

(RESEARCH ARTICLE)



Assessment of ghrelin and resistin levels in a group of obese men with metabolic syndrome

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Abstract

Background: Obesity is a chronic disease associated with numerous complications, including metabolic syndrome, type 2 diabetes, and cardiovascular diseases. Adipose tissue functions as an endocrine organ, producing hormones that play a crucial role in regulating metabolic homeostasis, such as ghrelin and resistin.

Objective: The aim of this study was to compare the levels of resistin and ghrelin in obese men with metabolic syndrome and age-matched men without metabolic syndrome.

Methods: Anthropometric measurements and biochemical assays were conducted to assess glycemia, resistin levels, insulin levels, and ghrelin levels.

Results: The study comprised 58 obese men with metabolic syndrome and 53 age-matched control group men. In obese individuals, there was a significant increase in insulin and resistin levels, while ghrelin levels were notably decreased compared to the control group. Additionally, a positive correlation was observed between resistin levels and parameters such as BMI, waist circumference, and insulin levels.

Conclusion: The findings from this study suggest that both resistin and ghrelin may serve as potential biomarkers for identifying metabolic syndrome in obese men.

Keywords: Ghrelin; Obesity; Metabolic syndrome; Insulin

1. Introduction

Metabolic syndrome, a global health concern impacting over one billion adults, is often closely linked with obesity [1]. Obesity is characterized by an excessive accumulation of body fat and significant changes in adipose tissue physiology. This condition is multifaceted, giving rise to a range of metabolic and cardiovascular related complications, including metabolic syndrome (MS), type 2 diabetes, dyslipidemia, hypertension, and coronary artery disease.

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Adipose tissue is a complex organ with endocrine capabilities, producing a multitude of hormones, including adipokines, which have been implicated in various studies as potential contributors to obesity and metabolic syndrome. These adipokines play pivotal roles in essential metabolic and endothelial functions, energy regulation, calorie expenditure, hunger/satiety balance, and insulin sensitivity [2–6].

Resistin, a 114-amino acid cysteine-rich adipocytokine, has been suggested as a possible link between obesity and diabetes, with implications for the development of insulin resistance [7]. Its primary physiological role may involve modulation of inflammatory, immune, and autoimmune responses [8]. Resistin's association extends beyond type 2 diabetes and obesity, encompassing various metabolic disorders [9].

Ghrelin, a hormone originating from gastrointestinal endocrine cells, acts as a regulator of appetite and is released during fasting periods. It plays a pivotal role in maintaining energy balance and regulating body weight [10]. Ghrelin, discovered in 1999, exerts its appetite-stimulating effects through interactions with specific hypothalamic receptors. When released, it activates the growth hormone secretagogue receptor (GHS-R) situated in the anterior lobe of the pituitary gland, leading to increased food intake [11]. Comprising 28 amino acids, ghrelin is an endogenous ligand for growth hormone secretagogue receptors [12]. Circulating ghrelin has been linked to appetite stimulation and energy balance regulation. Furthermore, ghrelin concentrations are associated with insulin resistance and hyperinsulinemia, suggesting its role in the feedback mechanism governing body weight [13]. Hence, it is considered a potential candidate gene for obesity and type 2 diabetes [14]. Beyond its appetite-related functions and energy homeostasis regulation, ghrelin exerts influence on various physiological processes, including hemodynamics, immune responses, glucose control, neurogenesis, and renal and pulmonary functions [15,16].

Ghrelin and resistin, both hormones produced by adipose tissue, have been implicated in the development of obesity and metabolic disorders. However, their precise roles in these conditions remain unclear. The aim of this study is to assess and compare the levels of resistin and ghrelin in obese men with metabolic syndrome and age-matched men without metabolic syndrome, while investigating whether these hormones can be used as markers of metabolic syndrome.

2. Material and Methods

Fifty-eight obese men with metabolic syndrome and 53 age-matched men without metabolic syndrome as a control group were recruited. They were 18 years of age and older. The recruitment was carried out at the day care unit of the "C" department of metabolic diseases at the National Institute of Nutrition and Food Technology from December 2021 to June 2022.

