HIGH-MOLECULAR WEIGHT ADIPONECTIN, AND TYG-BMI, ARE BETTER PREDICTIVE MARKERS THAN TYG INDEX AND HBA1C TO PREDICT PRE-DIABETES IN OVERWEIGHT ADULTS

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ABSTRACT:

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Background: The prevalence of pre-diabetes has been increased rapidly not in developing countries only. Pre-diabetes is associated with overweight. The diagnosis criteria of pre-diabetes are controversial issue.

Aim of the work: The aim of this study was to establish useful parameters to predict pre-diabetes in overweigh adults.

Subject and Methods: Thirty-eight adult participants were enrolled and they were divided into two groups 22 were control healthy volunteers and 16 participants were overweight. Biochemical investigations (glucose level, lipid profile), and High-molecular weight adiponectin (HMW-Adipo) hormone were done for both groups.

Results: The results showed that the level of HMW-Adipo was significantly reduced in the overweight group, associated with an increase in fasting plasma glucose (FPG), triglycerides, and reduction in high-density lipoprotein (HDL-C) in the overweight group. The Pearson correlation for Triglyceride glucose- Body Mass Index (TyG-BMI), Body Mass Index (BMI), and tri-Ponderal index were positively correlated with FPG; while HMW-Adipo was negatively correlated with FPG. The area under the curve for TyG-BMI, PI and HMW-Adipo showed an excellent prediction for pre-diabetes in overweight adults.

Conclusion: HMW-Adipo and/or TyG-BMI are better predictive markers for pre-diabetes adults rather than TyG-index and impair fasting glucose alone.

Keywords: Pre-diabetes, high molecular weight Adiponectin, overweight, Triglyceride Glucose-Body mass index.

INTRODUCTION:

Due to changes in lifestyle and nutritional habits, the prevalence of obesity and overweight has increased not only in developing countries but in low- and middle-income countries as well^(1&2). Overweight and/or obesity are one of the most causative agents for diabetes. The prevalence of diabetes mellitus has increased globally⁽³⁾. The risk of death due to diabetes increases to 46.2% in people lower than 60 years worldwide⁽⁴⁻⁶⁾. In 2017, 374 million adults

were pre-diabetes and this number expected to increase to 540 million by 2045. Impair glucose tolerance (IGT) and/or impair fasting glucose (IFG) are associated with prediabetes. Overweight and/or obesity are associated with pre-diabetes. The diagnosis of pre-diabetes is controversial issue. Diagnosis of pre-diabetes is depending on the criteria of The Health World Organisation (WHO) and American Diabetic Association (Raimi, #14), impair of glucose tolerance and/or impair fasting plasma glucose level and increase HbA1c⁽⁵⁻⁷⁾. Previously, impair fasting glucose was defined as blood glucose level ranging from 110-126 mg/dl (6.1-6.9 mmol/L). Recently, in 2003 the ADA reduced the range of IFG to 100-126 mg/dL, 5.6-6.9 $\text{mmol/L.})^{(5,8\&9)}$. The recommendation of the ADA is that overweight and/or obese adults have to have annual follow-up on their fasting plasma glucose and HbA1c^(5&7). Adiponectin hormone, which is secreted from adipose tissue (white cells), has a critical role in regulation glucose and lipid metabolism^(10&11). It has different complexes low-molecular weight (LMW), middlemolecular weight (MMW), and Highweight (HMW). The molecular latter complex has been shown to be more effective with anti-hyper-glycaemic treatment⁽¹²⁾. A low level of adipo-nectin has been reported in obese and high-fat-diet rodents⁽¹³⁾.Triglyceride glucose index (TyG index) is one of the parameters that is used to measure insulin resistance⁽¹⁴⁻¹⁶⁾. It is also used as predictive parameter to predict T2D in pre-diabetes in obese patients⁽¹⁷⁾</sup>, and it is also a predictor for cardiovascular disease in T2D⁽¹⁸⁾. Barry et al 2016 reported that measuring of HbA1c is not sensitive or specific and fasting plasma glucose level is also not sensitive but specific for prediabetes⁽¹⁹⁾. Moreover, impair glucose tolerance is disheartened due to many reasons⁽⁹⁾.

