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ORIGINAL ARTICLE

Influences of Dysregulated Resistin mRNA and Its Plasma Protein Levels on the Risk of Incident Type 2 Diabetes in Subjects with Obesity

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ABSTRACT

Background: Resistin is an adipokine involved in developing obesity, insulin resistance, and comorbidities, such as type 2 diabetes mellites (T2DM). The present study aimed to estimate the circulating levels of Resistin mRNA and its plasma protein in patients with obesity in children vs adults and to correlate their levels with metabolic dysfunction parameters particularly, T2DM.

Methods: This study included 80 subjects: 30 healthy subjects as the control group and 50 obese patients. The enrolled patients were classified into a pediatric group (n=25, age 8-18 years) and an adult group (n=25, age >18). Circulating resistin was measured by ELISA,and resistin mRNA was determined by real-time PCR.

Results: Among the obese pediatric group, plasma resistin and its mRNA levels were significantly higher in the T2DM obese group(15.4±1.26 and 2.51±0.31, respectively) in comparison to other group (9.9±2.17, and 1.6±0.43, respectively), P <0 .001.Additionally, in the obese adult group, plasma resistin and its mRNA levels were significantly higher in the T2DM obese group (37.2±3.8and 6.54±0.56, respectively) in comparison to other group (20.4±2.287, and 4.34±0.263, respectively), P <0 .001. Interestingly, Age, BMI, FPG,2 HPP, FSI, HOMA-IR, HbA1c, and LDL values were significantly positively correlated with plasma resistin and its mRNA values.

Conclusions: Plasma resistin and its mRNA were elevated in obese subjects, especially those with T2DM.In addition, plasma resistin and its mRNA values were significantly positively correlated with metabolic dysfunction parameters.

Keywords: Obesity; Type 2 diabetes mellitus; resistin; children; Metabolic dysfunction.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common metabolic disease, its prevalence is increasing worldwide. Gathering evidence indicates the essential role of the obesity epidemic in raising the prevalence of T2DM [1]. In previous reports, authors have stated that obesity is involved in the etiopathogenesis of DM, particularly T2DM and its progression [2].

It has been hypothesized that obesity is a state of immune dysregulation [3], and adipose tissue (AT) dysfunction [4] is characterized by altered adipokines secretion by adipocytes and an increase of insulin resistance (IR) [5]. During obesity excess fat

accumulates around organs, for example, the pancreas, which leads to an adequate amount of insulin secretion, which leads to the progression of T2DM [6].

Recent researchers conducted interesting studies to explore the pandemic of obesity and its comorbidities. It seems reasonable that IR and adipokine dysregulation are the main pathogenetic factors [7]. Taken together, these findings implied that obesity etiology is complex and this needed further exploration [8].

Resistin is a polypeptide adipokine encoded by the RETN gene, intriguing research demonstrated that resistin is substantially expressed in the immune system [9]. Furthermore, it has a valuable role in metabolic syndrome susceptibility [10].Despite the pandemic of obesity and its comorbidity such as T2DM, there is still a lack of early and sensitive biomarkers of T2DM [11]. Consequently, the discovery of precision predictors of T2DM is needed. Therefore, we conducted the current research to investigate resistin mRNA and its plasma protein in obese children versus obese adults and to correlate their levels with metabolic dysfunction aspects particularly, T2DM.

METHODS

This case-controlled study conducted 50 patients without prior T2DM history and 30 healthy controls. The diagnosis of obesity is based on BMI; in children, BMI was equal to or above the 95th percentile, while in adults BMI >30. The flowchart of this study is presented in supplementary figure 1. We explained the research aim and technique to all participants and received informed consent before the study began. Investigations were performed according to operating methods in Zagazig University Hospital. HOMA-IR was calculated [12] and the cutoff in children according to previous studies [13]. Concerning the assessment of plasma resistin, the level was measured by ELISA.

Ethics approval and consent to participate: Written notified consent was obtained from all studied subjects, and the research was accepted by the research ethical committee of the Faculty of Medicine, Zagazig University, (IRB≠, 461/23-JUNE-2024).