We excluded women, age <18 years old, psychiatric illness or malignant diseases or user of psychiatric drugs. The control group consisted of men who were selected from the companions of patients in the "C" department and matched with the cases by age. The study was a case-control study conducted in collaboration with the Biochemistry and Technology Laboratory at the Faculty of Science in Tunis.

Anthropometric parameters such as age, height, weight and waist circumference (WC) were ascertained. Blood pressure measurements were recorded. Obesity was defined as having a body mass index (BMI) greater than 30 kg/m². BMI is calculated by weight divided by height².

All men underwent a **biological assessment** including the following parameters: total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), glycemia (g/l), resistin, and ghrelin. The blood glucose level was measured by enzymatic method with glucose oxidase, Beckman kit, adapted on a Beckman synchron CX9 analyzer. Triglycerides were measured by enzymatic method with a Beckman synchron CX7 kit. Cholesterol was measured by enzymatic method with a cholesterol oxidase, Beckman kit, adapted on a Beckman synchron CX9 analyzer. The HDL-cholesterol level was measured by a direct assay method with the Randox kit, adapted on a Beckman synchron CX9 analyzer.

The LDL concentrations were calculated by the Friedwald formula:

$$\text{LDL (mmol/L)} = \text{Total Cholesterol (mmol/L)} - \text{HDL Cholesterol (mmol/L)} - (\text{Triglycerides (mmol/L)} / 2.2) \text{ when TG} \leq 4.5 \text{ mmol/L.}$$

Ghrelin levels were measured by Radioimmunoassay technique by competition using kits commercialized for research by the Linco laboratory (LINCO Research, Inc., Missouri, United States), GHRA-88HK kit for active ghrelin with a sensitivity of 7.8 pg/mL.

Resistin levels were measured by ELISA method, "Millipore # EZHR-95K with sensitivity ranging from 0.16 ng/mL to 10 ng/mL.

The criteria used in our study to define **metabolic syndrome (MS)** are:

- Waist circumference ≥ 94 cm
- Triglycerides ≥ 1.7 mmol/L (1.5 g/L)
- HDL-cholesterol < 1.03 mmol/L (0.4 g/L)
- Blood pressure (mm Hg) $\geq 130/85$
- Fasting blood glucose ≥ 5.6 mmol/L (1g/L)[17,18].

2.1. Ethical consideration

The men who participated in the study were informed of the study's objectives beforehand.

All participants gave written consent for participation in the study and informed about the aim of the experiment. The study protocol was approved by the ethical committee of the national institute of nutrition of tunis, to protect the rights and welfare of the human subjects.

2.2. Statistical analysis

For data entry, we used Excel version 2007 software and SPSS 11.5 software for statistical analysis. To compare two means, we used the Student's t-test for independent series or the nonparametric Mann-Whitney test for small sample sizes. To compare percentages on independent series, we used Pearson's chi-squared test, or in case of invalidity, the bilateral Fisher exact test. To study the correlation between two quantitative variables, we used the Pearson correlation coefficient or the Spearman correlation coefficient based on ranks if invalid. The degree of concordance between two qualitative variables was evaluated by the Cohen's Kappa coefficient, with interpretation varying depending on the study field and context.

For the risk factor research, we established Receiver Operating Curves (ROC) to estimate the threshold value of ghrelinemia and resistinemia, which are considered risk factors for obesity. We calculated the Odds ratio to represent the number of times the probability (risk) of an event is multiplied in case of exposure to a factor compared to non-exposure.

In the univariate study, we used a multivariate analysis with a two-step descending method to search for relationships between various parameters. Firstly, we chose BMI as the dependent variable and ghrelinemia, insulinemia, glycemia, waist circumference, and resistinemia as explanatory variables. Then, we chose ghrelin, resistin, and insulin as dependent variables and BMI, glycemia, waist circumference, and other parameters as explanatory variables.

3. Results

The characteristics of our population are present in table 1.

To determine the risk threshold for ghrelinemia, we used the Receiver Operating Curve (ROC) method. The estimated threshold value corresponding to 37 pg/mL. The area under the curve evaluates the diagnostic value of the Ghrelin test, and its value is $0.961 > 0.9$, indicating that this test is highly informative. Using a ghrelin threshold of 37 pg/mL, resulting in 89.7% true positives (sensitivity) and 84.9% true negatives (specificity).

