



EVALUATION OF ADIPOSITIVITY PHENOTYPES: LIPID ACCUMULATION PRODUCT INDEX, VISCERAL ADIPOSE INDEX AND BODY ROUNDNESS INDEX AS PREDICTOR MARKERS FOR METABOLIC SYNDROME DEVELOPMENT IN TYPE 2 DIABETES MELLITUS

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Visceral obesity is strongly associated with Metabolic syndrome (MetS) and increases the risk of cardiovascular disease in type II diabetes mellitus (T2DM). We aimed in this study to determine the best discriminator of obesity indexes to predict the occurrence of MetS in T2DM patients. The present study was conducted on 129 T2DM patients (Mets+: 70.54% & MetS-: 29.45%) during the period from 2020 to 2021. MetS+ patients have higher HbA1C, TG, and obesity indexes (BMI, WC, BF%, BRI, VAI, LAP) compared with MetS- group with a lower HDL-cholesterol in the MetS+ group. The average of BF%, VAI, and LAP increased with increasing the number of MetS components according to NCEP-ATPIII criteria. In addition, the optimal cutoff points for obesity indexes were determined. Therefore, LAP with cutoff: 46.48 (AUC: 0.774, sensitivity: 80.2%, and specificity: 62.5%), VAI with cutoff: 1.73 (AUC: 0.668, sensitivity: 71.4%, and specificity: 54.2%), and BRI with cutoff: 5.22 (AUC: 0.774, sensitivity: 82.4%, and specificity: 58.3%) seemed to be as useful indexes in MetS prediction among T2DM patients.

Keywords: Obesity, LAP, VAI, RBI, and MetS.

INTRODUCTION

The incidence of type 2 Diabetes Mellitus (T2DM) is increasing considerably worldwide; with a rising prevalence in developing countries due probably to lifestyle and aging of the population¹. In 2017, approximately, 451 million adults were estimated with Diabetes according to International Diabetes Federation (IDF) statistics^{1,2}. In Syria, the prevalence of diabetes was 17.8% in females and 16.4% in males according to Global Nutrition Report (GNR) in 2019.

Dysfunction of adipose tissue is considered one of the proposed mechanisms for metabolic complications in T2DM such as dyslipidemia, renal dysfunction, and Metabolic Syndrome (MetS)^{4&5}. Dyslipidemia is a common metabolic abnormality of lipid profile

presented in T2DM with an elevated both Triglyceride (TG) and Low-Density Lipoprotein-Cholesterol (LDL-C) levels, with a decreased level of high-density lipoprotein-Cholesterol (HDL-C).

MetS has more notable increases worldwide; it varies from 8% to 43% in men and from 7% to 56% in women; it is a complex of interrelated risk factors for cardiovascular disease (CD), including dysglycemia, raised blood pressure, dyslipidemia, and obesity (particularly central adiposity) according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) as proposed criteria for the diagnosis of MetS⁶.

Obesity among MetS parameters ranks fifth in the list of causes of mortality worldwide, especially central obesity which is strongly associated with insulin resistance (IR),

