Study of serum ghrelin and resistin levels and their correlation with zinc and magnesium in men with type 2 diabetes

Sinda Ennigrou 1, Faika Ben Mami 2, Kamel Ben Mahrez 3, Chiheb Ben Rayana 4 and Fethi Ben Slama 5,*

1 Faculty of Pharmacy of Monastir.
2 Head of Diabetology and Therapeutic Dietetics - National Institute of Nutrition.
3 Director of the Research Laboratory of Biochemistry and Technobiology Faculty of Sciences of Tunis - LR01ES05.
4 Faculty of Pharmacy of Monastir - Clinical Biochemistry Laboratory - National Institute of Nutrition.
5 Director of Nutrition Department - Higher School of Health Sciences and Techniques of Tunis.

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Abstract

Introduction: The objectives of our work were to compare the serum concentrations of lipid parameters, insulin, resistin, ghrelin, zinc and magnesium between two groups of men with obese type 2 diabetes and a control group and to study possible correlations between these different parameters.

Material and methods: This was a monocentric case-control study during the period 19 October 2015 to 18 November 2015. It included biological parameters from two separate samples: a group of 41 male, obese, type 2 diabetic patients and a group of 34 diabetes-free controls.

Results: Mean plasma ghrelin concentrations were significantly lower in patients with type 2 diabetes compared to those in the control group: (14.05 ± 2.35 pg/mL) versus (45.45 ± 13.59 pg/mL). Mean resistance was significantly higher in diabetics (10.09 ± 2.63 ng/mL) compared to healthy subjects (2.22 ± 0.58 ng/mL). In multivariate analysis, body mass index (BMI) and insulin levels were factors that could influence zincemia variability, while BMI and ghrelinemia appeared to be predictors of magnesium variability.

Discussion: Most correlation studies are based on serum zinc concentration. The different possible correlations between resistin, zinc, magnesium and ghrelin require an increase in the size of the study population, as well as an increase in nutritional surveys during the different stages of type 2 diabetes and obesity.

Conclusion: It would be interesting to evaluate, according to the stages of obesity, serum levels of magnesium and ghrelin, on the one hand, and serum levels of zinc and insulin, on the other hand.

Keywords: Diabetes; Zinc; Magnesium; Ghrelin; Resistin

1. Introduction

Diabetes mellitus and associated obesity are epidemics around the world. Tunisia is not spared by these two scourges. Type 2 diabetes is a heterogeneous, polygenic disease characterized by chronic hyperglycemia due to abnormal insulin secretion or failure of insulin to work. Obese individuals are characterized by insulin resistance and hyperinsulinemia, predisposing to glucose intolerance, diabetes and cardiovascular disease [1,2].

*Corresponding author: Fethi Ben Slama
Director of Nutrition Department - Higher School of Health Sciences and Techniques of Tunis.
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Adipose tissue, long considered a tissue of energy reserves, is currently recognized as an endocrine organ, secreting peptides, adipokines, such as leptin, adiponectin and resistin. In humans, the relationship between circulating concentrations of resistin and the existence of insulin resistance, diabetes or obesity is not well established [3].

Ghrelin is an hormone produced primarily in the stomach by fundal cells. It plays a role in the short and long term regulation of energy balance, appetite and weight gain [4].

Low levels of ghrelin have been shown to be independently associated with type 2 diabetes and insulin resistance [4,5]. Zinc, a trace element described as a powerful antioxidant, is involved in insulin secretion. Low plasma zinc levels are frequently observed in type 2 diabetes mellitus [6,7].

Magnesium deficiency is frequently associated with diabetes mellitus. This magnesium depletion impairs carbohydrate metabolism and insulin sensitivity in patients with type 2 diabetes [7,8].

The objective of our work is to compare the serum concentrations of lipid parameters, insulin, resistin, ghrelin, zinc and magnesium between two groups of men: a group of type 2 diabetics, obese and a control group (non-diabetic and non-obese), and to study the possible correlations between these different parameters.

2. Material and methods

Purpose of the work: Compare the serum concentrations of lipid parameters, insulin, resistin, ghrelin, zinc and magnesium between two groups of men: a group of type 2 diabetics, obese and a control group (non-diabetic and non-obese), and to study the possible correlations between these different parameters.