RNA Isolation and qRT-PCR:Total RNA was separated from the PBMCs with TRIzol reagent (Invitrogen, California, USA) matching with the manufacturer's directions. The primer sequences are shown in. GAPDH worked as a reference. The primers were as follows.

Gene	Forward (5'-3:)	Reverse primer (5'-3')
Resistin mRNA	5′-TCTAGCAAGACCCTGTGC-3′	5′-CAGGTTTATTTCCAGCTCC-3′
GAPDH	5′-TGGGGAAGGTGAAGGTCGGA-3′	5′-GGGATCTCGCTGCTCGAAGA-3′

STATISTICAL ANALYSIS

This study's results were done using SPSS version 26 (Version 26.0. Armonk, NY: IBM Corp). The researchers chose to use the t-test, the Mann-Whitney U Test. Also, we applied the following tests to analyze the results, Pearson correlation, linear regression test, and the receiver operating characteristic (ROC) curve analysis. P-value < 0.05 was considered significant.

RESULTS

Of the 120 enrolled subjects we initially identified for inclusion, 80 subjects and 40 were excluded for the following reasons: 29 met the exclusion criteria as mentioned in the flowchart of the study, figure 1and 11 subjects declined to participate in the study. We conducted 30 health controls (15 children and 15 adults and 50 patients with obesity. To prevent any effects of sex and age variations on gene expression we match age and sex between both case and control groups. The clinical and biochemical characteristics of the studied groups are presented in Table 1. As expected, there were significant differences between control groups and obese groups regards dysmetabolic parameters, P<0.001*.

According to our research findings, among 25 obese children, only 3 patients had newly discovered T2DM and 6 patients out of 25 adult obese patients had newly discovered T2DM as shown in table 2. In the current research we aimed to assess the difference between the obese pediatric group and the obese adult group as regards metabolic component parameters as well as diabetic profile parameters. Thus, we compared the non-diabetic obese group and the diabetic group in Table 2. We detected that among the pediatric group, BMI, FPG,2 HPP, FSI, HOMA-IR, and HbA1c were significantly higher in the diabetic group compared to the non-diabetic group, P< 0.001*.

Regarding the adult obese group, the values of the following parameters: FPG,2 HPP, FSI, HOMA-IR, and HbA1c (%), were significantly higher in the

diabetic group compared to the non-diabetic group, P<0.001*.

The most important findings in the current research are the results of plasma Resistin and Resistin mRNA testing in the studied groups. Firstly, we compared both the control and case groups as shown in Table 1 and we detected significantly higher values of plasma Resistin in the obese group (17.6±8.9) compared to the control group (5.34±1.09). Table 1, P <0 .001.Concerning Resistin mRNA levels, we detected significantly higher values of plasma Resistin in the obese group (3.3±1.73) compared to the control group (0.8±0.17). Table 1, P <0 .001.

For further evaluation of the impact of age and the presence of T2DM, we did further analysis of plasma Resistin and its mRNA levels in the subgroups and we detected that in the obese pediatric group, plasma Resistin and its mRNA levels were significantly higher in T2DM obese group(15.4±1.26 and 2.51±0.31, respectively) compared to non-diabetic obese group (9.9±2.17, and 1.6±0.43, respectively) table 2, P <0 .001. Additionally, in the obese adult group, plasma Resistin and its mRNA levels were significantly higher in the T2DM obese group (37.2±3.8and 6.54±0.56, respectively) compared to the non-diabetic obese group (20.4±2.287, and 4.34±0.263, respectively) table 2, P <0 .001. Interestingly, adult groups had significantly higher values of plasma Resistin and Resistin mRNA levels compared to the pediatric group Table 2, P <0 .001.

We have confirmed that by applying Pearson correlation, Age, BMI, FPG,2 HPP, FSI, HOMA-IR, HbA1c, and LDL values were significantly positively correlated with plasma Resistin and its mRNA values in obese groups as described in Table 3, P <0 .001.On the other hand, HDL values were significantly negative correlated with plasma Resistin and Resistin mRNA values, table 3, P <0 .001.