AIM OF THE WORK:

This study aimed to investigate

1. The changes in lipid profile and the level of high-molecular weight adiponectin in overweight adults and whether HMW-adiponectin can be used as predictive marker for pre-diabetes.

2.Whether lipid parameter ratio TG/HDL, TyG index, TyG-BMI and/or Tri-Ponderal index could be used as predictive markers to assume the development of diabetes in pre-diabetes overweight adult persons.

PATIENTS AND METHODS:

study conducted Thirty-eight This participants and they were divided into two groups. Group A was control (n=22), and group B (n=16) was overweight participants. All participants in group B had no previous medical treatment for anti-hyperglycaemia and/or anti-hyperlipidaemia. Demographic information (Age, gender, weight, and length) were collected. Body mass index obtained through dividing weight⁽⁹⁾ on the square of length (m^2) . PI was assessed as the ratio of weight⁽⁹⁾ to cubic length $(m^3)^{(20,21)}$. All participants asked for 14h fasting before antecubital venous blood were 5 ml withdrawn. The sample was left for 15-30 min on the bench before serum separation at 4000 rpm for 20 min Biochemical tests were performed directly after centrifugation and the rest was stored at -8 0°C for further investigations. Adiponectin (High-molecular weight) hormone was done by sandwich ELISA following the instruction of manufacture.

Statistical analysis:

The results were analysed by using GraphPad PRISM software 8.4 and all results are expressed as Mean \pm SEM. Statistically significant was performed Student's unpaired *t*-test *P*-value <0.05.

Ethical Consideration:

All participants were informed and they signed the consent form before blood collection. Iraqi Ministry of Health and Marjan Medical city approved this project (1452, 25/09/2023), and this study followed the Declaration of Helsinki.

RESULTS:

In this study our first goal was to test the changes in lipid profile in overweight adults. Female participants were 60% in both groups. The mean age for the overweight group was 47.44 ± 2.3 vs. 48.95 ± 2.07 for the control group. Overweight participants had а significant increase in weight compared with the control group (80.94±3.49 vs 62.41±1.52, respectively) as shown in Table (1). Triglycerides and very low-density lipoprotein (VLDL) showed a significant increase in the overweight group (1.575 ± 0.14) vs 1.209±0.1 and 0.315±0.02 vs 0.241±0.02, respectively). A significant decrease in highdensity lipoprotein cholesterol (HDL-C) was

noticed in the overweight group compared with the control group $(1.2\pm0.055 \text{ vs} 1.37\pm0.055, \text{ respectively})$. Whereas, lowdensity lipoprotein cholesterol (LDL-C) showed a trend toward a non-significant increase in the overweight group $(2.97\pm0.3 \text{ vs} 2.35\pm0.2)$. Both triglyceride to HDL and LDL to HDL ratios, like TG and VLDL, were increased in the overweight group $(1.4\pm0.18 \text{ vs} 0.94\pm0.1, \text{ and } 2.64\pm0.34 \text{ vs} 1.82\pm0.19, \text{ respectively})$ Table (1).

	Control group	Overweight	P-value
		group	
Age (years)	48.95±2.07	47.44±2.3	0.437
Gender			
Female n (%)	13 (60)	10 (60)	
Male n (%)	9 (40)	6 (40)	
Weight (Kg)	62.41±1.52	80.94±3.49 ***	<0.0001
TC (mmol/L)	3.97±0.205	4.48±0.29	0.149
TG (mmol/L)	1.209±0.1	1.575±0.14 *	0.036
HDL-C (mmol/L)	1.37±0.055	1.2±0.055 *	0.038
LDL-C (mmol/L)	2.35±0.2	2.97±0.3	0.088
VLDL (mmol/L)	0.241±0.02	0.31.5±0.02 *	0.036
LDL/HDL ratio	1.826±0.19	2.64±0.34 *	0.032
TG/HDL ratio	0.94±0.1	1.4±0.18 *	0.025
Non-HDL (mmol/L)	2.6±0.21	3.2±0.126	0.068