2.1. Patients and method

This was an epidemiological observational study, single-center, "case-control" type in adult subjects.

2.2. Study population

2.2.1. Inclusion criteria

- Obese adult male patients with type 2 diabetes, recruited from patients in the "C" department of Nutrition and Therapeutic Dietetic diseases at the National Institute of Nutrition.
- Non-obese and non-diabetic witnesses, of the same sex, collected among the voluntary accompanists of patients followed at the outpatient consultation for diabetology and metabolic diseases at the National Institute of Nutrition. All controls were judged to be non-obese, free from diabetes and any other metabolic disease or physical disability, after a physical examination by the specialist Doctor of the investigation team.

2.2.2. Non-inclusion criteria

- Type 1 diabetic patients
- Type 2 diabetic patients whose age of diabetes is over 5 years
- Patients with a metabolic complication

2.3. Sampling methods

The study focused on biological parameters carried out on two separate samples:

- A sample of 41 male subjects, obese type 2 diabetics recruited from patients hospitalized in the "C" department of nutritional diseases and therapeutic dietetics at the National Institute of Nutrition.
- A sample of controls made up of men free from diabetes and any other metabolic disease or physical disability, recruited from among the voluntary supporters of patients consulting at the National Institute of Nutrition. In total we were able to collect 34 witnesses. These were matched with those in the diabetic group according to age.
2.4. Data collection

2.4.1. Anthropometric data collection

An information sheet was established for each patient and for each witness in order to collect information on the individual characteristics of the subjects. This sheet included the following variables:

- age (years),
- the body mass index (BMI = weight in Kg / height in m2). to calculate the BMI, we had to weigh and measure the height of each respondent. In fact, each man was weighed twice by two different people with a bad weighing machine. Regarding the size, we used the same procedure using a micro measuring rod. Subsequently, we calculated the average of the two weighings and the two sizes. The WHO classification has been used to identify the weight status of patients [9],
- systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken for each subject using the same procedure as for weight and height gain.

2.5. Biological assessment performed

The blood sample was taken from an antecubital vein for the subjects studied, in a lying position, after a 12-hour fast. All subjects (cases and controls) underwent a biological assessment comprising the following parameters: fasting blood sugar, total cholesterol (CT), triglyceridemia (TG), insulinemia, resistinemia, ghrelinemia, zincemia and magnesemia.

2.6. Data entry and analysis

Data were entered using "Excel version 2007" software and analyzed using SPSS version 15.0 software. In the descriptive study, we calculated means and standard deviations for the quantitative data. Student’s t test was used for the comparison of two means on two independent samples. In the analytical study, in univariate analysis, the relationships between two quantitative variables were made using Pearson’s linear correlation coefficient (r).

The correlation was interpreted according to the value of this coefficient [10]:

- < 0.20: zero or very bad correlation
- 0.21 - 0.41: poor correlation
- 0.41 - 0.60: average correlation
- 0.61 - 0.80: good correlation
- 0.81 and more: very good correlation

In order to choose among the explanatory or independent variables, those which best explain the variability of the variable to be explained or dependent, we carried out a multivariate analysis of multiple linear regression according to the backward method: all the explanatory variables are included in the model then the least significant variables (highest p-value and above the chosen significance threshold) are removed one by one until all the remaining variables are significant [11].

The analysis was carried out in two stages:

- first, we introduced magnesemia as a dependent variable and BMI, fasting blood sugar, insulinemia, resistinemia and ghrelinemia as explanatory variables into the model;
- Secondly, we introduced zincemia as a dependent variable and BMI, fasting blood sugar, insulinemia, resistinemia and ghrelinemia as explanatory variables into the model. For all statistical tests, the significance level chosen was 0.05.

2.7. Ethical considerations

Both for the cases and for the witnesses, a verbal agreement was obtained to participate voluntarily in the study after explaining the objectives and the interest of this scientific work, during a well-structured individual interview with the medical specialist. They were informed of their right to refuse and of strict respect for the confidentiality of the information collected.
3. Results

3.1. Individual characteristics of patients and controls

The mean age of type 2 diabetic patients was 50.51 years (standard deviation: 6.26) with extremes ranging from 39 to 62 years. The mean age of controls was 50.74 years (standard deviation: 5.95) with extremes ranging from 39 to 61 years. The difference was not significant. The means of body mass index (BMI), waist circumference (TT), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in subjects with diabetes compared to control subjects. (Table I).