CD, and worse metabolic profile in T2DM^{7&8}. Central (abdominal) fat is composed of visceral and subcutaneous adipose tissue; therefore, visceral fat is more strongly correlated with metabolic abnormalities and cardiovascular disease than subcutaneous fat^{9&10}. Visceral adipose tissue provides a microenvironment of low grade- inflammatory by pro-inflammatory cytokines' secretion (IL-6, TNF- α) with a higher rate of lipolysis (increased serum free fatty acids and TG). In addition, it is associated with increased levels of Resistin hormone and decreased levels of Adiponectin hormone. The prevalence of obesity in Syria has reached 24.1% and 38.3% for males and females, respectively according to the report of GNR in 2019 based on BMI index. To evaluate adiposity phenotypes abnormalities, it is clear that traditional obesity indexes such as Body Mass Index (BMI) and Waist Circumference (WC) do not differ between visceral and subcutaneous fat; they cannot effectively distinguish between the fat and muscle¹¹. Recently, previous studies have investigated the relationship between MetS-development and adiposity phenotypes including Lipid Accumulation Product (LAP), Body Fat Percentage (BF%), Visceral Adipose Index (VAI), Body Roundness Index (BRI), as new putative anthropometric indexes associated with MetS in T2DM. In fact, LAP, VAI, and BRI are more important and effective indexes to reflect the degree of lipid accumulation and fat distribution in comparison with WC and BMI which reflect the overall obesity¹¹. In addition, these indexes are easy and less expensive methods in comparison with dual-energy X-ray absorption, computed tomography scans, and magnetic resonance imaging as techniques designed to estimate obesity¹². LAP is an index, which combines waist circumference and triglyceride (TG) that could better measure the degree of visceral fat accumulation^{11&13}, used to detect impaired glucose tolerance and IR among populations with higher risk for diabetes, CD, and mortality in adults¹³. BF% presents the percentage of body fat, which is correlated with insulin sensitivity in the obese population; it combines the measurement of BMI, age, and sex¹⁴.

VAI represents a substitute marker of dysfunction and distribution of adipose tissue and its independent correlation with cardio-

metabolic risk; it combines the measurement of WC, BMI, TG, and HDL-C. Recent studies have determined a close relationship between the use of VAI, IR, and MetS in T2DM^{15&16}. BRI is a useful and simple obesity marker, which considers WC (cm) and height (m) for more understanding of the concepts of obesity, especially central obesity. Thus, adiposity phenotypes could better evaluate the degree of lipid accumulation associated with IR and visceral obesity for MetS in T2DM^{16&17}. In 2009, the criteria proposed by (NCEP-ATP III) for MetS was modified with respect to WC which seemed to vary in different populations as well as in the Asian population¹⁸. In summary, it could be better for men and women to evaluate indexes such as LAP, VAI, and BRI as predictor markers for MetS associated with central obesity in T2DM^{17&18}.

Therefore; we aimed in this study to evaluate adiposity tissue phenotypes (LAP, BRI, WC, and VAI) as visceral-obesity markers in comparison with overall-obesity indexes (BMI and BF%) for the prediction of MetS in T2DM -Syrian patients.

Experimental section

The current study investigated 180 participants, at Tishreen University Hospital (TUH) and the Diabetes Center of Lattakia City, Syria. Demographic data and clinical information of participants were collected using a standardized questionnaire. The study was performed in the period from November 2020 to December 2021.

Ethical Approval

All procedures were approved by the Institutional Board of Tishreen University. The decision involved Ethical Approval (number: 2774). An informed written consent was taken from all participants.

Exclusion criteria

Patients with type 1 diabetes mellitus were excluded in this study.

Study Design

This study included 180 participants: 129 T2DM patients and 51 subjects as healthy controls. MetS was diagnosed according to NCEP-ATPIII criteria with the presence of three of the following¹⁷:-

1. Blood pressure over 130/85 mmHg.
2. FBG \geq 100 mg/dl, or previously diagnosed T2DM.
3. HDL-C <40mg/dl in men and <50 mg/dl in women.
4. TG \geq 150 mg/dl or specific treatment for high TG.
5. WC >88 cm in women, and >102 cm in men.

T2DM patients with MetS were re-classified into three subgroups with increasing severity of MetS according to the number of criteria:-

- **MetS-3:** patients with 3 criteria of NCEP-ATPIII
- **MetS-4:** patients with 4 criteria of NCEP-ATPIII
- **MetS-5:** patients with 5 criteria of NCEP-ATPIII

Weight (kg) and height (m) were measured with light clothes, barefoot, obesity indexes were calculated using special formulas as following: -

- 1) **Body Mass Index (BMI)** was calculated by the weight (kg)/height² (m)¹⁹.
- 2) **Lipid Accumulation Index (LAP)** in (cm.mmol.L): calculated using following formulas¹⁶:-
 - a. LAP (male): [(WC (cm)-65) *TG (mmol/L)].
 - b. LAP (female): [(WC (cm)-58) * TG (mmol/L)].
- 3) **Visceral Adiposity Index (VAI)**^{18,20}
 - c. VAI (male): (WC/ [39.68+(1.88*BMI)] x (TG/1.03 *1.31/ HDL-C
 - d. VAI (female): (WC/ [36.85+(1.89*BMI)] x (TG/0.81 *1.52/ HDL-C

With WC in cm, BMI in kg/m², and HDL-C in mmol/L.