Table 1: Characterisation and lipid markers for the participan	ts
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Abbreviations: HDL-C High-Density Lipoprotein-Cholesterol; LDL-D Low-Density Lipoprotein-Cholesterol; TC Total Cholesterol, TG Triglycerides; and VLDL Very-Low Density Lipoprotein. *P<0.05 vs. control group

Next, we investigate the levels of fasting glucose, HbA1c and body parameters in both groups. Fasting plasma glucose (FPG) was increased significantly in the overweight group (5.6±0.09 vs 4.7±0.132, respectively) Diagram (1 A). HbA1c, unlike FPG, had a non-significant difference between the two groups. Diagram (1 B). The body mass index is a parameter that is widely used to determine the overweight and obesity. The overweight group showed a significant increase in the body mass index (BMI) compared with the control group (28.94±0.69 vs 22.2±0.41, respectively) Diagram (1 C). Previous studies reported that weight does not, always, correspond to high squared;

therefore, the tri-Ponderal index⁽⁴⁾ was used together with the BMI. Like the BMI, PI also showed a significant (P < 0.01) increase in the overweight group (17.41±0.46 vs 13.28±0.3) Diagram (1 D). The association between TyG-BMI and metabolic syndromes has been reported previously specially with insulin resistance (IR). Although TyG index was associated with IR^(16,22). Here, we measure both Triglyceride TyG-BMI and TyG index for both groups. The results showed that TyG-BMI and TyG index were significantly elevated in the overweight group (137.2±3.35 vs 100.5±2.34 and 4.74±0.047 vs 4.52±0.041, respectively) Diagram 1 (E and F).



Diagram 1: Biochemical markers, (A) Fasting plasma glucose; (B) HbAc%; (C) BMI, Body mass index, (D) PI, Tri-ponderal index; (E) TyG-BMI, Triglycerides glucose-BMI; and (F) TyG index, Triglycerides glucose index. Results are expressed as Mean±SEM, *P<0.01, **P<0.001 and ***P<0.0001.

Brismar et al., 2023 reported that adiponectin is an independent predictor for pre-diabetes. Here, we test the level of High-Molecular Weight Adiponectin (HMW-Adipo.) in the serum of both groups. Our results revealed that the overweight participants had a significant reduced level of adiponectin compared with the control group $(131.5\pm11.8 \text{ vs } 239\pm12.17, \text{ respectively})$ Diagram (2).



Diagram 2: High-Molecular Weight Adiponectin level. Results are expressed as Mean ± SEM, ***P<0.0001

Furthermore, we investigate the Pearson correlation (r) for FPG with Triglyceride-Glucose Body Mass Index (TyG-BMI), BMI, PI, TyG Index, and HMW-Adipo. Results showed that FPG had a positive correlation with all parameters except with HMW- Adipo. (r was 0.76, 0.73, 0.705, 0.56, and - 0.5, respectively) Confidence Intervals (CI 0.58 to 0.87, 0.54 to 0.85, 0.49 to 0.83, 0.29 to 0.74, and -0.71 to -0.22, respectively) Diagram 3 (A-E).



Diagram 3: Linear Correlation for FPG with (A) TyG-BMI; (B) BMI; (C) PI; (D) TyG index; and (E) HMW-Adipo.

A negative correlation was also seen for HMW-Adipo with TyG-BMI, BMI, PI, and TyG index (r were -0.66, -0.65, -0.62, and -

0.34, and CI -0.81 to -0.43, -0.8 to 0.4, -0.78 to -0.38, and -0.59 to -0.02 respectively) Diagram 4 (A-D).



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Diagram 4: Linear Correlation of HMW-Apio. with (A) TyG-BMI; (B) BMI; (C) PI and (D) TyG index.

