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An evaluation of F-box / WD repeat protein 7 level in conjugation with total fatty acids in women with type 2 diabetes mellitus

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Diabetes and prediabetes are some of the most serious social and medical issues of the present day. It is fitting to identify a distinct category of women aged 40 to 60 who have diabetes mellitus (DM) or prediabetes to discover new biomarkers related to DM diagnosis. As this age group is predominantly overweight, which is considered a risk factor for several health issues, it is one of the most serious social and medical problems today that interferes with the physiological and metabolic lipid profile, as well as other proteins linked to metabolic effects.
The objective: **to examine F-box and WD repeat domain-containing protein 7 (FBXW7) levels in relation to total fatty acids (TFAs) in women with type 2 DM (T2DM) in order to investigate their potential interaction.**
Materials and methods**. The current study included 124 women who were divided into three groups: G1 included 31 patients with prediabetes, G2 – 65 women with T2DM; G3 (control) consisted of 28 women without pathology. The level of FBXW7 and TFAs were determined using enzyme-linked immune sorbent assay. The level of fasting serum glucose and lipid profile were determined using spectrophotometer, and the level of HbA1c – by a fully auto technique.**
Results**. Serum levels of FBXW7 were significantly higher in women with prediabetes compared to both the G2 and G3, possibly due to tissue damage which is associated with the onset of DM. TFAs concentrations revealed distinct patterns across the groups, G3 had the highest concentration. These findings indicate a gradient in fatty acid levels, with G3 showing significantly higher concentrations. Cluster analysis showed that 90% of the data were homogenized in cluster 1, where the distributions of parameters matched the original data distribution. In contrast, cluster 2 displayed different distributions. Furthermore, TFAs was identified as a more significant predictor than FBXW7 in diabetic patients.**
Conclusions**. These results highlight the importance of TFAs and FBXW7in the diagnosis and progression of DM women with obesity.**
Keywords: *F-box / WD repeat protein 7 level, total fatty acids, type 2 diabetes, prediabetes, cluster analysis.*

Оцінка рівня білка F-box / WD repeat protein 7 у кон'югації із загальними жирними кислотами у жінок із цукровим діабетом 2-го типу

H. S. Mahdy, E. M. Taha

Діабет та переддіабет є одними з найважливіших соціальних та медичних проблем сьогодення. Для виявлення нових біомаркерів, які можуть мати вагоме значення в діагностиці цукрового діабету (ЦД), доцільним є обстеження жінок віком від 40 до 60 років із ЦД або переддіабетом. Ця вікова група переважно має надмірну масу тіла, що вважається фактором ризику розвитку низки захворювань і є однією з найсерйозніших суспільних та медичних проблем, оскільки впливає на фізіологічний і метаболічний ліпідний профіль, а також на рівні інших білків, пов'язаних із метаболічними процесами.
Мета дослідження: аналіз рівня білка F-box / WD repeat protein 7 (FBXW7) у кон'югації з рівнем загальних жирних кислот (ЗЖК) у жінок із ЦД 2-го типу з метою дослідження їх потенційної взаємодії.
Матеріали та методи. Дослідження включало 124 жінки, яких було розподілено на три групи: до 1-ї увійшла 31 пацієнтка з переддіабетом, до 2-ї – 65 жінок із ЦД 2-го типу; 3-тю (контрольну) становили 28 жінок без встановленої патології. Рівень FBXW7 та ЗЖК визначали методом імуноферментного аналізу. Рівень глюкози в сироватці крові натщесерце та показники ліпідного профілю визначали за допомогою спектрофотометра, а рівень HbA1c – повністю автоматизованою методикою.
Результати. Рівень FBXW7 у сироватці крові був значно вищим у жінок 1-ї групи порівняно з пацієнтками 2-ї та 3-ї груп, що, ймовірно, пов'язано з ушкодженням тканин, яке відбувається на ранніх етапах розвитку ЦД. Концентрація ЗЖК була найвищою в 3-й групі. Отримані результати свідчать про наявність градієнта рівнів жирних кислот між досліджуваними групами. Кластерний аналіз показав, що 90% даних були гомогенізовані в кластері 1, де розподіл параметрів відповідав початковому розподілу даних. Натомість кластер 2 демонстрував відмінні типи розподілу. Крім того, ЗЖК були визначені як більш значущий предиктор, ніж FBXW7, у пацієнток із ЦД.
Висновки. Отримані результати підкреслюють важливу роль ЗЖК і білка FBXW7 у діагностиці та прогресуванні ЦД у жінок з ожирінням.
Ключові слова: *рівень F-box / WD repeat protein 7, загальні жирні кислоти, цукровий діабет 2-го типу, переддіабет, кластерний аналіз.*