Table 1 Comparison of the average individual characteristics in diabetic patients and in controls

<table>
<thead>
<tr>
<th>Individual characteristics</th>
<th>Diabetic patients (n= 41)</th>
<th>Control patients (n= 34)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (ans)</td>
<td>50.51 (standard deviation : 6.26)</td>
<td>50.74 (standard deviation : 5.95)</td>
<td>p = 0.8</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>30.16 (standard deviation : 2.81)</td>
<td>21.30 (standard deviation : 1.51)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Waist size (cm)</td>
<td>105.34 (standard deviation: 9.48)</td>
<td>79.43 (standard deviation : 5.49)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>140.49 (standard deviation: 10.29)</td>
<td>123.06 (standard deviation : 9.48)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mm Hg)</td>
<td>88.85 (standard deviation : 4.30)</td>
<td>79.32 (standard deviation : 4.05)</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

3.2. Biochemical parameters of patients and controls

The means of total cholesterol, triglycerides, glycated hemoglobin (HbA1c) and fasting blood sugar were significantly higher in subjects with diabetes compared to controls. The mean HOMA-IR index was also significantly higher in diabetic subjects compared to controls (4.87 versus 1.15; p <0.001).

Conversely, the mean HDL (“High Density Lipoprotein”) cholesterol was significantly higher in the control group compared to the group of diabetic subjects (1.13 mmol / L versus 0.76 mmol / L; p <0.001) (Table II).

Table 2 Comparison of the means of the biochemical parameters in diabetic patients and in controls

<table>
<thead>
<tr>
<th>Biochemical parameters</th>
<th>Diabetic patients (n= 41)</th>
<th>Control patients (n= 34)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.39 (standard deviation: 1.09)</td>
<td>4.27 (standard deviation : 0.65)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.81 (standard deviation : 0.22)</td>
<td>0.99 (standard deviation : 0.52)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>0.76 (standard deviation : 0.18)</td>
<td>1.13 (standard deviation : 0.15)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.61 (standard deviation : 0.98)</td>
<td>5.50 (standard deviation : 0.43)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>7.46 (standard deviation : 1.18)</td>
<td>5.01 (standard deviation : 0.31)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>HOMA-IR (indice)</td>
<td>4.87 (standard deviation : 2.34)</td>
<td>1.15 (standard deviation : 0.50)</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

HOMA-IR : « Homeostasis Model Accessment of Insulin Resistance; HbA1c : " Glycated hemoglobin"
Regarding the Zinc and magnesium values, our results showed that the mean serum magnesium level was lower in the group of diabetic subjects compared to the control group: 22.0 mg / L versus 23.2 mg / L; the difference was statistically significant (p = 0.05). The mean zincemia were lower in the group of diabetic subjects compared to the group of control subjects: 808.1 µg / L versus 865.2 µg / L; the difference was statistically significant (p = 4.10^-3) (Table III).

**Table 3** Comparison of the means of the parameters of zincemia and magnesemia in diabetic patients and in controls

<table>
<thead>
<tr>
<th>parameters</th>
<th>Diabetic patients (n= 41)</th>
<th>Control patients (n= 34)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zincemia (µg/dl)</td>
<td>80.81 (standard deviation : 7.99)</td>
<td>86.52 (standard deviation : 8.74)</td>
<td>p = 4 10^-3</td>
</tr>
<tr>
<td>Magnesemia (mg/L)</td>
<td>22.0 (standard deviation : 2.4)</td>
<td>23.2 (standard deviation : 2.8)</td>
<td>p = 0.05</td>
</tr>
</tbody>
</table>

Furthermore, we found that the mean insulinemia and resistinemia levels were significantly higher in diabetic subjects compared to control subjects, while the mean ghrelinemia rate was significantly higher in control subjects compared to diabetic subjects (45,45 pg / ml versus 14.05 pg / ml; p <0.001) (Table IV).