The results of the linear regression test to investigate the independent factors that were associated with plasma Resistin in the prediction of T2DM was that only age, FPG,2 HPP, and HbA1c were the independent factors that were associated with plasma Resistin, table 4, P <0 .001. Regarding Resistin mRNA, the independent factors that were associated with it were age and FBG, table 4, P <0 .001.

To explore the efficiency of plasma Resistin and Resistin mRNA in predicting obesity among the studied group. We applied ROC curve analysis, and the results revealed that AUC of plasma Resistin = 0.987(95% CI=0.970-1.000), a sensitivity of 96%, and a specificity of 87.7% at a cutoff of 6.3 (Fig. 2a), P <0 .001.While the AUC of Resistin mRNA = AUC=0.986(95% CI=0.968-1.000), a sensitivity of 92%, and specificity of 99% at a cutoff of 0.9 (Fig. 2a), P <0 .001.

To investigate the effectiveness of plasma Resistin level in differentiating between pediatric and adult obese patients, ROC curve outcomes showing that AUC = =0.970(95% CI=0.912-1.000), sensitivity of 96.7% and specificity of 85 % at a cutoff of 11.8 (Fig. 2b, P <0 .001. Enigmatically, the power of plasma Resistin level as a diagnostic marker of T2DM among obese groups had an AUC of 0.820 (95% CI=0.668-0.972) at a cut-off value =15.3 ng/mL with 80% sensitivity and 53% specificity (Fig. 2c), P <0 .001. However, the AUC of Resistin mRNA = 0.794 (95% CI=0.624-0.964), a sensitivity of 80%, and specificity of 50% at a cutoff of 2.7 (Fig. 2c), P <0 .001.

Table 1: Clinical and Biochemical Characteristics of the Studied Groups

Variable	Control (n = 30)	Obese (n = 50)	P-value
	Mean ± SD	Mean ± SD	
Age (/years)	20.9±13.12	19.8±9.57	0.668
Sex: Male /Female	17/13	29/21	0.907
SBP (mm Hg)	123.1± 3.14	129.6± 7.1	<0.001*
DBP (mm Hg)	77.3±5.13	87.5±4.1	<0.001*
BMI (kg/m^2)	23.9±1.34	37.9±3.69	<0.001*
FPG (mg/dL)	86.06± 8.4	103.4± 30.9	<0.001*
2 HPP (mg/dL)	123.06±8.41	140.4± 30.9	<0.001*
FSI (µU/mL)	6.8±1.36	25.3±8.66	<0.001*

Variable	Control (n = 30)	Obese (n = 50)	P-value
	Mean ± SD	Mean ± SD	
HOMA-IR	1.4±0.338	5.04±1.1	<0.001*
HbA1c (%)	4.3±0.224	6.2±1.07	<0.001*
TC (mg/dL)	184.6± 16.06	197.5± 13.16	<0.001*
TG (mg/dL)	195.6± 16.06	208.5± 13.16	<0.001*
HDL c (mg/dL)	49.2±7.19	42.3±6.025	<0.001*
LDL c (mg/dL)	158.4± 27.22	186.6± 19.64	<0.001*
Plasma Resistin (ng/ml)	5.34±1.09	17.6±8.9	
Resistin mRNA relative expression level	0.8±0.17	3.3±1.73	

SBP; Systolic blood pressure, DBP; Diastolic blood pressure , 2 HPP ;2 h post prandial , BMI, body mass index; FSI, fasting serum insulin; FPG, fasting plasma glucose ; HOMA-IR, homeostasis model assessments of insulin resistance; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein-cholesterol HbA1c,hemoglobin A1c.Obesity in children defined according to WHO as BMI z-score >2SD.*Significant difference (P ≤ 0.05).