4) **Body Roundness Index (BRI)**²⁰ **BRI**

$$364.2-365.5*(1-((WC/2*3.14)/(0.5*height))^2)^{1/5}$$

With WC and height in m (meter).

5) **Percentage of Body Fat (FAT%=BF%)**

calculated using the following formula²¹:

$$BF\%: 1.2(BMI)+0.23(age) - 10.8 (sex) -5.4$$

With age being in years and sex being designated as 1 for males and 0 for females,

Samples collection and laboratory investigations

Under aseptic precautions, an overnight fasting blood samples from the T2DM and non-T2DM participants were taken into two tubes:-

a - **Plain Vacutainer tubes**

samples were centrifuged at 1500 rpm for 10 min at 25°C and separated serum was analyzed for biochemical tests (Fasting Blood Glucose FBG, HDL-C, Total Cholesterol TC, and TG).

b - **EDTA tube**

for Glycated Hemoglobin (HbA1C) test. Serum LDL-C was calculated using Friedewald's formula:
LDL-C= Total Cholesterol- (HDL-C+TG/5)

Analytical Measurements and Instrumentation

FBG was tested by HumaLyzer Primus; Semi-Automatic Microprocessor Controlled Photometer/Germany. LDL-C, HDL-C, TC, and TG were measured by Mindary BS-380 clinical chemistry analyzer/China. All biochemical investigations were performed according to the manufacturer's protocol using commercially available Kits from Biosystem[®], Spain.

HbA1C was measured using the technique of High-Performance Liquid Chromatography (HPLC) by Tosoh Automated Glycohemoglobin Analyzer (HLC[®]-723GX)/India.

Statistical Analysis

Results were analyzed using the Statistical Package for Social Sciences (SPSS) version 20 for windows. Data were presented as mean \pm standard deviation (SD). Student's t-test was used to compare the means of different variables between two independent samples (MetS+ and MetS -). Analysis of variance (ANOVA) of one factor was used to identify differences in mean between the three groups of patients. Receiver operating characteristic (ROC) was conducted to evaluate the ability of six indexes in the prediction of MetS in T2DM

patients. Results with p-value <0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Results

(Table 1) shows a comparison between MetS+ patients and MetS- patients in T2DM patients. In the MetS+ group (n=91, 70.54%); the mean age was 46.63±11.35 years while in the MetS- group (n=38, 29.45%); the mean age was 45.19±10.6 years and the difference between the two groups was not significant (p>0.05).

Results concerning diabetic characteristics (FBG and HbA1C) were also studied. The mean of FBG was (180.39 ± 13.7 mg/dl) in the MetS+ group and (170.46 ± 11.5 mg/dl) in the MetS group with a significant difference between groups (p<0.05). In addition, the mean of HbA1C was 8.54 ± 2.23 % for the MetS+ group and 7.26 ± 1.03% for the MetS- group and the difference was also statistically significant (p <0.05). The average of the duration on diabetes was higher in the MetS+ group (8.54 ± 6.7 years) compared with the MetS- group (3.91 ± 4.12 years) with a statistically significant difference between the two groups (p <0.05).

Table1: A comparison between MetS+ patients and MetS- patients according to age, glycemc control, lipid profile, and obesity indexes.