**Table 4** Comparison of the means of the hormonal parameters in the diabetic patients and in the controls

<table>
<thead>
<tr>
<th>Hormonal parameters</th>
<th>Diabetic patients (n= 41)</th>
<th>Control patients (n= 34)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinemia (µU/l)</td>
<td>11,52 (écart-type : 2,80)</td>
<td>5,29 (écart-type : 1,30)</td>
<td>p &lt; 0,001</td>
</tr>
<tr>
<td>Resistinemia (ng/ml)</td>
<td>10,09 (écart-type : 2,63)</td>
<td>2,22 (écart-type : 0,58)</td>
<td>p &lt; 0,001</td>
</tr>
<tr>
<td>Ghrelinemia (pg/ml)</td>
<td>14,05 (écart-type : 2,35)</td>
<td>45,45 (écart-type : 13,59)</td>
<td>p &lt; 0,001</td>
</tr>
</tbody>
</table>

**Figure 1** Correlation between Zincemia and BMI in diabetics
Following univariate analysis, we found that in the group of diabetic subjects, zincemia was significantly negatively correlated with BMI, respectively ($r = -0.70; p < 0.001$); with fasting blood sugar ($r = -0.76; p < 0.001$); with fasting insulinemia ($r = -0.84; p < 0.001$) and with resistinemia ($r = -0.48; p = 2.1 \times 10^{-3}$) (Figures 1 to 4). On the other hand, the correlation was positive and significant between the zincemia and the ghrelinemia ($r = 0.36; p = 0.02$) (Figure 5).

**Figure 2** Correlation between Zincemia and fasting glucose in diabetics

**Figure 3** Correlation between Zincemia and insulinemia in diabetics
Furthermore, magnesemia was significantly negatively correlated with BMI, respectively ($r = -0.69; p < 0.001$); fasting blood sugar ($r = -0.57; p < 0.001$); insulinemia ($r = -0.5; p < 0.001$) and resistinemia ($r = -0.58; p = 2 \times 10^{-3}$) (Figures 6 to 9). On the other hand, the correlation was positive and significant between zincemia and ghrelinemia ($r = 0.68; p < 0.001$) (Figure 10).
Figure 6 Correlation between Magnesemia and BMI in diabetics

Figure 7 Correlation between Magnesemia and fasting glucose in diabetics

Table 5 Multivariate Analysis by Multiple Linear Regression Model of Zincemia on BMI, Fasting Blood Glucose, Insulinemia, Resistinemia and Ghrelinemia in Diabetic Subjects

<table>
<thead>
<tr>
<th></th>
<th>Slope estimate (regression coefficient)</th>
<th>Standard error</th>
<th>Student’s t-value</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>126,584</td>
<td>7,084</td>
<td>17,869</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.782</td>
<td>0.287</td>
<td>-2.724</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Insulinemia</td>
<td>-1.925</td>
<td>0.288</td>
<td>-6.690</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>
Multivariate analysis by the model of multiple linear regression according to the descending method of the plasma zinc on BMI, fasting glucose, insulinemia, résistinemia and ghrélinemia in diabetic subjects showed that the BMI and insulinemia were predictors of the variability of zincemia (Table V).

![Figure 8](image1.png) **Figure 8** Correlation between Magnesemia and insulinemia in diabetics

![Figure 9](image2.png) **Figure 9** Correlation between Magnesemia and resistinemia in diabetics

**Table 6** Multivariate Analysis by Multiple Linear Regression Model of Zincemia on BMI, Fasting Blood Glucose, Insulinemia, Resistinemia and Ghrelinemia in Diabetic Subjects

<table>
<thead>
<tr>
<th></th>
<th>Slope estimate (regression coefficient)</th>
<th>Standard error</th>
<th>Student’s t-value</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>28,502</td>
<td>3,511</td>
<td>8,118</td>
<td>p &lt; 0,001</td>
</tr>
<tr>
<td>BMI</td>
<td>0,449</td>
<td>0,088</td>
<td>-5,106</td>
<td>p &lt; 0,001</td>
</tr>
<tr>
<td>Ghrelinemia</td>
<td>0,501</td>
<td>0,105</td>
<td>4,776</td>
<td>p &lt; 0,001</td>
</tr>
</tbody>
</table>
On the other hand, multivariate analysis by the multiple linear regression model according to the top-down method of magnesemia on BMI, fasting blood sugar, insulinemia, resistinemia and ghrelinemia in diabetic subjects showed that the BMI and ghrelinemia were predictors of variability in magnesemia (Table VI).