Table 2: Clinical and Biochemical Characteristics of the Children Vs Adult Studied Groups

Variable	Obese subjects (n=50)						
	Pediatric group N= 25			Adult group N=25			P3 value
	Non - diabetic N=22	T2DM N=3	P1value	Non -diabetic N=19	T2DM N=6	P2 value	
Age (/years)	11.07±1.76	13.7±2.20	0.355	27.8±6.53	29.1±5.6	0.624	<0.001*
Sex: Male /Female	15/7	2/1	0.957	9/10	3/3	0.915	0.155
SBP (mm Hg)	129.7±7.5	132.2±4.7	0.443	128.7± 7.8	130.3±4.1	0.586	0.570
DBP (mm Hg)	87.8±3.81	89.5±1.73	0.512	86.9±4.67	86.6±4.7	0.896	0.336
BMI (kg/m^2)	40.1±3.49	36.8±0.92	<0.001*	35.7±3.5	37.6±1.1	0.152	<0.001*
FPG (mg/dL)	88.9±6.8	137.2±31.8	<0.001*	90.8±8.96	171.8±17.2	<0.001*	0.117
2 HPP (mg/dL)	125.9± 6.8	174.2±31.8	<0.001*	127.8±8.9	208.8±17.2	<0.001*	0.053
FSI (µU/mL)	22.1±2.7	23.1±4.8	<0.001*	23.7±7.68	43.5±6.3	<0.001*	0.129
HOMA-IR	4.8±0.81	5.1±0.66	<0.001*	5.2±1.34	5.23±0.38	<0.001*	<0.001*
HbA1c (%)	5.1±0.47	7.2±1.9	<0.001*	5.4±0.14	8.5±1.83	<0.001*	<0.001*
TC (mg/dL)	196.04±13.8	205.7±7.2	0.193	194.6±13.61	206.6±6.3	0.063	0.992
TG (mg/dL)	207.04±13.8	216.7±7.2	0.752	205.6± 13.6	217.6± 6.3	0.063	0.992
HDL c (mg/dL)	42.7±6.5	39.2±0.95	0.318	43.2±6.7	40.1±1.4	0.252	0.897
LDL c (mg/dL)	185.1±21.3	194.2±6.9	0.419	184.1±21.9	195.1±5.9	0.247	0.995
Plasma Resistin	9.9±2.17	15.4±1.26	<0.001*	20.4±2.287	37.2±3.8	<0.001*	<0.001*
Resistin	1.6±0.43	2.51±0.31	<0.001*	4.34±0.263	6.54±0.56	<0.001*	<0.001*

SBP; Systolic blood pressure, DBP; Diastolic blood pressure , 2 HPP ;2 h post prandial , BMI, body mass index; FSI, fasting serum insulin; FPG, fasting plasma glucose ; HOMA-IR, homeostasis model assessments of insulin resistance; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein-

cholesterol HbA1c,hemoglobin A1c.Obesity in children defined according to WHO as BMI z-score >2SD.*Significant difference (P ≤ 0.05)
P1: compared between diabetic and non -diabetic obese children
P2: compared between diabetic and non -diabetic obese adults
P3: compared between obese adults and children

Table 3: Pearson Correlation Coefficient Between Resistin Plasma (Ng/Ml) and mRNA Levels with Clinical and Metabolic Characteristics of Studied Subjects.

Variables	Plasma Resistin		Resistin mRNA	
	r	P	r	P
Age	0.674	<0.001*	0.788	<0.001*
SBP	0.103	0.475	0.059	.683
DBP	0.109	0.450	0.203	0.158
BMI	0.344	<0.001*	0.286	<0.05*
FPG	0.704	<0.001*	0.543	<0.001*
2 HPP	0.711	<0.001*	0.511	<0.001*
FSI	0.601	<0.001*	0.581	<0.001*
HOMA-IR	0.312	<0.001*	0.558	<0.001*
HbA1c	0.742	<0.001*	0.613	<0.001*
TC	0.258	0.070	0.085	0.557
TG	0.102	0.476	0.063	0.665
HDL	-0.289	<0.05*	-0.297	<0.05*
LDL	0.316	<0.05*	0.428	<0.05*

***Statistically significant** (P < 0.05).

Table 4: Linear Regression Analyses to assess Independent Variables against Resistin Serum and mRNA Levels (Dependent Variable) Among Obese Patients.