Type 2 diabetes mellitus (T2DM) is a chronic illness that can be induced by low insulin levels, impaired insulin action, or both. It is characterized by elevated blood sugar levels. Insulin has a profound impact on various organs and systems, making it exceedingly difficult to underestimate its influence. Disorders in the regulation process of insulin, a carbohydrate "conductor", are the cause of metabolic disorders and irreversible changes in the human body [1–3]. Complex interaction between insulin resistance and pancreatic beta-cell activity define the physiology of diabetes [2, 4].

Prediabetes is an increased risk diabetes development in the women. Prediabetes is the term for blood sugar levels that are raised but not high enough to be classified as T2DM. Several factors contribute to the development of prediabetes – insulin resistance, genetics, age, obesity, physical inactivity, and unhealthy diet. Obesity is very important among the many factors that affect the female body because parts of metabolic syndrome, like insulin resistance, high insulin levels, and unhealthy fat levels in the blood, greatly affect the body [5]. When involving women in health promotion initiatives and prediabetes treatment, it is important to consider their readiness to make adjustments and their understanding of prediabetes. This step is critical because prediabetes elevates the risk of endothelial dysfunction, development and functioning of the reproductive system, atherosclerosis, and cardiovascular disease in addition to increasing the chance that it may advance to diabetes [5, 6].

Numerous proteins released by the liver that reach the blood and control systemic glucose homeostasis have been discovered in recent studies on obesity. The E3 ubiquitin ligase F-box and WD repeat domain-containing protein 7 (FBXW7) is one of these proteins that is noticeably downregulated in obese human patients' livers. FBXW7 exhibits a regulatory function in the metabolism of fat and glucose in the liver [7]. Most FBXW7 substrates control many biological functions such as cell cycle progression, apoptosis, and differentiation. The chromosomal band 4q32 contains the *FBW7* gene, which codes for the protein FBXW7, that is also known as FBW7, hAgo, and hCdc4 SEL-10. Three subtypes of FBXW7 are found in the cytoplasm, nucleoli, and nucleoplasm, respectively: FBXW7α, FBXW7β, and FBXW7γ. FBXW7α is the one of the three subtypes that engages in ubiquitination the most [8, 9]. F-box proteins play a crucial role in a wide range of biological processes, such as cell division and death, carcinogenesis, and deoxyribonucleic acid damage and repair. On the other hand, the expression of FBXW7 in the liver of an obese person confers several beneficial metabolic effects, including protection against hyperglycemia, insulin resistance, and glucose intolerance [7]. FBXW7 is a protein located on chromosome 4 that has a molecular weight of around 79 KD and 707 amino acids [10].

T2DM is influenced by many lifestyle factors, including smoking, being overweight or obese (particularly in the belly), and being physically active, in addition to unmodifiable risk factors like age and family history of the illness, and it is mainly affected by diet [11]. Food is a significant modifiable factor in T2DM prevention [12]. The contribution of dietary fats and lipids to the prevention of T2DM is up for dispute [13]. There are substantial correlations between the primary components of metabolic syndrome, including dyslipidemia, insulin, glucose metabolism, obesity, body mass index (BMI), blood pressure, and vitamin D levels. Dietary lipids contain a variety of fatty acids that directly influence the risk of T2DM. Metabolic functions necessitate each fatty acid's unique chemical composition [14].