![Figure 10 Correlation between Magnesemia and ghrelinemia in diabetics](image)

4. Discussion

Diabetes is an endocrine disorder of multiple etiologies characterized by chronic hyperglycemia, resulting from a defect in the synthesis and / or action of insulin. Its seriousness lies in its acute or chronic complications, which can be fatal for the patient [1,2]. Type 2 diabetes is the most common form of diabetes (90% of diabetes cases in Western countries) [12]. He is also responsible for the outbreak of the pandemic of this disease because of his extreme sensitivity to lifestyle. Indeed, the increase in the incidence of obesity, the importance of calorie intake, sedentary lifestyle and the aging of the population are important factors in this worrying development.

In Tunisia, according to the IDF ("International Diabetes Federation"), the prevalence of diabetes has been estimated among adults aged 20 to 79 at 9.8% (95% confidence interval: 7.8-14.5). The estimated number of diabetics, for the same age group, was 762 thousand 200 in 2017 and will increase to 1 million 198 700 miles in the year 2045 [13].

From a pathophysiological point of view, type 2 diabetes combines insulin resistance in peripheral tissues and a qualitative and quantitative secretory defect in the β cells of the "Langerhans" islands, which secrete insulin. Adipose tissue, long considered a tissue of energy reserves, is currently recognized as an endocrine organ, secreting peptides, adipokines, such as resistin, a hormone implicated in the genesis of obesity and insulin resistance observed in diabetes. type 2 [3].

Ghrelin is a hormone secreted primarily by the fundal cells of the stomach. It is involved not only in the release of GH, but also in weight control by stimulating appetite [4]. Studies have shown that the metabolism of several trace elements such as zinc and magnesium is altered in type 2 diabetics. Indeed, the disturbance of their homeostasis can be implicated in the pathogenesis of diabetes [6,7].

In this work, we set out to evaluate the serum levels of resistin and ghrelin and their correlations with zinc and magnesium in adult subjects with type 2 diabetes, through a single-center, case-control study.
We worked on two separate samples: a group consisting of 41 male patients, obese, type 2 diabetics and a group consisting of 34 controls free from diabetes and any other metabolic disease or physical disability. Patients with type 2 diabetes were recruited from patients hospitalized in the "C" department for nutritional diseases and therapeutic dietetics at the National Institute of Nutrition and Food Technology of Tunis (INNTA). The Witness cases, of the same sex, were collected from among the voluntary companions of patients who were consultants to INNTA. These were matched to those in the diabetic group according to age.

In Egypt, in the study conducted by Badran M et al. [7], with the objective of evaluating the levels of 24 trace elements in patients with type 2 diabetes, the sample was composed of 40 patients with type 2 diabetes and 36 healthy volunteers, recruited from different hospitals in Tanta University. Volunteer controls and patients had the same socioeconomic status. In Morocco, Safi S et al. [8] had carried out a case-control study. The objective was to study the prevalence of magnesium deficiency in a Moroccan diabetic population and its correlation with glycemic control. The 121 diabetic patients were collected after their consent, from the endocrinology consultation at the Moulay Ismail military hospital in Meknes. The 51 healthy subjects matched for age, sex and body mass index (BMI) were recruited after consent after a general health check-up.

In our study, the mean age of patients with type 2 diabetes was 50.51 years (standard deviation: 6.26). The mean age of controls was 50.74 years (standard deviation: 5.95).

In the Egyptian study by Badran M et al. [7], the mean of age in the male subjects was in the group of diabetic patients 53.41 years (standard deviation: 7.62) and in the control group it was 51.78 years (standard deviation: 8.75).

In the Moroccan study by Safi S. et al. [8], the mean of age in the type 2 diabetic groups and healthy subjects was respectively 52.47 years (standard deviation: 9.9), and 50.88 years (standard deviation: 8.9 years).