We did the same thing for insulinemia. The estimated threshold value according to the curve is $6.15 \mu\text{U/l}$ (area under the curve = $0.990 > 0.9$) with a sensitivity of 96.6% and specificity of 84.9%.

The estimated threshold for Resistin was 6 ng/ml, with an area under the curve of 1, indicating perfect diagnostic value. The sensitivity of the test was 96.6%, and the specificity was 100%.

Table 1 Characteristics of the population

	Obese with MS	Controls	p
Age (years)	49.26±11.22	49.17±11.51	0.96
WC (cm)	105.48±6.63	76.27±3.25	0.0001
BMI (Kg/m ²)	30.62±2.07	22.75±1.24	0.0001
Systolic blood pressure (mmHg)	141.38±9.68	121.42±4.53	0.0001
Diastolic blood pressure (mmHg)	86.96±3.85	77.17±3.18	0.0001
Fasting glycemia (g/l)	1.27±1.53	0.94±0.03	0.0001
HDL-C (mmol/l)	1±0.27	1.18±0.12	0.0001
LDL-C (mmol/l)	3.48±0.62	2.63±0.83	0.0001
CT (mmol/l)	6.5±0.85	4.39±0.86	0.0001
TG (mmol/l)	2.03±0.41	0.92±0.15	0.0001
Ghrelin (pg/ml)	25.45±7.58	52.47±13.72	0.0001
Resistin (ng/ml)	9.2±2.23	3.14±0.85	0.0001
Insulin (μU/l)	12.4±3.82	5.01±1.12	0.0001

Whereas, Table 1 demonstrates the comparison between the mean levels of ghrelin, resistin and insulin in obesities and controls. Differences among means level of hormones across groups were compared as shown in Table 2 and fig 1 and 2.

Table 2 Association between anthropometric parameters and ghrelin, resistin and insulin in obese patients with metabolic syndrome

Groups	Parameters	Correlation	Ghrelin	Resistin	Insulin
Obese with MS	WC	r	-0,370	0,785	0,446
		p	0,004	0,0001	0,0001
	IMC	r	-0,356	0,742	0,331
		p	0,006	0,0001	0,011
Controls	WC	r	-0,360	0,604	0,469
		p	0,008	0,0001	0,0001
	IMC	r	-0,377	0,715	0,685
		p	0,005	0,0001	0,0001

In the "Obese with MS" group, there is a moderately strong negative correlation between WC and Ghrelin levels, indicating that as waist circumference increases, Ghrelin levels tend to decrease. Conversely, there is a strong positive correlation between WC and Resistin levels, suggesting that as waist circumference increases, Resistin levels increase as well. Similar associations are observed when considering Body Mass Index (IMC) within this group.

In the "Controls" group, the relationships between parameters show some parallels with the "Obese with MS" group. There are significant negative correlations between WC and Ghrelin levels as well as strong positive correlations between WC and Resistin levels, mirroring the trends observed in the obese group. Similarly, IMC exhibits a negative correlation with Ghrelin levels and a positive correlation with Resistin levels. Furthermore, in both groups, there are strong positive correlations between WC and Insulin levels ($r = 0.469$ in the "Controls" group and $r = 0.685$ in the "Obese with MS" group), suggesting a connection between central adiposity (indicated by WC) and insulin resistance.