In order to prevent T2DM, current dietary guidelines recommend a diet high in vegetable fat and low in animal and total fat. Increased consumption of omega-3, polyunsaturated, and monounsaturated fatty acids and decreased consumption of trans and saturated fatty acids lend greater credence to this idea [15]. The first main class of fatty acids, saturated and polyunsaturated fatty acids influence glucose metabolism, lipogenesis, insulin sensitivity, obesity, and diabetes via several routes. Additionally, several medications taken by women demonstrate a statistically significant shift in indicators of lipid metabolism [16, 17]. Other analytical studies indicated that supplementary probiotic administration results in a significant reduction in Homeostatic Model Assessment for Insulin Resistance and fasting glucose levels. Positive outcomes of undoubtedly poor or very low evidence for probiotic supplements were observed regarding glycemic management, lipid profile, hormone levels, waist/hip circumference, and fasting glucose [18]. Moreover, the essential amino acids known as valine, leucine, and isoleucine, or branched-chain amino acids (BCAAs), serve as substrates, regulators, and precursors to other amino acids in the metabolism of proteins and energy [19]. Recent studies on obese people have demonstrated a strong relationship between insulin resistance and BCAAs levels; some researchers have even proposed that elevated BCAAs levels could be helpful in anticipating the onset of T2DM [20]. The second main kind are long-chain fatty acids, which have a chain length of 12 carbons or more. Long-chain fatty acids account for the vast bulk of the energy that is stored in humans and other animals [21].

To care for women's health and reduce the risk of diabetes development, researchers must consider the relationship between metabolic syndrome and important metabolic markers to predict the early onset of the disease. Researchers have conducted numerous studies in this regard. Many inflammatory and metabolic issues, like high levels of cytokines [22], vitamin D level [23], and signs of oxidative stress [22], are often seen in diseases such as diabetes. Polycystic ovary syndrome [23], COVID-19 [24], and osteopenia [25], showing that there are shared biological processes and overall problems in the body which are typical for metabolic disorders. Women with diabetes mellitus (DM) and prediabetes are susceptible to inflammatory processes. Chronic infections like brucellosis can intensify systemic inflammation, potentially hastening metabolic disruptions that lead to insulin resistance and compromised glucose homeostasis. Moreover, studies have demonstrated that inflammatory reactions linked to COVID-19 exacerbate glycemic control, especially in patients with preexisting metabolic risk factors [24]. Osteopenia, which is often seen in women with DM, might be linked to long-term inflammation and problems with calcium and phosphate balance, making it harder to manage the disease. Obesity, which is common in many health issues, not only raises the chances of getting T2DM and prediabetes but also worsens

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inflammation, creating a harmful cycle that weakens the immune system, harms bone health, and disrupts metabolism. Collectively, these interconnected factors highlight the necessity for a comprehensive strategy in the prevention and management of DM and its antecedents in women.

The objective is to confirm the levels of the protein FBXW7 and investigate its correlation with the levels of total fatty acids (TFAs) in the blood of women with T2DM.

MATERIALS AND METHODS

Patients

A case-control study was performed at Baghdad Hospital – Medical City from late December 2023 to March 2024. 124 women participated in this study. The patients were divided into three groups: prediabetic patients (G1, n = 31), patients with T2DM (G2, n = 65), and the control (G3, n = 28). The diagnosis of T2DM was diagnosed by diabetologists and endocrinologists. After analyzing the symptoms, the cumulative blood sugar level hemoglobin A1c (HbA1c) was measured, and 31 prediabetic individuals were also diagnosed based on their HbA1c levels following symptom assessment. G3 consisting of 28 healthy individuals with normal HbA1c level.

The participants provided informed consent, and the study received approval from both the hospital and the University of Baghdad.

Inclusion criteria:

- Diagnosed T2DM, the confirmed diagnosis based on American Diabetes Association criteria.
- The duration of the diabetes was 1 year.
- Age range: the participants were aged 40 to 60 years.
- Stable medication use: the participants were on stable doses of anti-diabetic medications (e.g., metformin, sulfonylureas) for at least 3 months before enrolling in the study.
- BMI between 25 and 35 kg/m^2.
- Fasting state: the participants must be able to attend study visits after an overnight fast of 8–12 hours.
- Informed consent: willingness to participate and provide written informed consent.

Exclusion criteria:

- Women with long-term health issues affecting the heart, liver, kidneys, bones, tumors, stomach, and intestines, as well as those taking medications that alter FBXW7 protein levels and free fatty acids, metabolic disorders, and type 1 diabetes.
- Additionally, the patient must not exhibit severe or uncontrolled hypertension.
- Current pregnancy or lactation.
- Recent infection or surgical intervention.
- The individual that participated in a different clinical trial during the last 3 months.