These results are consistent with our study as regards the average age of the subjects surveyed with the absence of significant difference between the two groups to be compared (cases and controls).

In our study, the mean BMI was 30.16 kg / m² (standard deviation: 2.81) in the diabetic group versus 21.30 kg / m² (standard deviation: 1.51) in the control group; the difference being statistically significant.

In the Egyptian study by Badran M et al. [7], the mean BMI was 22.45 kg / m² (standard deviation: 1.0) in male diabetic subjects compared with 21.34 kg / m² (standard deviation: 1.5) in patients with diabetes. healthy male subjects. An Indian study conducted by Doddigarla Z et al. [14], had shown that the mean BMI was 26 kg / m² (standard deviation: 4.5) in the group of diabetic patients versus 23 kg / m² (standard deviation: 2) in the control group; the difference being very significant (p <0.0001).

A cross-sectional study, carried out at the National Institute of Nutrition of Tunis by Abdesselem H et al. [15] in type 2 diabetic patients over 18 years of age, treated with oral antidiabetics and recruited at the outpatient clinic between May 2013 and August 2014, whose objective was to evaluate my correlations between insulin sensitivity and insulin secretion with anthropometric and metabolic parameters, showed the means of BMI and waist circumference (WC) were 30.5 kg / m² (standard deviation: 5 , 7) and 101.2 cm (standard deviation: 11.9) respectively. These results agree with our study concerning type 2 diabetic subjects (mean BMI: 30.16 ± 2.81 kg / m², mean WC: 105.34 ± 9.48 cm).

Magnesium is the second most important intracellular cation after potassium. The kidneys maintain this element at normal levels, between 1.7 and 2.4 mg / dl. For the past fifteen years, studies have linked magnesium to diabetes [16,17]. In our study, the mean plasma magnesium concentration was significantly lower in our diabetic patients compared to the control group (22.0 mg / L versus 23.2 mg / L; the difference is significant). Magnesium deficiency is frequently reported in type 2 diabetes. In fact, it is responsible for inhibiting the secretion of insulin and increasing resistance to this hormone, by reducing the activity of tyrosine kinase and this causes autophosphorylation of the insulin receptor [8].In addition, it turns out that the cause of plasma magnesium deficiency in patients with type 2 diabetes is not fully understood.

Increased urinary magnesium excretion by osmotic diuresis in poorly balanced diabetic patients has often been implicated in this deficit [16,17]. Other factors have been suggested, such as reduced magnesium intake by a diet low in cereals or poor cellular uptake of magnesium observed in states of insulin resistance [7].

In addition, hyperglycemia would indeed promote urinary excretion of zinc. Plasma zinc deficiency is frequently reported in type 2 diabetes [16,17]. A 2016 study reported that in people with type 2 diabetes, low zinc status was
associated with poor blood sugar control [7]. In our study, the mean plasma zinc concentration was significantly lower in our diabetic patients compared to the group of healthy non-diabetic subjects (808.1 versus 865.2 µg / L; p = 0.004). Our results are consistent with those of other authors. The cause of the decreased zinc level in the diabetic subject may be following renal elimination (osmotic diuresis). High blood sugar can interfere with the active transport of zinc through kidney tubular cells. In addition, studies have shown that zinc is involved in the actions of insulin. Thus, Zinc deficiency can worsen insulin resistance in type 2 diabetes [16,17]. Similar results to ours have been found by other authors who have studied Zinc and Magnesium status in type 2 diabetics [7, 18 - 20].

The cause of the decreased zinc level in the diabetic subject may be following renal elimination (osmotic diuresis). Hyperglycemia may interfere with the active transport of zinc through renal tubular cells [7,20]. In addition, studies have shown that zinc is involved in the actions of insulin. Thus, Zinc deficiency can worsen insulin resistance in type 2 diabetes [6,7,19]. In our study, mean resistinemia was significantly higher in obese diabetics (10.09 ± 2.63 ng / mL) compared to non-diabetic and non-obese subjects (2.22 ± 0.58 ng / mL) (p < 0.001). This result agrees with that found in Jordan by Gharibeh MY et al. [21] (8.50 ± 0.50 ng / mL) versus (6.30 ± 0.30 ng / mL) (p <0.0006).