Model		Unstandardized Coefficients		Standardized Coefficients	t	P value	95% C.I.	
		B	SE	Beta			Lower Bound	Upper Bound
Plasma Resistin	**Constant**	14.128	27.272		0.518	0.607	-40.909	69.164
	Age	-0.657	0.248	-0.270	-2.649	<0.05*	-1.158	-0.157
	BMI	-0.040	0.064	-0.139	-0.632	0.531	-0.170	0.089
	FPG	0.630	0.173	0.607	3.649	<0.001*	0.281	0.978
	2 HPP	3.365	1.649	0.401	2.041	<0.05*	0.038	6.693
	FSI	0.107	0.105	0.156	1.013	0.317	-0.106	0.319
	HOMA-IR	-0.205	0.227	-0.137	-0.902	0.372	-0.664	0.254
	HbA1c	-3.229	1.177	-0.362	-2.743	<0.01*	-5.605	-0.854
Resistin mRNA	**Constant**	0.868	6.553		0.132	0.895	-12.356	14.092
	Age	-0.149	0.060	-0.318	-2.496	<0.05*	-0.269	00-.029
	BMI	-0.009	0.015	-0.155	-.565	0.575	-0.040	.022
	FPG	0.099	0.041	0.495	2.389	<0.05*	0.015	0.183
	2 HPP	0.687	0.396	0.425	1.735	0.090	-0.112	1.487
	FSI	0.017	0.025	0.131	0.681	0.499	-0.034	0.068
	HOMA-IR	0.040	0.055	0.139	0.731	0.451	-0.070	0.150
	HbA1c	-0.539	0.283	-0.314	-1.904	0.064	-1.109	0.032