Blood sample collection and laboratory analysis

Ten milliliters of venous blood were collected from participants. Blood samples were divided into aliquots. HbA1c was assessed using whole blood. Following the coagulation of five milliliters of blood, we separated the serum at ambient temperatures using centrifugation at 5000 rpm for 15 minutes. The serum was aliquoted into vials. On the same day, spectrophotometry evaluated the lipid profile and fasting blood glucose utilizing a portion of the collected serum. The leftover serum was put into labeled storage vials for organization and then kept at –20 °C for more research on the FBXW7 protein and free fatty acids, which were measured using an enzyme-linked immunosorbent assay (ELISA).

FBXW7 assay

To identify FBXW7 in samples, a quantitative enzyme-linked sandwich-ELISA approach (FBXW7 protein kit supplied by Elyue, China) was used. Samples were transferred to wells and mixed with the specific antibody after prescreening a microplate with the antibody. Each well of the microplate was then filled with an antibody specific for detecting human FBXW7, which was labeled with horseradish peroxidase, and incubated. The authors kept the well in an incubator after adding the 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution to each well. A blue dye is produced in the solution by an enzyme-catalyzed process. The color then turns yellow when the solution is injected. The solution is stopped to stop the substrate reaction. The yellow solution is read at 450 nm. A standard curve is then constructed using the optical density (OD) value to determine the concentration of human FBXW7 in the samples.

TFA assay

The competitive-ELISA principle served as the foundation for the ELISA method used in this assay (Total fatty acid kit supplied by Elyue, China). An antibody that was coated to human TFA was applied beforehand to the microtiter plate strips. With the antibody to human TFA, a competitive inhibition process was started between HRP-labeled human TFA and total human TFA (standards or samples). The TMB substrate solution was added to each well after the unbound material had been cleaned away, and the wells were then incubated. The solution turns blue due to the enzyme-catalyzed reaction, then yellow when a stop solution is introduced to halt the substrate reaction. The yellow solution is read at a wavelength of 450 nmol. A standard curve is then drawn between the OD value and the sample concentration to determine TFA in the samples.

Lipid profile assay

All tests were done using the Selectra Pro XL fully automated photometric method, except for the HbA1c test, which was performed using the G8 HPLC Analyzer and the HbA1c kit is purchased (both from Tosoh Corporation, Japan). Japan. Triglyceride kit, Fasting Glucose kit, Cholesterol kit, and, HDL-Cholesterol kit were purchased from Roche Diagnostics GmbH, Germany.

Ethical approval

All the experimental procedures in this study were conducted in accordance with the Helsinki declaration of medical studies and approved by the Research Ethics Committee of the College of Science for Women, Baghdad, Iraq (ethical code: 22/3477 in 12.12.2023).

Statistical analysis

ANOVA (analysis of variance) was used to compare the average levels of biochemical parameters between three groups: prediabetic women, T2DM women, and healthy controls. The authors used a 95% confidence interval (CI) to assess the reliability of the estimated group means. When necessary, the authors conducted the Tukey's multiple comparisons test to determine the significance of variance among groups. Additionally, cluster analysis was utilized to discern patterns and possible subgroups within

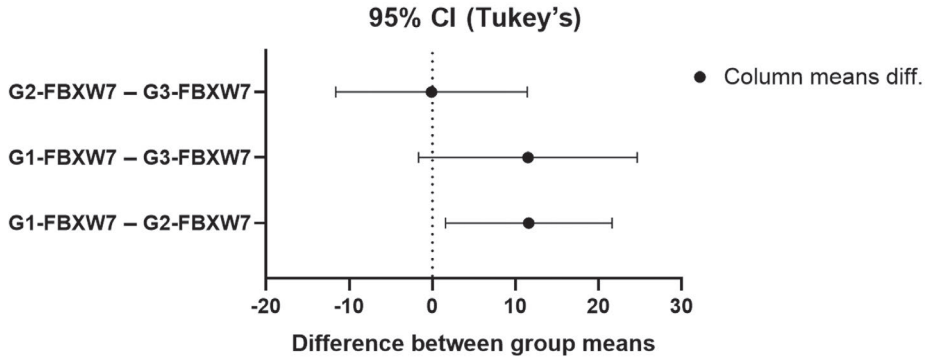

Fig. 1. 95% CI and the variation in group means for FBXW7 protein

Notes: FBXW7 – F-box and WD repeat domain-containing protein 7; CI – confidence interval.

the data based on biochemical commonalities. This strategy facilitated the categorization of participants with analogous metabolic characteristics. Finally, the authors used predictor importance analysis to evaluate how much each variable helped in distinguishing between the groups. This investigation identified the most significant biomarkers for differentiating prediabetes, DM, and control states.