Finally, we calculated the Area Under the Curve⁽¹³⁾ for the TyG-BMI, PI, HMW-Adipo, FPG, TyG-index, and HbA1c. The results of the AUC showed that TyG-BMI, PI, and HMW-Adipo demonstrate excellent predictors for pre-diabetes in overweight adults (0.994, 0.947, and 0.94; CI 0.97 to 1.0,

0.93 to 1.0, and 0.85 to 1.0, respectively, *P-value* <0.0001). While, the AUC for FPG and TyG-index showed good predictors (0.89 and 0.8, CI 0.78 to 0.99 and 0.66 to 0.93, respectively, *P-value* 0.001) Diagram 5 (A-F).



Diagram 5: The area under curve for (A) TyG-BMI; (B) PI; (C) HMW-Adipo; (D) FPG; (E) TyG index; and (F) HBA1c.

DISCUSSION:

Overweight and obesity are the major risk for developing diabetes. Although, other metabolic complications, such as cardiac complications, are mostly associated with the pre-diabetes ⁽²³⁻²⁵⁾. Many studies have reported that pre-diabetes adults who are overweight or obese have been undiagnosed for many years⁽²³⁾. Complications associated with diabetes are widely distrusted such as (CVDs, retinopathy). In the present study we aimed to demonstrate the useful parameters that could be used to predict pre-diabetes in overweight adults. Our main findings are that the overweight persons have slightly irregular glucose level and lipid metabolism without changing in HbA1c. Although the level of HMW-Adipo is decreased in the overweight persons. The criteria of diagnosis of prediabetes are depending on i) impair glucose tolerance (IGT) > 140mg/dl.; ii) impair of fasting glucose (IFG) >126 mg/dl ; and iii) high HbA1c level >6.5% according to the ADA and WHO⁽⁵⁻⁷⁾. The criteria of impair fasting glucose was reduced in 2003 to 100 mg/dl. (5.6mmol/L) by the $ADA^{(3,8,26)}$. Although, the diagnosis of pre-diabetes is depending on several criteria such as obesity and/or overweight and insulin resistance. However, in this study the level of fasting glucose seems to be within normal range but those participants show a moderate elevation in the BMI. Increased BMI is associated with many metabolic syndromes. Our findings show that overweight participants had a significant increase in their BMI and this increase associated with increase in VLDL, LDL/HDL triglycerides, and TG/HDL ratios with a significant decrease in HDL-C and our results are in agreement with previous study by Bhatti et al⁽²⁷⁾. These results indicated that increase BMI is associated with lipid profile dysfunction and similar to the previous studies which is indicated that reduction in BMI is useful to profile⁽²⁸⁾. restore lipid Moreover.

dyslipidaemia and obesity and/or overweight are one of the risk factors that are associated with metabolic syndromes such as insulin resistance, pre-diabetes, and T2D. Overweight participants had irregular glucose and lipid metabolism Diagram (1) and Table (1).

It has been reported that TyG index and TG/HDL ratio are good parameters to predict insulin resistance (14,17,18). Those parameters were slightly increased in the overweight group, while FPG, BMI, TyG-BMI and PI showed highly differences in the overweight group. Although FPG level was positively correlated with BMI, TyG-BMI and PI. The area under the curve also showed excellent prediction for pre-diabetes in overweight adults. This indicated that prediction of prediabetes in overweight people could be delivered from TyG-BMI and PI together with estimation of FPG. The preinflammatory hormone adiponectin that is secreted from adipose tissue reduce in many metabolic disorders in children and adults⁽²⁹⁻ 32) Adiponectin is expressed in three oligomeric complexes. One of these complexes is high molecular weight (HMW) adiponectin⁽³²⁾. Moreover. Adiponectin hormone proposed to intermediate the metabolism of glucose and lipid and it releases from adipose tissue and many studies reported that patient with diabetes and prediabetes associated with low level of adiponectin hormone^(13,33). In this study we proposed that HMW-Adipo is decreased in overweight adults and this could be a critical parameter for prediction of pre-diabetes. Our results show that the level of HMW-Adipo was reduced in the overweight group and it has a negative correction with FPG, TyGindex, PI, and BMI. The AUC for HMW-Adipo was excellent which make it as one of the predictive parameters to predict prediabetes in overweight adults as shown in Diagram (5).

