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Review Article



# Ghrelin And Resistin Status in Obese Diabetic Women with Metabolic Syndrome

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## Abstract

**Background/Aims:** This is a comparative study that aims to evaluate serum levels of ghrelin, resistin, insulin and identify possible correlations that may exist between these parameters in a population of an obese diabetic woman with metabolic syndrome and to assess their spontaneous alimentation.

**Methods:** Measurement of ghrelin, resistin, glucose, insulin and lipid profile were performed in 53 obese diabetic women with metabolic syndrome and 52 healthy women subjects. A food survey was conducted in the study.

**Results:** Our data show a significant difference in levels of ghrelin and resistin between the two groups. In fact, ghrelin level in obese diabetics is (25.46 ± 3.59 pg / ml) against (50.66 ± 6.84 pg / ml) for the control and resistin rate is (9.17 ± 1.68 ng / ml) against (3.17 ± 0.51 ng / ml) for the control group. A significant negative correlation was revealed between ghrelin and glucose ($p = 0.003$), ghrelin and insulin ($p = 0.002$) and ghrelin and resistin ($p = 0.001$). In addition, a significant positive correlation was found between resistin and BMI ($p < 0.001$) likewise resistin and insulin (p 0.001). Our food survey showed a significant difference in nutrient intake between the two groups of the study ($p<0.001$).

**Conclusions:** The present study revealed the relation of resistin and ghrelin to obesity associated with diabetes and metabolic syndrome, and the impact of diet on lipid parameters and metabolic profile.

**Keywords:** Obesity; Diabetes; Resistin; Ghrelin; Metabolic syndrome; Food

## Background

Obesity is a chronic multifactorial disease responsible for a global epidemic, some authors would even go as far as to announce it as a pandemic of the 21st century [1, 2]. The current obesity epidemic concerns many developed and developing countries,

including Tunisia, which seems to be at an already advanced stage [3]. Because of its prevalence and the severity of its complications, obesity is associated with many comorbidities, such as high blood pressure, type 2 diabetes, dyslipidemia, sleep apnea, certain cancers and major cardiovascular diseases [4]. The status of adipose tissue as an endocrine organ secreting biologically active molecules (such as resistin), involved in energy balance and carbohydrate-lipid metabolism, has made it possible to better understand the mechanisms involved in the pathophysiology of obesity and its complications [5]. It has been proposed that resistin might serve as a molecular link between inflammation, metabolic parameters, and vascular dysfunction, and can thus contribute to the risk for metabolic syndrome (MetS) and type 2 diabetes (T2DM) [6]. A common consequence of obesity is the development of insulin resistance associated with T2DM. In fact, in subjects with obesity, several mechanisms intervene to install increased resistance to insulin, which will be responsible for the onset of T2DM as well as for the genesis of its complications [1]. The increasing prevalence of metabolic syndrome and the consequent cardiovascular diseases, like atherosclerotic diseases and T2DM has stimulated an active search for novel risk factors. The hormones regulating energy balance are of special interest as potential risk factors for MetS. Ghrelin, is a peptide hormone from stomach, which seems to be able to modify glucose and insulin metabolism [7]. Previous studies have reported a dysregulation of circulating ghrelin in children and adults with metabolic syndrome [8, 9]. In this context, we carried out a comparative study in order to assess the serum levels of resistin, ghrelin, insulin and blood glucose and to establish the possible correlations that may exist between ghrelin, resistin, and other lipids and biochemical parameters in a population of diabetic obese women. We also conducted a food survey to assess the quality of the food ration of our study population and the caloric intake it generates.