Parameter	T2DM (n=129)		
	MetS+ (n=91,70.54%)	MetS- (n = 38, 29.45 %)	P-Value*
Age (Years)	57.90 ± 9.11	55.12 ± 8.03	0.06
FBG (mg/dl)	180.39±13.7	170.46±11.5	0.03*
HbA1C (%)	8.54±2.23	7.26±1.03	0.00*
Duration of disease (years)	8.54±6.7	3.91±4.12	0.04*
TG (mg/dl)	147.36±50.41	130.53±39.54	0.00*
Total Cholesterol (mg/dl)	141.18±13.04	138.23±24.32	0.12
LDL-Cholesterol (mg/dl)	99.32±21.03	92.23±11.04	0.06
HDL-Cholesterol (mg/dl)	51.34±13.43	60.23±4.9	0.00*
BMI	28.80±4.42	24.15±11.32	0.001*
WC	105.57±12.65	98.56±10.13	0.024*
BF%	37.70±7.39	30.14±15.21	0.000*
BRI	6.98±2.03	4.23±1.15	0.031*
VAI	2.46±1.36	1.15±1.12	0.04*
LAP	71.25±32.65	30.12±11.02	0.000*

MetS+: T2DM patients with metabolic syndrome, MetS -: T2DM who do not have metabolic syndrome, * The difference between groups is significant (<0.05).

Lipid profile was also compared as shown in (Table 1); the mean of TG was higher in the MetS+ group (147.36 ± 50.41 mg/dl) compared with the MetS- group (130.54 ± 39.54 mg/dl) with a significant difference ($p < 0.05$). On the other hand, the mean of Total-cholesterol (141.18 ± 13.04 mg/dL), and LDL-cholesterol (99.32 ± 21.03 mg/dL) was higher in the MetS+ group compared with the MetS- group (138.23 ± 24.32 mg/dl, and 92.23 ± 11.04 mg/dL, respectively) but the differences between the two groups were not significant ($p > 0.05$). The MetS+ group also showed a statistically significant decrease in HDL-cholesterol (51.34 ± 13.43 mg/dL) compared with the MetS- patients (60.23 ± 4.9 mg/dl) ($p > 0.05$). A comparison in obesity indexes was also studied, BMI and WC were studied as traditional obesity indexes of MetS. The data showed that BMI score and WC were higher in

the MetS+ group (28.80 ± 4.42 kg/m² and 105.57 ± 12.65 cm, respectively) in comparison with the MetS- group (24.15 ± 11.32 kg/m² and 98.56 ± 10.13 cm, respectively) and the differences in mean were significant ($p < 0.05$). The non-traditional obesity indexes were also studied as shown in (Table1). BF%, BRI, VAI, and LAP were also higher in the MetS+ group ($37.70 \pm 7.39\%$, 6.98 ± 2.03 , 2.46 ± 1.36 , and 71.25 ± 32.65 , respectively) compared with the MetS- group ($30.14 \pm 15.21\%$, 4.23 ± 1.15 , 1.15 ± 1.12 , and 30.12 ± 11.02 , respectively) and the differences between groups were statistically significant ($p < 0.05$).

(Table 2) shows a comparison between MetS+ patients according to the number of NCEP-ATPIII criteria, there was no significant difference between the three groups regarding to age, FBG, HbA1C, duration of diabetes, and total cholesterol ($p > 0.05$).

Table 2: A comparison between MetS patients according to number of (NCEP-ATPIII) criteria.

Parameter	MetS+ (n=91,70.54%)	MetS- (n = 38, 29.45 %)	P-Value*
Age (Years)	58.55±6.7	58.34±10.09	0.366
FBG (mg/dl)	162.12±23.12	172.12±20.13	0.062
HbA1C (%)	8.45±2.28	8.39±2.20	0.427
Duration of disease (years)	6.9±6.2	10.06±7.0	0.125
TG (mg/dl)	135.82±33.78	151.72±33.8	0.199
Total Cholesterol (mg/dl)	146.52±28.36	134.93±33.83	0.209
LDL-Cholesterol (mg/dl)	123.12±11.72	129.42±12.43	0.145
HDL-Cholesterol (mg/dl)	57.96±14.87	49.08±11.24	0.000**
BMI	28.48±3.8	29.06±3.8	0.221
WC	102.91±11.40	106.72±13.92	0.261
BF%	35.96±7.70	38.47±6.96	0.019**
BRI	5.64±1.6	6.2±1.9	0.263
VAI	1.81±0.62	2.7±1.57	0.001***
LAP	59.42±18.06	76.50±37.15	0.015**

*The difference is significant between MetS-3 & MetS-4.