RESULTS AND DISCUSSION

The study showed that there was no statistically significant age difference between the groups, indicating that individual age matches were adequate. The homogeneity in age distribution guarantees that any detected variations in other variables are not affected by age-related factors. However, a significant difference in BMI was noted between women in G1 and G3 as shown in Table 1.

Current study was focused on the level of FBXW7, and TFA. Serum levels of FBXW7 protein were significantly higher (3.860 ± 0.514 ng/mL) in G2 compared to G1 and G3 as shown in Table 2 and Fig. 1. This increase may be due to tissue damage from the onset of diabetes, leading to decreased FBXW7 levels in tissues and increased secretion into the blood [26]. No significant difference in FBXW7 protein level was observed between G2 and G3. However, FBXW7 levels were significantly lower in G1 compared to G2. Serum concentrations of free fatty acids exhibited distinct patterns among the three groups. Comprising prediabetic patients, demonstrated a fatty acid concentration of

Table 1

Statistical analysis of age and BMI levels across all study groups

Parameters	Statistical indicators	G1 (n = 31)	G2 (n = 65)	G3 (n = 28)
Age, years	M ± SE	50.4 ± 1.4	50.4 ± 1.0	47.0 ± 1.9
	Lower 95% CI of M	47.5	48.4	43.0
	Upper 95% CI of M	53.4	52.5	51.0
	p-value	0.9		
BMI, kg/m^2	M ± SE	28.9 ± 0.7	27.8 ± 0.3	26.7 ± 0.7
	Lower 95% CI of M	27.5[a]	27.1	25.1
	Upper 95% CI of M	30.4	28.5	28.3
	p-value	0.04		

Notes: M ± SE – Mean ± Standard Error; CI – confidence interval; BMI – body mass index; one-way ANOVA with Tukey's multiple comparisons test at the level of 0.05; [a] – represented significant analysis between G1 and G3.

Table 2

Statistical analysis of FBXW7 and TFA levels across all study groups

Parameters	Statistical indicators	G1 (n = 31)	G2 (n = 65)	G3 (n = 28)
FBXW7, ng/mL	M ± SE	3.860 ± 0.514[a, c]	2.00 ± 0.19[c]	2.71 ± 0.27
	Lower 95% CI of M	2.79	2.31	2.12
	Upper 95% CI of M	4.93	3.08	3.29
	p-value	0.02		
TFA, µmol/L	M ± SE	15.0 ± 1.7[a, c]	18.7 ± 1.8[b, c]	24.8 ± 4.0
	Lower 95% CI of M	11.4	15.0	16.5
	Upper 95% CI of M	18.5	22.5	33.1
	p-value	0.05		

Notes: M ± SE – Mean ± Standard Error; TFA – total fatty acid; CI – confidence interval; FBXW7 – F-box and WD repeat domain-containing protein 7; one-way ANOVA with Tukey's multiple comparisons test at the level of 0.05; [a] – represented significant analysis between G1 and G3; [b] – represented significant analysis between G2 and G3; [c] – represented significant analysis between G1 and G2.

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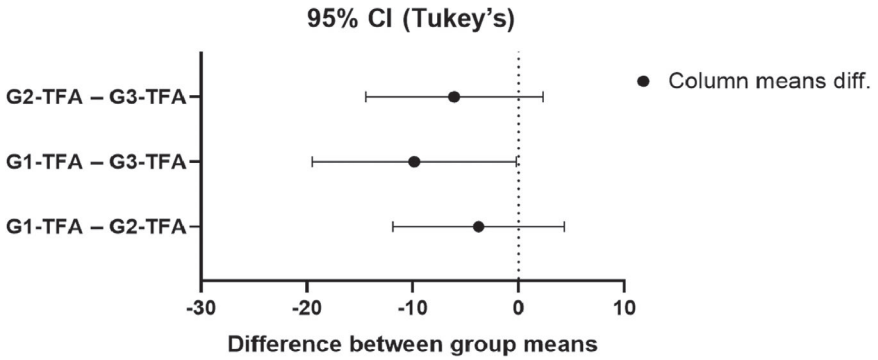

Fig. 2. 95% CI and the variation in group means of TFA

Notes: TFA – total fatty acid; CI – confidence interval.