Conclusion:

In conclusion, we concluded that measuring the level of HMW-Adipo and TyG-BMI together with the FPG are better predictive markers for pre-diabetes overweight prediction in adults. The limitations of this study are that the number of participants is small, and with a limited population, there is only one governorate. Further study with a high number of participants from different governorates is highly recommended.

Competing interests:

The authors have no conflicts of interest regarding these investigations.

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يعد الأديبونيكتين عالي الوزن الجزيئي، و مؤشر كتلة الجسم الدهون الثلاثية الكلوكوز علامات تنبؤية أفضل من مؤشر الدهون الثلاثية الجلوكوز والسكر التراكمي لمرحلة ما قبل السكري لدى البالغين الذين يعانون من زيادة الوزن

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قسم المختبرات الطبية- كلية التقنيات الصحية والطبية جامعة الفرات الاوسط التقنية – الكوفة - العراق ¹ مستشفى مرجان التعليمي - وزارة الصحة دائرة صحة بابل - بابل العراق ² قسم المختبرات الطبية - المعهد التقني/كوفة جامعة الفرات الاوسط التقنية – كوفة - العراق ³

لقد تزايدت معدلات الإصابة بمرحلة ما قبل السكري بسرعة ليس في البلدان النامية فقط. ترتبط مرحلة ما قبل السكري بزيادة الوزن. معايير تشخيص ما قبل السكري هي قضية مثيرة للجدل الهدف من هذه الدراسة هو تحديد معايير مفيدة للتنبؤ بمرحلة ما قبل السكري لدى البالغين الذين يعانون من زيادة الوزن.

شملت الدراسة ثمانية وثلاثين مشاركًا بالغًا وتم تقسيمهم إلى مجموعتين، 22 من المتطوعين الأصحاء و16 مشاركًا يعانون من زيادة الوزن. تم إجراء الفحوصات البيوكيميائية (مستوى الكلوكوز، تحليل الدهون الكامل)، و هرمون الأديبونيكتين ذو الوزن الجزيئي العالى لكلا المجموعتين.

أظهرت النتائج أن مستوى هرمون الأديبونيكتين ذو الوزن الجزيئي العالي انخفض بشكل ملحوظ في المجموعة ذات الوزن الزائد المرتبط بزيادة نسبة الكلوكوز في بلازما الصيام، والدهون الثلاثية، وانخفاض البروتين الدهني عالي الكثافة في المجموعة ذات الوزن الزائد.

كانت علاقة بيرسون لـ مؤشر كتلة الجسم الدهون الثلاثية الكلوكوز , مؤشر كتلة الجسم مرتبطة بشكل إيجابي مع نسبة الكلوكوز في حالة الصيام ؛ بينما كان مستوى هرمون الأديبونيكتين ذو الوزن الجزيئي العالي مرتبطًا سلبًا بنسبة الكلوكوز في حالة الصيام. كما ظهرت المنطقة الواقعة تحت منحنى مستوى هرمون الأديبونيكتين ذو الوزن الجزيئي العالي م مؤشر كتلة الجسم الدهون الثلاثية الجلوكوز تنبوًا ممتازًا لمرحلة ما قبل الإصابة بالسكري لدى البالغين الذين عانون من زيادة الوزن.

الاستنتاج: يعتبر هرمون الأديبونيكتين ذو الوزن الجزيئي العالي و/أو مؤشر كتلة الجسم الدهون الثلاثية الكلوكوز من العلامات التنبؤية الأفضل للبالغين في مرحلة ما قبل الإصابة بالسكري بدلاً من مؤشر الدهون الثلاثية الكلوكوز وفشل الكلوكوز الصائم وحده.