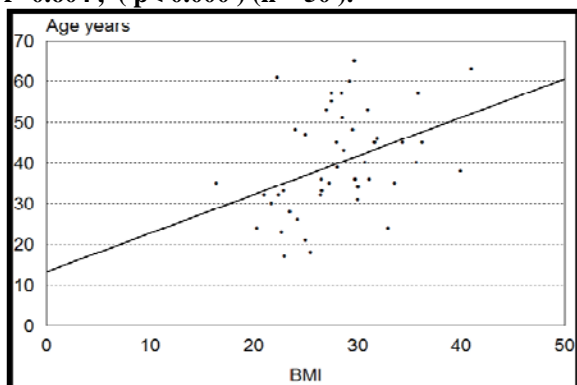


( $n = 50$ ).

**Figure (3) : correlation between resistin and age in FMS patients ( $r = 0.405$ ), ( $p = 0.004$ ), ( $n = 50$ ).**



**Figure(4): correlation between waist circumference and age in patients with FMS ( $r = 0.604$ , ( $p < 0.000$ ) ( $n = 50$ ).**



**Figure (5) : correlation between BMI ( $\text{Kg/m}^2$ ) and age (year),( $r = 0.397$ ), ( $p = 0.004$ ),( $n = 50$ ).**

### Discussion:

The role of resistin in FMS was not assessed by previous studies to the best of our knowledge. A significant positive correlation between resistin and waist circumference is found in this study figure (2). The significant positive correlation between resistin and WCr comes in agreement with other previous studies (11,12), since resistin expression was found to be higher in human abdominal adipose tissue than other adipose tissue depots. Resistin mRNA concentration were similar in both abdominal and omental depots while its concentration was lower in thighs leading to the conclusion that abdominal fat could explain the increased risk of type 2 diabetes associated with central obesity (13). In this study we found a significant positive correlation between resistin and age figure (3), a significant positive correlation between correlation between waist circumference and age figure (4), and a significant positive correlation between BMI and age figure (5). Only two studies mentioned that resistin correlates with age but without any explanation (12,14). The correlation between waist circumference and age determined with several factors:

1. The effect of sex hormones : since the adipocytes show receptors attenuated to the androgen and estrogen, testosterone inhibits the activity of lipase lipoprotein and stimulates mobilization of triglyceride (TGs) in the adipocytes, which leads to lower accumulation of this tissue in males (15), estrogen, like testosterone, has control on the lipase lipoprotein and reduce adipocyte growth in females, this effect of sex hormones suggests that a decrease in their secretion may promote accumulation of intraabdominal adipose tissue (IAAT) once menopause occurs in women and andropause in men (16). As adipocytes grow larger they become dysfunctional and large adipocytes are insulin resistance, hyperlipolytic and resistant to the anti-lipolytic effect of insulin. Visceral adipose tissue contains greater number of large adipocytes while subcutaneous adipose tissue contain small adipocytes which are more insulin-sensitive and have high avidity for free fatty acids and TGs uptake preventing their deposition in non-adipose tissue (17,18).

2. The effect of the hypothalamic –pituitary- adrenal axis : The increased fat in IAAT is also related to the action of the (HPA –axis), and stimulation of the hypothalamus produces corticotropin-releasing hormone which stimulates the secretion of cortisol in adrenal glands which favors the accumulation of TGs in the IAAT and inhibits their mobilization (15). In cases with chronic stress leads to elevated cortisol levels that leads to accumulation of visceral adipose tissue (19). Its noteworthy that among the anthropometric measurements, WCr has been promoted as a tool to establish distribution of adipose tissue in the central area and the risk of developing metabolic syndrome in adults (20). Plasma level of resistin, produced by adipose tissue, might be present at high circulating level in subject with high fat content (12). In the present

study patients are predominantly overweight (40%) and obese (36%) and their waist circumference is higher than the healthy controls (Mean  $\pm$ SD) , (100.34  $\pm$  13.21) cm vs. (92.63  $\pm$  10.67) cm table (1) .In human , evidence was accumulated that resistin expression is high in mononuclear peripheral blood cells and other non adipocytes of adipose tissue than in adipose tissue themselves (21,22) .Therefore absolute plasma levels of resistin were increased with generalized obesity and its relationship with clinical parameter of visceral obesity was not linear. This could explain some of the inconsistent finding in human studies (22) .In this study resistin did not correlate with pain intensity measured by VAS or any clinical manifestation or any of the symptoms of FMS .In conclusion Resistin has been found to be significantly higher in FMS patients than healthy subjects and its concentration correlate strongly with waist circumference , for further investigation detection of the expression of Resistin, peripheral blood mononuclear cells, muscle biopsies, and muscle biopsies of tender points (if possible) in patients with primary FMS This should add more information on the role of this adipokine in the pathogenesis of fibromyalgia.

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