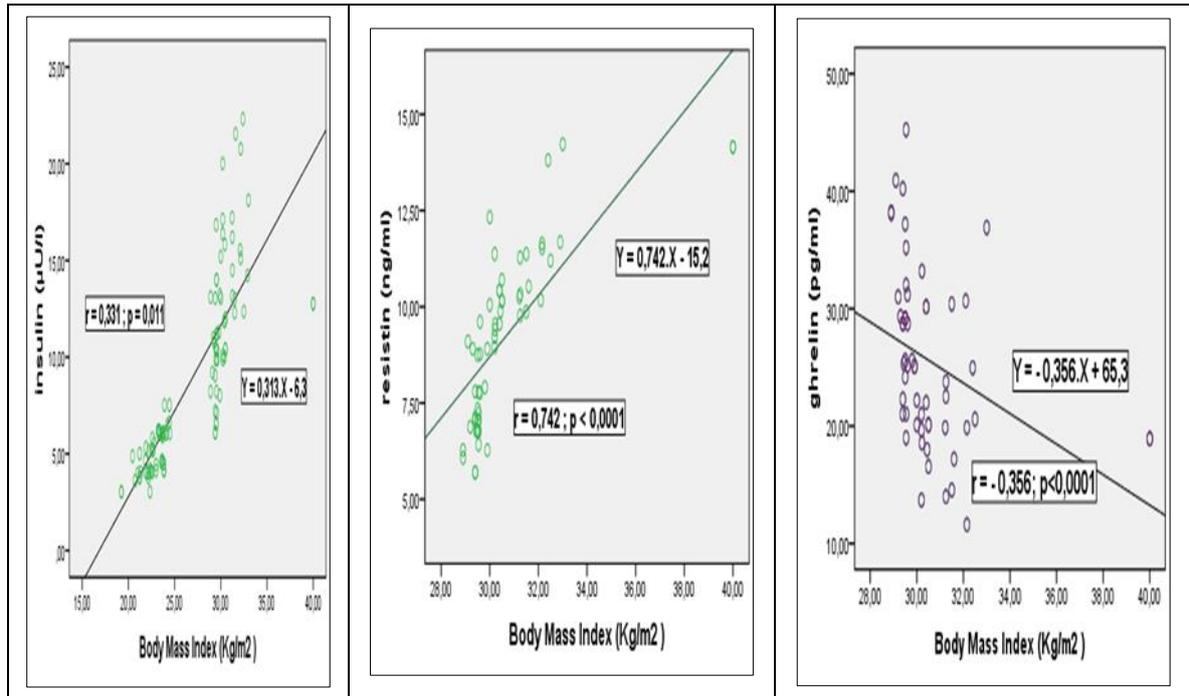


Figure 1 Correlation curve of ghrelin, resistin, and insulin as a function of BMI in obese men

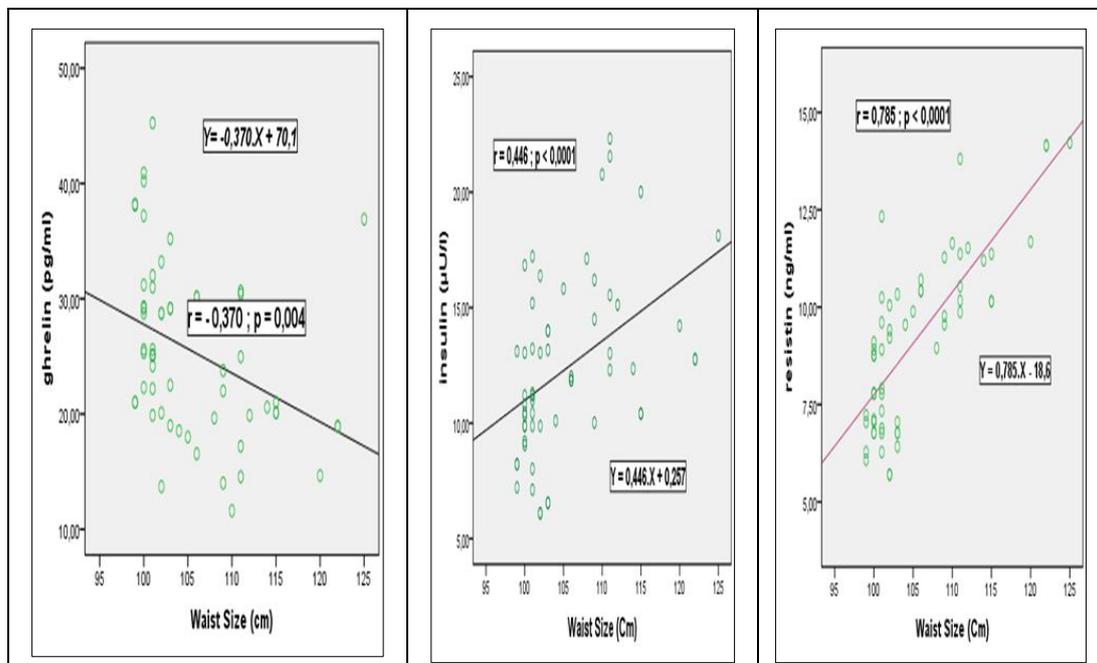


Figure 2 Correlation curve of ghrelin, resistin, and insulin as a function of WC in obese men

Table 3 presents the correlation coefficients between the studied hormones when each was compared against another in all groups. All six pairs were found to be significant.