15 μmol/L. Women with T2DM, showed a slightly higher level of 18.7 ± 1.8 μmol/L, as shown in Table 2 and Fig. 2. G3, exhibited the highest concentration at 24.8 ± 4.0 μmol/L. The results show a clear difference in fatty acid levels, with G3 having much higher amounts than the G2 and G1.

The comparative examination of metabolic parameters between G2 and G3 has produced significant discoveries. Significant differences were identified in very-low-density lipoprotein (VLDL) and triglyceride (TG), as shown in Table 3. The levels of total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) did not significantly differ between the G2 and G3. Fasting blood glucose (FBG) and HbA1c levels showed significant differences among all studied groups (Table 3).

Table 3

Statistical analysis of TG, cholesterol, LDL, HDL, VLDL, FBG, and HbA1c levels in all study groups

Parameters	Statistical indicators	G1 (n = 31)	G2 (n = 65)	G3 (n = 28)
TG, mg/L	M ± SE	169.0 ± 18.4	200.0 ± 13.2[b]	144.0 ± 13.5
	Lower 95% CI of M	132.0	173.0	116.0
	Upper 95% CI of M	207.0	226.0	172.0
	p-value	0.03		
Cholesterol, mg/L	M ± SE	192.0 ± 10.9	191.0 ± 5.3	188.0 ± 7.4
	Lower 95% CI of M	169.0	180.0	173.0
	Upper 95% CI of M	214.0	201.0	203.0
	p-value	0.9		
HDL, mg/L	M ± SE	20.5 ± 1.7	25.5 ± 1.6	23.5 ± 2.3
	Lower 95% CI of M	16.9	22.2	18.3
	Upper 95% CI of M	24.1	28.7	28.1
	p-value	0.17		
LDL, mg/L	M ± SE	137.0 ± 9.3	125.0 ± 4.4	136.0 ± 7.4
	Lower 95% CI of M	118.0	117.0	121.0
	Upper 95% CI of M	156.0	134.0	151.0
	p-value	0.3		
VLDL, mg/L	M ± SE	33.8 ± 3.6	39.9 ± 2.6[b]	28.8 ± 2.7
	Lower 95% CI of M	26.3	34.6	23.2
	Upper 95% CI of M	41.3	45.2	34.3
	p-value	0.039		
FBG, mg/L	M ± SE	97.5 ± 3.0[a, c]	149.0 ± 9.5[b, c]	92.9 ± 3.4
	Lower 95% CI of M	91.3	175	85.7
	Upper 95% CI of M	104	214	100
	p-value	0.0001		
HbA1c, %	M ± SE	6.00 ± 0.03[a, c]	8.50 ± 0.19[b, c]	5.30 ± 0.04
	Lower 95% CI of M	5.9	8.1	5.2
	Upper 95% CI of M	6.0	8.9	5.4
	p-value	0.0001		

Notes: M ± SE – Mean ± Standard Error; CI – confidence interval; TG – triglyceride; HDL – high-density lipoprotein; LDL – low-density lipoprotein; VLDL – very-low-density lipoprotein; FBG – fasting blood glucose; one-way ANOVA with Tukey's multiple comparisons test at the level of 0.05; [a] – represented significant analysis between G1 and G3; [b] – represented significant analysis between G2 and G3; [c] – represented significant analysis between G1 and G2.

Cluster analysis of the data for DM patients

Cluster analysis organizes data into clusters, grouping items according to their similarity using a statistical approach. When authors have a new dataset and are in the early stages of understanding it, cluster analysis can provide a much-needed guide. Cluster analysis has been applied to the 65 women with T2DM, and the results showed that those women were divided into two clusters using the data from FBXW7 and TFA (Fig. 3).

As shown in Fig. 3 in cluster 1 the distribution of both parameters TFA, and FBXW7 were fit with the original distribution of all the data. Whereas the distribution in cluster 2 differed. Also, the results showed that cluster 1 size was 90% which mean that the data is homogenized, and the two variables showed similar distribution in cluster. When compared FBXW7 protein with TFA in case of diabetic the results showed that TFA was more predictor parameters rather than FBXW7 (Fig. 4). Cluster analysis results indicated that the studied factors, TFA and FBXW7, are important for diagnosing and tracking diabetes in women because they are related to metabolic syndrome.