** The difference is significant between MetS-3 & MetS-5.

*** The difference is significant between MetS-4 & MetS-5.

The average of TG, BMI, WC, and BRI increased with increasing the number of NCEP-ATPIII criteria (MetS-5 > MetS-4 > MetS-3) but the difference was not also significant ($p>0.05$). The average of BF%, VAI, and LAP increased with increasing the number of MetS components and the differences between the

three groups were statistically significant ($p<0.05$).

Receiver operating characteristic (ROC) curves were generated to obtain the area under the curve (AUC) and to determine the cutoff points of six obesity indexes for MetS diagnosis in T2DM patients as shown in (Table 3) and (Fig.1).

Table 3: Characteristic curve (ROC) analysis, sensitivity, specificity, AUC and sut-off values of BRI, LAP index, VAI and BMI.

Parameters	Cut-off	AUC	Sensitivity%	Specificity%
BMI	27.18	0.716	64.8	70.8
BRI	5.22	0.774	82.4	58.3
LAP	46.48	0.771	80.2	62.5
VAI	1.73	0.668	71.4	54.2
WC	95.5	0.774	81.3	58.3

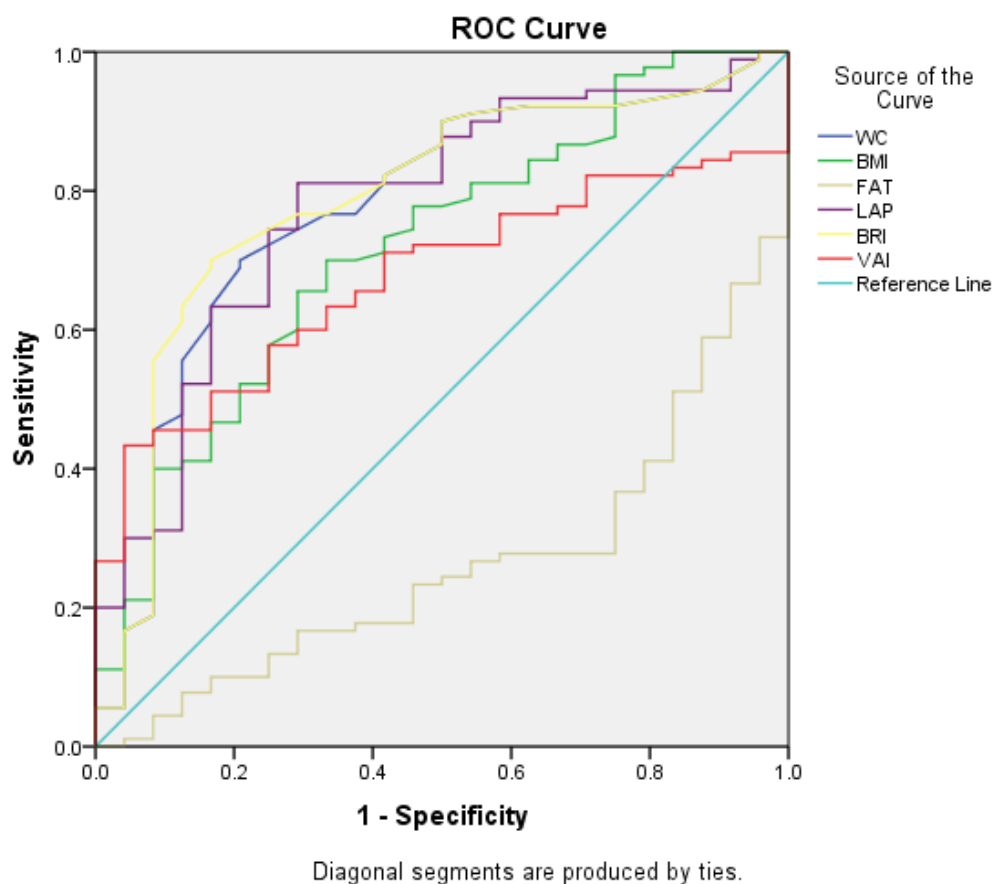


Fig.1: ROC curves of BMI, BRI, VAI, LAP and FAT% indexes for prediction of MetS in T2DM patients.

BRI greater than 5.22 has 82.4% sensitivity and 58.3% Specificity in predicting MetS in T2DM (AUC: 0.774, $p < 0.05$), WC greater than 95.5 has 81.3% sensitivity 58.3% and Specificity in predicting MetS in T2DM (AUC: 0.774, $p < 0.05$), BMI greater than 27.8 has 64.8% sensitivity and 70.8% Specificity in predicting MetS in T2DM (AUC: 0.716, $p < 0.05$), LAP greater than 46.48 has 80.2% sensitivity and 62.5% Specificity in predicting MetS in T2DM (AUC: 0.771, $p < 0.05$), and VAI greater than 1.73 has 71.4% sensitivity and 54.2% Specificity in predicting MetS in T2DM (AUC: 0.668, $p < 0.05$). Therefore, BRI and WC were the best indexes for predicting MetS in T2DM. On the other hand, BF% could not be used for this purpose (AUC: 0.265, $p < 0.05$).

Discussion