## Materials and methods

### Study population

Our case/control survey concerned 53 obese diabetic women with metabolic syndrome and 52 healthy women matched by age. MetS was diagnosed according to the International Diabetes Federation (IDF) [10]. Exclusion criteria were as follows: age less than 18 years, pregnancy, kidney disease, liver disease, malignancy, any and endocrine disorder. The study population was recruited from the "C" unit of nutrition and therapeutic diet diseases at the National Institute of Nutrition and Food Technology (INNTA). The women selected for the survey were informed in advance of the objectives of the study. A nutritional assessment, including total caloric intake and the distribution of nutrient intake was conducted using a dietary history questionnaire. The weight and height were measured in each study participant and body mass index (BMI = weight / height2) was calculated.

### Blood sampling and Laboratory assays

A fasting, venous blood sample was collected from each study participant. All women benefited from a biological assessment, including; blood glucose, insulin, total cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-C). Low-density lipoprotein cholesterol (LDL-C) level was calculated according to the Friedewald's formula [11]. The HOMA (homeostasis model assessment) score of insulin resistance was calculated as described earlier [12]. Ghrelin was measured by a commercial RIA kit (Radio Immuno Assay, LINCO Reaserch, Inc, Missouri, United States) GHRA-88HK for the active ghrelin with a sensitivity of 7.8 pg/ml. Resistin level was determined using ELISA (Enzyme-Linked Immunosorbent Assay Millipore # EZHR-95K ELISA with a sensitivity ranging from 0.16 ng/ml to 10 ng/ml.

### Statistical analysis

Statistical analysis was performed using SPSS 11.5 software. Continuous variables are presented as means ± standard deviation (SD). Comparisons of two means on independent groups were performed using the student's test. Correlations were tested using the Pearson correlation coefficient. The food survey data were coded according to the computer software directory« BILNUT » version 1991, to which was added a list of 239 foods and ready meals, specific to our country.

## Results

### Characteristics of the study population

There was no significant age difference between the two study groups. Comparing the average BMI in the two groups, we found a statistically significant difference ($p<0.001$). BMI was significantly higher in obese diabetic women than in the control group. The obese diabetic population had a significantly higher fasting blood glucose and insulin level as well as a disturbed lipid profile compared to the control group. Likewise, resistin was much higher in obese diabetics compared to the control group (Table 1).

**Table 1:** Clinical characteristics.

| | Control (n=52) | Obese with MetS (n=53) | p |
|---|---|---|---|
| Age (years) | 49.346±11.829 | 49.503±11.162 | 0.942 |
| BMI | 22.736±1.292 | 30.499±1.718 | <0.001 |
| Total cholesterol (mmol/l) | 4.473±0.876 | 6.478±0.849 | <0.001 |
| Triglycerides (mmol/l) | 0.953±0.140 | 2.049±0.4239 | <0.001 |
| HDL-C (mmol/l) | 1.181±0.132 | 1.028±0.271 | <0.001 |
| LDL-C (mmol/l) | 2.719±0.849 | 3.4331±0.614 | <0.001 |

| | | | |
|---|---|---|---|
| Glycemia (mmol/l) | 5.146±0.265 | 6.968±0.797 | <0.001 |
| Insulin(ng/ml) | 5.163±1.249 | 12.667±3.804 | <0.001 |
| Ghrelin (ng/ml) | 50.659±13.689 | 25.461±7.788 | <0.001 |
| Resistin (ng/ml) | 3.1685±1.033 | 9.174±2.137 | <0.001 |
| HOMAR-IR | 1.190±0.329 | 3.975±1.448 | <0.001 |

MetS: Metabolic Syndrome, HDL-C: HDL-Cholesterol, LDL-C: LDL-Cholesterol

### Correlation coefficient in obese with MetS

Correlations between ghrelin, resistin, insulin and the other parameters were represented in Table 2. In the obese with MetS population, we found a significant positive correlation between BMI, blood glucose, resistin, and insulin. As well as a significant negative correlation between ghrelin, BMI, blood glucose, resistin and insulin.