Cluster analysis was also applied using FBG, and HbA1c the routine diagnostic parameters and TFA, with FBXW7 the new parameters. The results conformed the distribution of the patients in to two clusters (Fig. 5).

This study aimed to measure the levels of FBXW7 and TFAs in women who are prediabetic, T2DM, and healthy to understand their potential roles in the development and progression of DM in women. The studied parameters (FBXW7, TFAs, BMI, TG, HDL, LDL, VLDL, cholesterol, FBG, and HbA1c) were discussed in physiological matters. Higher BMI in the G2 compared to G3 could indicate that increased body weight is a significant risk factor for developing diabetes especially in women. This difference in BMI underscores the importance of managing body weight to prevent the onset of T2DM, especially in women identified as prediabetic. It also highlights the need for targeted interventions focusing on weight reduction and lifestyle modifications to mitigate the risk of progressing to T2DM. Further research is warranted to explore the mechanisms by which BMI influences diabetes progression and to develop effective strategies for weight management in prediabetic populations. Overall, these findings contribute to the understanding of the role of BMI in diabetes progression and emphasize the importance of weight management in preventing T2DM.

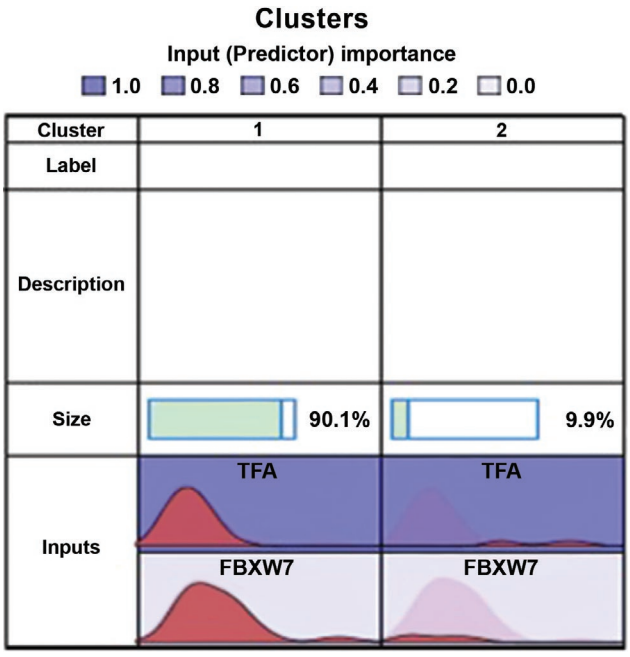

Fig. 3. Distribution of women in to two clusters

Notes: TFA – total fatty acid; FBXW7 – F-box and WD repeat domain-containing protein 7.

There is a triangle connection (BMI, FBXW7, TFA) that might help to explain how obesity can lead to prediabetes and T2DM, making FBXW7 a possible marker and control center for fat processing and insulin response. There is a negative link between FBXW7 levels and BMI / TFAs, indicating that low body fat and TFA levels might cause a rise in FBXW7 expression. This downregulation may hinder its typical regulatory functions, facilitating the advancement of metabolic disorders such as T2DM.

The elevated fatty acid concentration in G3 may be associated with their dietary habits, potentially reflecting a higher consumption of fats. This data indicates that G3 diet contains a higher concentration of fatty acids, especially