In the "Obese with Metabolic Syndrome" group, the analysis reveals that Insulin levels exhibit a moderately negative correlation with Ghrelin levels, implying that higher insulin levels are associated with lower ghrelin levels. Conversely, there is a strong positive correlation between Insulin and Resistin levels. Furthermore, Ghrelin levels show a moderate negative correlation with Resistin levels, suggesting that as ghrelin levels decrease, resistin levels tend to increase. Similarly, in the "Controls" group, the correlations follow similar patterns.

Table 3 Analysis of Insulin, Ghrelin, and Resistin Levels in Obese Individuals with Metabolic Syndrome and Controls

	Pair	r	p
Obese with MS	insulin Vs Ghrelin	-0,417	0,001
	Insulin Vs Resistin	0,612	0,0001
	Ghrelin Vs Resistin	-0,445	0,0001
Controls	insulin Vs Ghrelin	-0,614	0,0001
	Insulin Vs Resistin	0,814	0,0001
	Ghrelin Vs Resistin	-0,561	0,0001

4. Discussion

The present study indicated that the levels of insulin, resistin, and ghrelin are higher in obese subjects when compared with lean subjects. These results demonstrate a positive correlation with obesity and highlight an important link between obesity and related metabolic syndrome. Our study revealed that plasma levels of insulin and resistin were significantly higher in the group of obese men with metabolic syndrome. In contrast, ghrelin levels were significantly lower in this group compared to the control group.

Obesity, insulin resistance, and the secretion of resistin by adipose tissue are intricately linked [19]. It is noteworthy that an excessive amount of resistin is among the cytokines that define the metabolic health status linked to obesity [20], and serum resistin concentrations are directly linked to inflammatory markers [21]. Furthermore, increased resistin levels are associated with decreased adipokine levels, which in turn counteract the protective actions of adiponectin, thereby fostering inflammation and contributing to conditions like Metabolic Syndrome [22].

Our study showed a significant positive correlation between **resistin and anthropometric parameters**. These results are in line with those found in a 2019 study conducted in Malaysia in a group of obese men with metabolic syndrome [23]. Another study in India in 2019 showed a relationship between resistin polymorphism and its degree of correlation with BMI [24]. The results suggest that the RETN -420C/G polymorphism is strongly associated with high levels of resistin and an increase in BMI [24]. Furthermore, diet and physical exercise decrease the level of resistin, which is usually accompanied by a reduction in BMI and body fat mass [25].

Our results showed a negative correlation between **BMI, WC and ghrelin** in both the obese men with MS and the control group. In fact, plasma ghrelin levels are inversely proportional to body mass index (BMI) and percentage of body fat [26–28]. Other studies have also confirmed that ghrelin levels are negatively correlated with BMI and insulin resistance [29]. As in other studies, low levels of ghrelin have been reported in subjects with morbid obesity, with levels being negatively associated with BMI, weight, and waist and hip circumferences [30].

Hence, clinical studies conducted in humans indicate that ghrelin serves as a valuable marker of nutritional status, as plasma hormone levels exhibit oscillations in opposing directions among individuals with obesity. Ghrelin, often referred to as the "hunger hormone," plays a crucial role in regulating appetite and energy balance. Its levels tend to rise before meals, signaling hunger, and decrease after eating. In individuals with obesity, the dynamics of ghrelin secretion may be altered. They might experience lower fasting ghrelin levels and reduced post-meal suppression compared to lean individuals. These alterations in ghrelin levels can be indicative of disruptions in hunger and satiety signals, which are fundamental aspects of nutritional status. Therefore, monitoring ghrelin levels can provide valuable insights into the appetite-related aspects of an individual's nutritional status, particularly in the context of obesity and its associated metabolic changes [31]. However, the study of ghrelin has several limitations. The absence of normalization in the measurement of ghrelin levels in terms of sampling time, sampling method, follow-up period, sample storage, and radioimmunoassay used could pose a problem of precision and reproducibility of results [28].