**Table 2:** Correlation coefficient in obese with MetS.

| | BMI | HDL-C | LDL-C | Glycemia | Insulin | Ghrelin | Resistin |
|---|---|---|---|---|---|---|---|
| BMI | 1 | -0.17 | | 0.65(**) | 0.39(**) | -0.358(**) | 0.74(**) |
| HDL-C | -0.17 | 1 | -0.37(**) | -0.02 | 0.01 | 0.157 | -0.26 |
| LDL-C | 0.05 | -0.37(**) | 1 | 0.05 | -0.25 | 0.032 | 0.01 |
| Glycemia | 0.65(**) | -0.02 | 0.05 | 1 | 0.40(**) | -0.402(**) | 0.68(**) |
| Insulin | 0.39(**) | 0.01 | -0.25 | 0.40(**) | 1 | -0.424(**) | 0.62(**) |
| Ghrelin | -0.36(**) | 0.16 | 0.032 | -0.40(**) | -0.42**) | 1 | -0.43(**) |
| Resistin | 0.74(**) | -0.26 | 0.01 | 0.68(**) | 0.62(**) | -0.434(**) | 1 |

(**) The correlation is significant at the 0.01 level (bilateral). n=53

### Comparison of dietary intake data

Our food survey revealed a significant difference in nutrient intake between the two study groups (Table 3). Quantitatively, the survey results show a statistically significant difference (p<0.001) between the calories intake of obese women and those in the control group. Furthermore, a significantly higher rate of lipid and carbohydrate calories (p<0.001) was observed in the ration of subjects with obesity compared to control. In contrast, the dietary fiber content was found to be lower in the obese population compared to the control group (p<0.001).

**Table 3:** Comparison of nutrient intake between obese MetS and non-obese women.

| | Control (n=52) | Obese with MetS (n=53) | p |
|---|---|---|---|
| Calories daily intake | 2219.17±125.96 | 3206.11±703.79 | <0.001 |
| Protein % | 12.185±1.385 | 11.789±1.815 | 0.212 |
| Fat % | 29.438±1.368 | 33.934 ±8.761 | <0.001 |
| Carbohydrate % | 54.29±8.483 | 58.57±2.064 | <0.001 |
| Calcium(mg) | 647.60±238.12 | 643.81±226.37 | 0.934 |
| Fiber (g) | 28.306±7.096 | 19.727±2.572 | <0.001 |

## Discussion

The results of our study show that plasma levels of total cholesterol, triglycerides, LDL-cholesterol, insulin, resistin and BMI values were significantly higher in the group of obese women with MetS compared to the control group. In contrast, HDL-cholesterol and ghrelin levels were significantly lower in MetS group compared to the control one. These results are explained by the phenomenon of insulin resistance. In fact, obesity is characterized by an insulin resistance involving high levels of insulin. This has atherogenic effects, which in turn cause the alteration of the lipid profile (with an increase in LDL-cholesterol and a decrease in HDL-cholesterol) and the hyperglycemia observed. Resistin, a hormone with an important role in the genesis of the atherosclerotic plaque, sees its concentration increases during obesity. Our results are in agreement with previous study which reported that the circulating level of resistin was higher in obese subjects than in those without obesity (19.32±0.53 ng/mL vs. 14.90±0.29 ng/mL, p=0.0024) [13]. The increased circulating resistin levels in women with metabolic syndrome might be also a result of the exacerbated adipose tissue macrophage recruitment in the context of obesity [14]. Siddiqui et al demonstrated the involvement of inflammation and endothelial

dysfunction in relation with resistin linked insulin resistance in type 2 diabetes. They also highlight the benefits of resistin in indicating the degree of insulin resistance status in pre-diabetes stage [15]. In addition, the level of ghrelin, the orexigenic hormone, decreases considerably in obesity. The state of positive energy balance induces a decrease in ghrelin secretion to reduce food intake (caloric intake). This result agrees with the data reported by Klimontov in 2019 that showed a significantly decreased ghrelin levels in patients with diabetes as compared to control [16]. A recent meta-analysis strengthens the clinical evidence supporting the low circulating ghrelin isoforms (acyl ghrelin and des-acyl ghrelin) in subjects with obesity and a shorter duration of acyl ghrelin suppression in obese subjects after meal intake. In fact, this meta-analysis supports the existence of physiological adaptation in ghrelin under obesity, and the simultaneous decline ghrelin isoforms is a symbol of positive energy balance [17].