***Statistically significant** ($P < 0.05$).

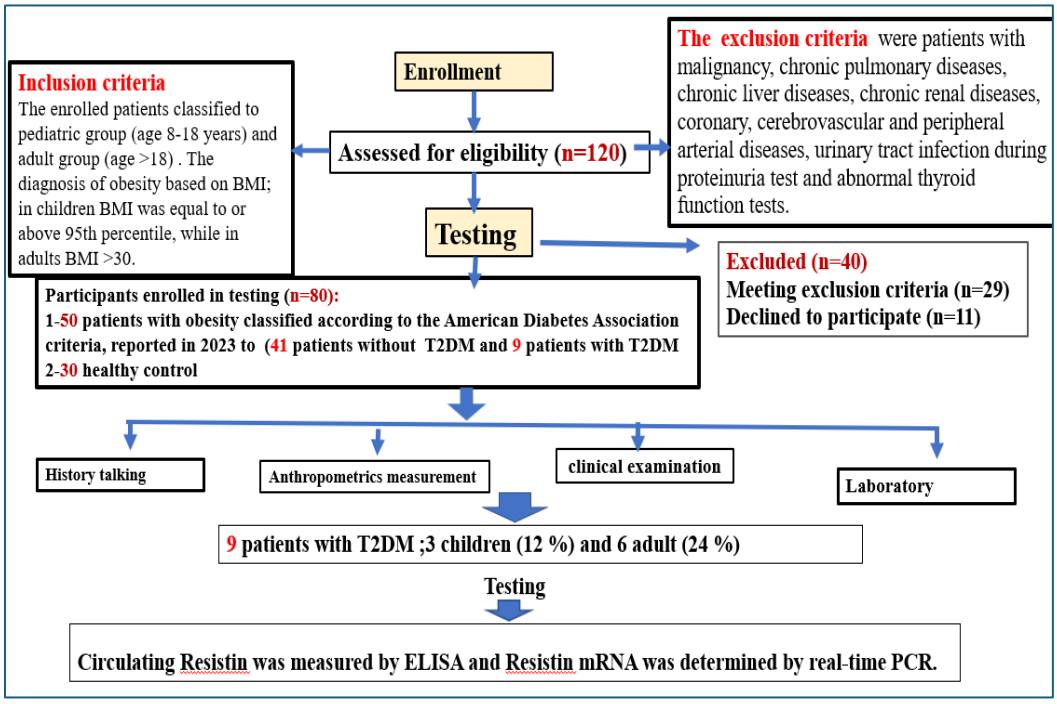

Figure 1: Flowchart of the study

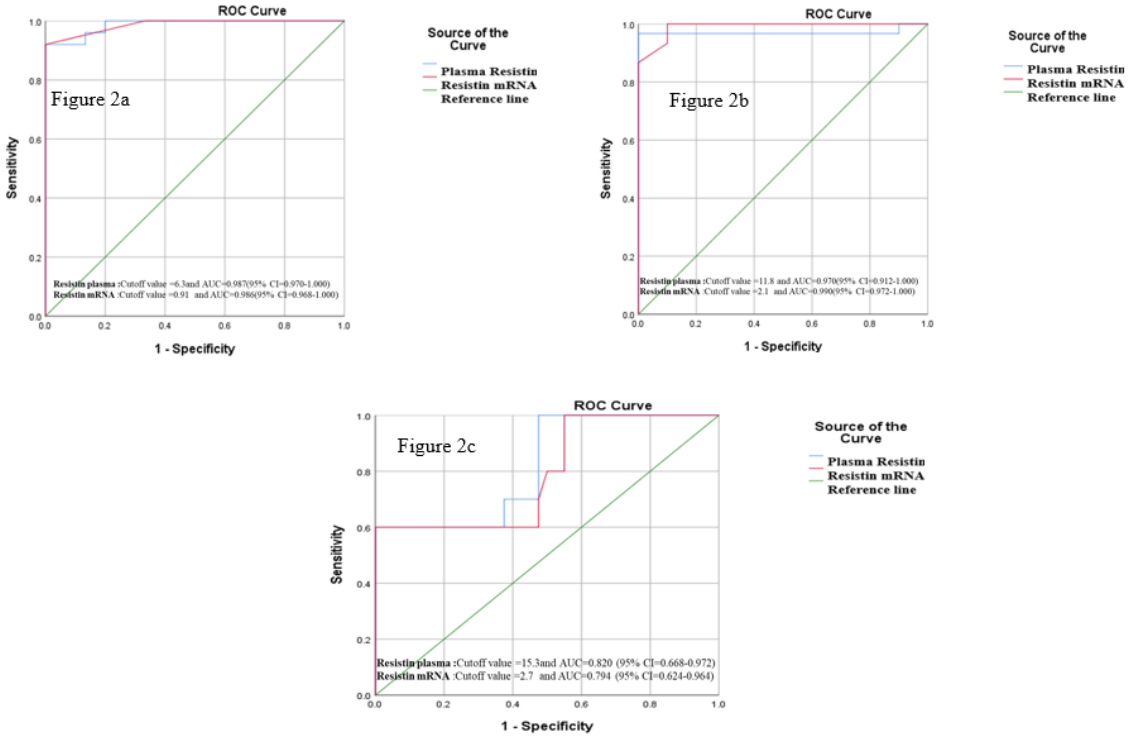

Figure 2: ROC curve analysis to determine the diagnostic power of Plasma Resistin (ng/ml) and Resistin mRNA relative expression levels in the differentiation between control and obese pediatric group(2a),obese pediatrics and obese adults (2b) and obese diabetic and non-diabetic group

DISCUSSION

We designed this research to investigate the levels of resistin mRNA and its plasma protein in obese children versus obese adults and to correlate their levels with metabolic dysfunction elements particularly, T2DM.

Despite the ongoing progress in screening diabetes, there is still a need for extensive research into the molecular mechanisms involved in the appearance and evolution of obesity-associated T2DM. The results of the current study detected that 3 out of 25 obese children (12%) had new onset T2DM. However, in adult obese subjects, 6 out of 25 obese children (24%) had new onset T2DM.

It is well known that pediatric obesity has arisen as an extensive public health alarm, as more than 30% of children worldwide are overweight and obese [14]. Intriguingly, childhood obesity progresses and is associated with many co-morbidities [15].

To investigate the potential mechanism underlying obesity and its comorbid metabolic disorder with age, we compared the obese pediatric group and obese adult groups. Additionally, for further evaluation of obesity's influence on diabetes and metabolic dysfunction development, we compared the non-diabetic obese group with the diabetic group. We found that among the pediatric groups, BMI, FPG,2 HPP, FSI, HOMA-IR, and HbA1c (%), were significantly higher in the diabetic group compared to the non-diabetic group, P< 0.001*. Concerning the adult obese group, the values of the following parameters: FPG,2 HPP, FSI, HOMA-IR, and HbA1c (%), were significantly higher in the diabetic group compared to the non-diabetic group, P<0.001*.