This study also showed a significant negative correlation **between ghrelin and resistin** in obese men with MS and in the control group. This negative correlation was confirmed in the literature [32]. Indeed, according to a molecular mechanism, the administration of resistin to pituitary cells in rats inhibited the binding of ghrelin to its receptor [33].

Similarly, a significant positive correlation between **insulin and resistin** was demonstrated in the group of obese men with MS, as well as in the control group. In human studies, individuals with insulin resistance had higher levels of resistin

than those with normal insulin action [34]. This can be explained by the fact that in humans, resistin is mainly produced by immune cells, especially macrophages, and could play a role in insulin resistance induced by inflammation [35]. These results are confirmed by other studies showing that high levels of resistin induce insulin resistance and exert pro-inflammatory effects. This is why it has been demonstrated that resistin plays a central role in various metabolic, inflammatory, and autoimmune diseases [36], and that its excessive production associated with insufficient adiponectin production represents a key mechanism of insulin resistance and metabolic and cardiovascular comorbidities observed in abdominal obesity. Hence, resistin has the potential to serve as a marker for insulin resistance [25]. Nonetheless, a recent study has revealed that resistin levels can exhibit both negative and positive correlations with insulin levels, depending on an individual's resistin genotype [37]. Furthermore, some research studies have not demonstrated a clear correlation between resistin levels and the degree of obesity or insulin resistance. It is important to note that the localization of resistin in human macrophages and its potential interactions with adipocytes are subjects of extensive ongoing research [38].

On the other hand, our study showed a negative correlation between **insulin and ghrelin** in both the group of obese men with MS and the control group. Plasma levels of ghrelin and insulin have been shown to be negatively correlated with reciprocal variations [14,34]. This relationship can be explained by the inhibition of insulin secretion by ghrelin, which has been demonstrated [39]. It has also been shown that insulin infusion in humans decreases ghrelin concentrations [14]. The mechanisms through which ghrelin suppresses insulin are likely to involve direct effects on pancreatic islets. In support of this idea, ghrelin has been shown to inhibit insulin secretion from isolated rodent pancreas and freshly isolated or cultured pancreatic islets. Conversely, the use of pharmacological agents to block the actions of GHSR (ghrelin receptor) has been demonstrated to enhance insulin release [40]. Pharmacological inhibition of ghrelin signaling could have therapeutic value in improving insulin resistance and type 2 diabetes [41].

4.1. Strengths and Limitations

This study presents several strengths that enhance its significance. Firstly, it conducts a comprehensive hormonal analysis by examining insulin, ghrelin, and resistin levels, shedding light on their interplay within both obese individuals with metabolic syndrome and a control group. Additionally, the study reports statistically significant correlations, lending robustness to the findings and underscoring the relevance of these hormonal relationships.

The present study has several limitations, including a relatively small sample size, which although within the calculated size, a larger sample size would have been desirable. However, due to the costs associated with multiplex technology, this was not feasible.

5. Conclusion

In summary, this study found that obese individuals with metabolic syndrome exhibited elevated levels of insulin, resistin, and lower ghrelin levels compared to lean controls. These hormonal changes reflect the close link between obesity and metabolic syndrome. Resistin was strongly associated with obesity and inflammation, while ghrelin showed a negative correlation with body weight and could serve as a marker of nutritional status. Monitoring these hormone levels could offer insights into metabolic health, particularly in obese individuals, and may have therapeutic implications for managing obesity and its related conditions.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declare that no conflict of interest exists for this work.

Statement of ethical approval

The study has received the ethical approval of the ethical committee of the national institute of nutrition of Tunis

Statement of informed consent

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

Author contributions

- Rym Ben Othman: Conceptualization, Data Collection, Data Analysis, Writing - Original Draft
- Ghofrane Sellami: Data Collection, Data Analysis, Writing - Original Draft
- Inchirah Karmous: Data Collection, Data Analysis
- Wahiba Douki: Data Collection, Writing - Review & Editing
- Faika Ben Mami: Data Collection, Data Analysis
- Olfa Berriche: Data Analysis, Writing - Review & Editing
- Kamel Ben-Mahrez: Conceptualization, Supervision, Writing - Review & Editing
- Fethi Ben Slama: Conceptualization, Supervision, Writing - Review & Editing

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