Our data showed a significant positive correlation between blood glucose and BMI both in the obese population with MetS ($r = 0.646$; $p<0.001$) and in the control group ($r = 0.556$; $p<0.001$). These results are consistent with the study of Pongstah et al. in 2012 and Netjasov et al. in 2013 [18, 19]. There is a direct correlation between BMI and resistin (insulin resistance hormone), whose reflection is an indirect correlation between BMI and glucose [20]. In fact, in response to a positive energy balance, adipocytes increase in size to store the excess lipids until they hypertrophy, hyperplasia and become incapable of properly performing their functions. We are witnessing an increase in the release of fatty acid and triglyceride that go into inadequate storage organs such as the liver, pancreas and skeletal muscle, causing the development of insulin resistance and consequently, hyperglycemia [21]. In the same context, we were able to establish a significant negative correlation between ghrelin and blood glucose in the group of obese women with MetS ($r = -0.402$; $p = 0.003$). Our results are in agreement with those found by Purnell et al.in 2003 and Saad et al.in 2013 [22, 23]. On the other hand, other studies failed to find a significant correlation between these two parameters [24, 25]. This discrepancy may be due to the existing differences between the populations studied in these various studies and that studied in ours.

The study of Briatore et al. in 2003 states the existence of a direct regulation between glucose and ghrelin independently of insulin. The intravenous administration of glucose-induced a decrease in ghrelin level in the person with diabetes and the healthy group independently of insulin (the peak of which was observed in the diabetic group only 10 minutes after the administration of glucose) [26]. This study also made it possible to establish a significant negative correlation between HDL-cholesterol and LDL-cholesterol for the two populations studied (Obese with MetS: $r = -0.422$; $p = 0.002$; control: $r = -0.370$; $p = 0.006$) [26].

The results of Morris et al. in 2009 agrees with our data showing a causal link between LDL-cholesterol and HDL-cholesterol [27]. On the pathophysiological level, these opposing changes in LDL and HDL could be explained. In fact, in front of excessive energy intake, the adipocyte increases in size to store excess TG [28].

The pathological expansion of the adipose tissue in subjects with obesity is determined by two mechanisms: hypertrophy and hyperplasia [29]. At this time, it becomes unable to perform its functions, which increases the release of FFAs (free fatty acids), as well as an increase in the secretion of interleukin 1 β, which stimulates adipocyte lipolysis. From the circulation, these FFAs will reach several organs such as the liver, where a small proportion is oxidized and the rest is esterified to give TG [30].

The increase in the availability of TG involves increased levels of VLDL (Very Low-Density Lipoprotein). Under the action of CETP (cholesteryl ester transfer protein), these VLDLs will exchange their TGs for cholesterol esters from HDL and LDL. These lipoproteins that become rich TG undergo depletion of lipid cores under the action of hepatic lipase to form small and dense particles of LDL and HDL [31]. As for HDL, they undergo degradation and they are rapidly purified from circulation, which explains their reduced levels, while these small and dense LDLs having a reduced affinity for LDL receptors, their natural pathway for elimination, their stay increases and therefore the plasma levels can increase [30].

A significant positive correlation between BMI and resistin was shown in the group of obese women with MetS ($r = 0.744$; $p<0.001$) as in the control group ($r = 0.576$; $p<0.001$). These results are in agreement with those found by Ben Slama et al. and those of Christou et al. [31, 32]. However, we are in disagreement with the study of Heilbronn et al. [33] that did not highlight any significant difference between resistin in obese and control and no link between resistin and obesity or BMI. These fluctuations in results may be explained by; the differences between the characteristics of the study populations, the size of the samples, the difference in age, in sex, the difference in affinity between the hormone and the receptor, as well as by the interaction of certain human factors and the resistin assay technique.