Researchers from Abu Dhabi detected those obese children had higher insulin resistance. Furthermore, 7% of the enrolled children had diabetes, 8.2% had impaired glucose tolerance (IGT), and 18.1% had impaired fasting glucose (IFG) [16]. The higher prevalence observed in this study compared to our results could contribute to the large sample size, the difference in the inclusion criteria in the Abu Dhabi study, and the difference in the genetic tendency and susceptibility of T2DM.

On the other hand, the results of an interesting study conducted in Southern Italy to assess the prevalence of IR and IGT in obese children and adolescents detected that more than 40% of the enrolled participants had IR. [17]. These contradictory results seem to be due to the difference in the study population and the difference in the anthropometric and laboratory cutoff values between these studies.

Our work demonstrates significantly higher values of plasma resistin and its mRNA levels in the case group in comparison to the healthy group. Based on important studies [18] and the results reported here, we suggest obesity is connected to adipokine aberrations. Resistin is a mediator of obesity, and T2DM [19]. Similarly, these results are consistent with the results of our earlier study [20]. In agreement with these results, the study of Steppan et al, detected that resistin levels were higher in obese subjects compared to normal-weight individuals [21]. Another interesting study conducted by Benomar et al revealed higher resistin levels contributed to insulin resistance through CD284 [22]. Interestingly, many reports showed that obesity is contributed to DM through immune dysregulations which are mediated by adipokines such as resistin [23-25]. Indeed, there is insufficient research on the role of gender in the pathogenesis of IR in children [26].

Taking these data together, we, therefore, assume that among the obese pediatric group, plasma resistin and its mRNA levels were significantly higher in the T2DM subjects in comparison to the other group, P <0 .001. Furthermore, in the obese adult group, plasma resistin and its mRNA levels were significantly higher in the T2DM obese subjects in comparison to the other group, P <0 .001. Interestingly, age, BMI, FPG,2 HPP, FSI, HOMA-IR, HbA1c, and LDL values were significantly positively correlated with plasma resistin and its mRNA values. To discover the independent factors that were associated with plasma resistin and its mRNA values we operated a linear regression test, and our results exhibited that age, FPG,2 HPP, and, HbA1c were the independent factors associated with plasma resistin. Nevertheless, age and FBG were independently associated with resistin mRNA.

In agreement with this research findings, Osawa et al. [27] underlined that mutation of the resistin gene is correlated with IR in T2DM. However, in contrast to our data, a variety of previous studies did not find correlations between resistin and IR in children and adults [28-31]. The reason for the contradiction in the findings can be due to the difference in the anthropometric and laboratory cutoff values between these studies.

Eventually, we verified whether plasma resistin and its mRNA could be used as strong biomarkers of obesity by applying the ROC curve. Our interesting

findings detected that plasma resistin and its mRNA had strong sensitivity and specificity in predicting obesity. Furthermore, plasma resistin and its mRNA had high sensitivity and specificity for differentiation between pediatric and adult obese patients. The power of plasma resistin and its mRNA as diagnostic markers of T2DM among obese groups was lower than the previous one.

STUDY LIMITATIONS & STRENGTHS

The small sample size and all participants from a single center are the study's limitations. However, our study is the first to explore Resistin mRNA and its plasma protein in patients with obesity in children vs adults and to correlate their levels with metabolic dysfunction parameters particularly, T2DM. There is a need for further large-scale multicenter longitudinal studies to confirm our findings in this vulnerable population.

CONCLUSIONS

Current evidence showed that plasma resistin and its mRNA were elevated in obese subjects, especially those with T2DM. In addition, plasma resistin and its mRNA values were significantly positively correlated with metabolic dysfunction parameters. Interestingly, plasma resistin level at cut-off value =15.3ng ml and resistin mRNA at cut-off value=2.7 could be a marker for early detection of T2DM in obese subjects with very high sensitivity and specificity Thus, they may be proposed as novel markers to predict T2DM susceptibility.

Conflict of Interest: None.

Financial Disclosures: None.

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