With the increasing prevalence of MetS worldwide in both healthy individuals and T2DM patients, it has been widely studied as one of the suggested complications for cardiovascular disease (CD) among diabetes mellitus patients. MetS is characterized as a state of chronic low-grade inflammation associated with an increased level of cytokines, atherosclerotic plaque formation and atherothrombosis^{22&23}. Therefore; it would be necessary to early diagnosis of MetS in patients with high risk to reduce morbidity and mortality. Various studies have investigated the influence of central obesity (visceral and subcutaneous) on the development of MetS in T2DM. In fact, visceral obesity is strongly associated with CD, worse metabolic profile, and Insulin Resistance (IR) in T2DM²⁴. The results showed that T2DM patients have poor glycemic control, lipid profile, and an increase in obesity indexes compared with healthy controls, which was assistance with the result of previous studies^{25&26}. In addition, the prevalence of MetS among T2DM patients was also studied, 70.54% of patients have MetS according to the guideline of NCEP-ATP III. The previous study has pointed to similar results; Biadgo et al.²⁶ reported that 66.7% of T2DM patients have MetS, while a lower prevalence of MetS (47.91%) was reported by Music et al.²⁷. These differences in results could be explained by the interaction of genetic

and environmental factors, changes in lifestyle, and difference in patients' characteristics.

The underlying etiology of MetS remains unclear. However, visceral obesity appears to have an important role in its development and is considered as a main component of MetS^{29&30}.

BMI was considered a useful indicator for obesity, but it is considered an index for general body mass and could not be used to evaluate visceral obesity³¹. For that reason, it seems to be more useful to have new obesity indexes such as LAP, BF%, VAI, WC, and BRI which are easier, more applicable, and less expensive tools than imaging studies for determining visceral obesity in patients^{20&32}. LAP index could better evaluate visceral lipid which combines in formula of measurement each of WC and TG, while BF% combines BMI, age and sex^{33&34}. VAI index combines in formula of measurement each of WC, BMI, TG, and HDL-Cholesterol. For BRI index, it combines in formula of measurement WC and height.