Our study also showed a significant positive correlation between resistin and insulin in both the obese with MetS ($r = 0.620$; $p<0.001$) and the control group ($r = 0.801$; $p<0.001$). These results are in agreement with those of Ben Slama et al. [31] and Liu et al. [34]. We showed a significant negative correlation between ghrelin and insulin for the two study groups, the obese with MetS ($r = -0.424$; $p = 0.002$) and the control group ($r = -0.626$; $p<0.001$). This correlation is consistent with the results of studies developed by Poykko et al. [35]. Previous studies, who evaluated the relationship between these two hormones in mice and rats, demonstrated this positive correlation between ghrelin and insulin in the pancreas [36, 37]. We also noticed a significant positive correlation between insulin and glycemia in the two groups in our study, the obese with MetS: $r = 0.395$; $p = 0.003$) and the control ($r = 0.655$; $p<0.001$). The same results was revealed by a previous study [38]. A significant negative correlation between ghrelin and resistin was also demonstrated in both obese women with MetS ($r = -0.434$; $p = 0.001$) and in the control group ($r = 0.496$; $p<0.001$). This confirms a direct link between these two hormones. These results are in concordance with those of Vendrellet al. [39]. We also found a significant negative correlation between ghrelin and

BMI in the obese population with MetS (r = -0.358; p = 0.009). Similar studies were reported by many previous studies [40, 41]. Our dietary survey revealed a statistically significant difference between the calories in the daily food ration of obese women and those in the control group. Therefore, the discreet development of obesity is directly linked to caloric intake. As for the quality of the diet, we were able to detect a significantly higher rate of lipid and carbohydrate calories in the ration of subjects with obesity compared to control. In contrast, dietary fiber content was found to be lower in the obese population compared to the control group. A meta-analysis showed that a prudent and healthy dietary pattern is a protective factor for MetS and that an unhealthy dietary pattern could be associated with an increased risk of developing MetS [42]. Parikh et al. examined the association of dietary fiber consumption with inflammatory biomarkers and total fatness in 559 adolescents. They have shown that the use of fibers decreases visceral adiposity and decreases the levels of inflammatory biomarkers, but the association between fibers and resistin remains insignificant [43].

## Conclusion

Lipid profile disturbances in subjects with obesity are related to the interaction between increased body fat and insulin resistance. Secreted in amounts proportional to BMI and body fat, resistin is significantly higher in obese people. Conversely, ghrelin, the orexigenic hormone, is substantially lower in this group. The dietary assessment approves the impact of the food ration quality and its calorie content on the weight status.

## Declarations

### Ethics approval and consent to participate

As the patients were recruited from the Department C of Nutrition and Diabetology Diseases, the study location, and the Witnesses were their companions, the treating physicians within the said department explained the objectives and the protocol of the study to the participants. These (cases and Witnesses) gave their consents to the physicians orally.

## Consent for publication

Not Applicable.

## Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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This work was not supported by any funding agency.

## Authors' Contributions

M.S. Contributed to study design, data collection, data analysis, interpretation, and preparation of draft manuscript. H.BJ. Contributed to the design, conception of the study, and to the review and editing of the manuscript. I.F. Contributed to data collection. K.B.M. was involved results interpretation and preparation of the initial draft of the manuscript. H.A.S. Contributed to the design, conception of the study, and to the review and editing of the manuscript. C.B.R. was involved in data verification and result interpretation F.B.M. verified the data and critical review of the article. W.D. verified the data and critical review of the article. F.B.S. Designed and supervised the research. All authors reviewed the manuscript.

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## Conflict of Interest

No conflict of interest.

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