There is currently interest in ghrelin focused more on the regulation of energy balance than on its involvement in the regulation of growth hormone secretion. It is the only peripheral hormone that stimulates appetite and the accumulation of fat. This hormone also increases gastric motility, gastric and pancreatic secretions, regulates glucose and lipid metabolism, stimulates cell differentiation in adipose tissue, inhibits adipocyte apoptosis, inhibits lipolysis and stimulates lipogenesis [22]. A growing body of evidence points to a suppressive role of ghrelin in the release of insulin from pancreatic islets. Low concentrations of ghrelin have been shown to be independently associated with type 2 diabetes and insulin resistance [4,5,22]. The results of our study showed that the mean plasma ghrelin concentrations were significantly lower in subjects with type 2 diabetes compared to those in the control group:(14.05 ± 2.35 pg / mL) versus (45.45 ± 13.59 pg / mL) (p <0.001). Other observational case-control studies have also shown low levels of ghrelin in individuals with obese type 2 diabetes (BMI between 30.0 and 34.9 Kg / m2) compared to healthy individuals.[ 23, 24].

The best possible explanation for the level of ghrelin in diabetic patients supposes a competition between the factors which increase the level of ghrelin (insulin deficiency) and the factors which decrease the level of ghrelin (obesity, glucose and hyperinsulinemia) [24]. Other authors have reported that insulinemia may alter the effect of nutritional status and energy balance on plamatic ghrelin. In particular, insulin may play a central role in the regulation of body weight through its down-regulating effects on plasma concentrations of ghrelin [4,5,22]. In our study, a significant negative correlation was observed in the groups of obese type 2 diabetic subjects between plasma zinc concentrations and BMI (r = -0.70), fasting blood sugar (r = -0.76), insulinemia (r = -0.84) and resistinemia (r = -0.48). However, there was a significant positive correlation between zincemia and plasma ghrelin concentration (r = 0.36). In addition, our results corroborate with those found by Dasarathan R et al. [25] in India on 100 diabetic subjects: the correlation was significantly negative between plasma zinc concentration and fasting glycemia, respectively, and body mass index (r (BMI) = -0.553 and r (fasting glycemia) = -0.492; p <10\(^{-3}\) ). We also found a significant negative correlation between magnesemia and BMI (r = -0.69), fasting blood glucose (r = -0.57), insulinemia (r = -0.50) and resistinemia (r = -0.58). However, there was a significant positive correlation between zincemia and plasma ghrelin concentration (r = 0.68).

We conducted multiple linear regression analysis to identify predictors of variability in zincemia on BMI, fasting blood glucose, insulinemia, resistinemia and ghrelinemia in diabetic subjects, we observed that alone BMI and insulinemia were factors that could influence the variability of zincemia with a statistically significant negative regression coefficient (respectively, \( \beta = -0.782 \) and \( \beta = -1.925 \)). Multiple linear regression analysis performed to identify predictors of magnesemia variability on BMI, fasting blood glucose, insulinemia, resistinemia and ghrelinemia in diabetic subjects, shows that BMI and ghrelinemia appear to be factors that may influence the variability of plasma magnesium concentrations with a statistically significant negative regression coefficient for BMI (\( \beta = -0.449 \)) and a statistically significant positive regression coefficient for ghrelin (\( \beta = 0.501 \)).

5. Conclusion

Our study is far from being a complete and perfect study to investigate the different possible correlations between resistin, zinc, magnesium and ghrelin. This process is complex and requires an increase in the number of the population studied, and also to deepen nutritional surveys during the different stages of type 2 diabetes and obesity. Complementary studies evaluating, on the one hand, the serum levels of magnesium and ghrelin according to the stages of obesity, and on the other hand, the serum levels of zinc and insulin according to the stages of obesity, would be interesting in order to be sure of the benefit of introducing food supplements that are sources of these micronutrients.
Compliance with ethical standards

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Disclosure of conflict of interest
All the authors of this article declare that there is no conflict of interest.

Statement of informed consent
Informed consent was obtained from all individual participants included in the study.

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