Obesity indexes were estimated in all T2DM patients, and data showed that BMI, WC, VAI, BF%, BRI, and LAP were higher in MetS+ patients compared with MetS- patients. These results were consistent with the result of Radetti et al³⁵, who reported that MetS+ patients have the highest average of both WC and BMI compared with Met- patients. After that, Obesity indexes were evaluated in MetS+ patients and compared according to the number of metabolic syndrome components (MetS-3, MetS-4, and MetS-5), the average of BF%, VAI, and LAP increased with the increasing number of components, while BMI, WC, and BRI did not show a statistically significant difference. The risk of cardiovascular disease is associated with increasing the number of MetS criteria³⁶. Therefore, increased levels of BF%, VAI, and LAP were associated with increasing the severity of MetS. We also evaluated the discriminatory ability of six obesity indexes as predictors of MetS in T2DM patients. Our study have showed that the optimal cutoff points were 27.18, 5.22, 46.48, 1.73, and 95.5 for BMI, BRI, LAP, VAI, and WC respectively. In a previous study, the optimal cutoff points determined for LAP were 49.71 (sensitivity = 85.2 %, specificity = 82.3 %) for women and 39.89 (sensitivity = 86 %, specificity = 82.3 %) for men.

specificity = 79.6 %) for men, Disparities with our results could be explained by different characteristics of study participants; our study included T2DM patients where the participants in Motamed et al. were healthy subjects³⁷. our study corresponded with the results of a recent study³⁸, which showed that the best indexes to predict the occurrence of MetS in both females and males were WC (AUC: 0.787) and BRI (AUC: 0.803) compared with BMI (AUC: 0.736).

Conclusion

BRI, LAP, WC, and VAI indexes are useful and applicable obesity markers for better estimation of the visceral adiposity than BMI and could be used for the prediction of MetS in T2DM patients. VAI which combines (WC, BMI, TG and HDL-C measurements) was the best marker to evaluate the severity of MetS (the number of NCEP-ATPIII criteria). While BRI and WC had the highest discriminatory ability, the VAI had the lowest. Different cutoff values of obesity indexes were also obtained in our society.

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نشرة العلوم الصيدلانية جامعة أسيوط



مشعر تراكم المنتجات الشحمية، مشعر الشحوم : تقييم واسمات النسيج الشحمي الحشوية، ومشعر محيط الجسم كعوامل تنبؤية للإصابة بالمتلازمة الاستقلابية لدى مرضى الداء السكري النمط الثاني

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ترتبط البدانة الحشوية بشكل وثيق بحدوث المتلازمة الاستقلابية وخطورة قلبية وعائية عالية لدى مرضى الداء السكري من النمط الثاني. هدفت هذه الدراسة إلى تحديد مشعر البدانة المناسب للتنبؤ بحدوث المتلازمة الإستقلابية لدى مرضى الداء السكري من النمط الثاني. شملت هذه الدراسة 129 مشاركاً من مرضى T2DM مرضى % 70,54 & MetS+ مرضى % 70,54 MetS- خلال الفترة الزمنية الممتدة من 2020 م إلى 2021 م. كان متوسط كل من TG، HbA1C، ومشعرات البدانة (BMI, WC, BF%, BRI, VAI, LAP) أعلى لدى مجموعة MetS+ مقارنة مع مجموعة MetS- مع مستويات أقل من HDL لدى مجموعة MetS+. ازداد متوسط كل من BF%، VAI، وLAP مع ازدياد عدد مكونات المتلازمة وفقاً لتصنيف NCEP-ATPIII. إضافة لما سبق، تم تحديد القيم الحدية للتنبؤ بحدوث المتلازمة لمشعرات البدانة المدروسة. يعتبر كل من LAP مع قيمة حدية: 46,48 (0,774) ، AUC: الحساسية: 80,2%، والنوعية: 62,5%)، VAI مع قيمة حدية: 1,73 (0,668) ، AUC: الحساسية: 71,4%، والنوعية: 54,2%)، وBRI مع قيمة حدية: 0,22 (0,774) ، AUC: الحساسية: 82,4%، والنوعية: 58,3%) من المشعرات المفيدة للتنبؤ بحدوث المتلازمة الاستقلابية لدى مرضى الداء السكري من النمط الثاني.