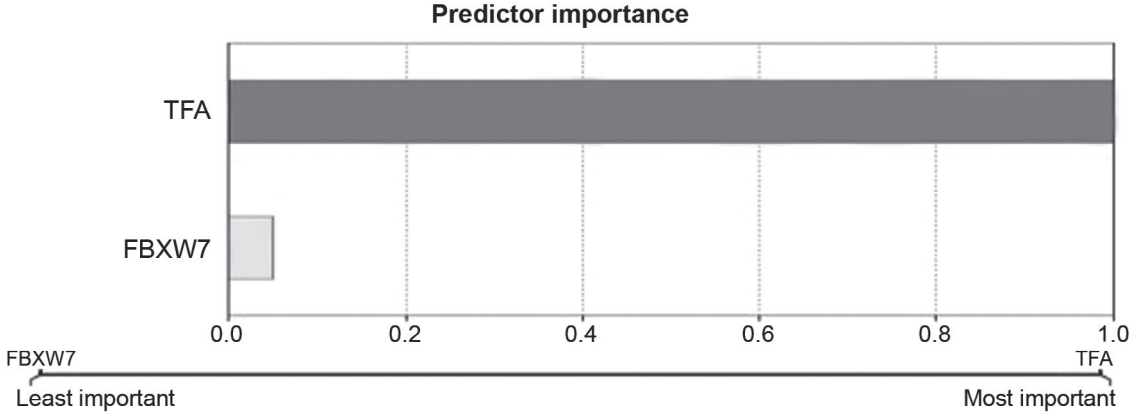

Fig. 4. Predictor importance of the two variables – TFAs, and FBXW7

Notes: TFAs – total fatty acids; FBXW7 – F-box and WD repeat domain-containing protein 7.

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long-chain fatty acids, which are recognized for their ability to increase serum fatty acid levels. Metabolic regulation refers to the processes that control the biochemical pathways involved in metabolism, ensuring homeostasis and efficient energy utilization within the organism. Lower levels in the G1 and G2 might indicate a problem with how fats are processed in the body, which is connected to the start and development of diabetes.

Insulin resistance, a characteristic of T2DM, can modify lipid metabolism, resulting in variations in fatty acid concentrations physiological adaptations, G1 fatty acid levels, although elevated compared to G2, remain considerably lower than those of G3. Such behavior may indicate preliminary metabolic alterations prior to the complete manifestation of DM. These individuals may be in a transitional metabolic state when the body's regulating mechanisms are starting to deteriorate yet have not progressed to the severity shown in full-blown diabetes.

The increased levels in G3 may indicate a lack of the metabolic dysregulation observed in diabetic situations. Elevated fatty acid levels may signify a more vigorous or distinct metabolic condition in contrast to individuals with impaired glucose and lipid metabolism. These observations underscore the importance of understanding the role of dietary fatty acids and their metabolic processing in the context of diabetes. The higher levels in G3 could imply that, while higher dietary fat intake raises serum fatty acid levels, it may not necessarily correlate with immediate adverse metabolic outcomes in non-diabetic women. Conversely, the lower levels in diabetic groups suggest metabolic alterations that warrant further investigation. These findings underscore the intricate relationship among food, metabolism, and disease state. They propose that regulating dietary fat consumption may be essential in preventing or alleviating the advancement of diabetes and underscore the necessity for additional research to examine these correlations more thoroughly. A high-fat diet, particularly one heavy in saturated fats, is a substantial risk factor for the development of T2DM. Elevated amounts of long-chain saturated fatty acids are a result of such diets [27–29].

Free fatty acids, and TFAs are altered differently during different gestation periods. Total plasma fatty acids levels increased in pregnant women with gestational DM (GDM) in early pregnancy, then decreased, which made alteration in the level of TFA, this results support what the author proved in the current study [30]. Other studies found that maternal free fatty acids in one pregnant woman's first trimester were positively correlated with the risk of GDM. Additionally, there were joint effects between FFAs on GDM risk [31]. On the other hand, elevated VLDL levels in G2 can be attributed to the dysregulation of lipid metabolism, which is a common feature in diabetes. This elevation is likely due to increased hepatic production and impaired clearance of VLDL particles in diabetic patients.

Diabetes profoundly affects glucose metabolism, it may not always significantly alter these lipid parameters [32]. It also highlights the complexity of lipid metabolism in diabetes, where some individuals may not exhibit typical dyslipidemia patterns. The clustering technique is a robust unstructured statistical method that categorizes data into discrete categories, or clusters, based on shared characteristics across subjects over several factors. This method is particularly beneficial when scientists investigate a novel dataset and aim to reveal concealed patterns or inherent groups within the population. This study employed cluster analysis on a dataset of 96 women diagnosed with T2DM. The research effectively categorized the patients into two separate clusters, indicating inherent variability among individuals with diabetes. These clusters presumably indicate metabolic or biochemical distinctions that may not be evident through conventional classification based only on clinical diagnosis. Differentiations in variables such as FBXW7, TFAs may facilitate the distinction. Identifying these clusters can yield insights into patient subgroups, illness development, or potential therapeutic efficacy.

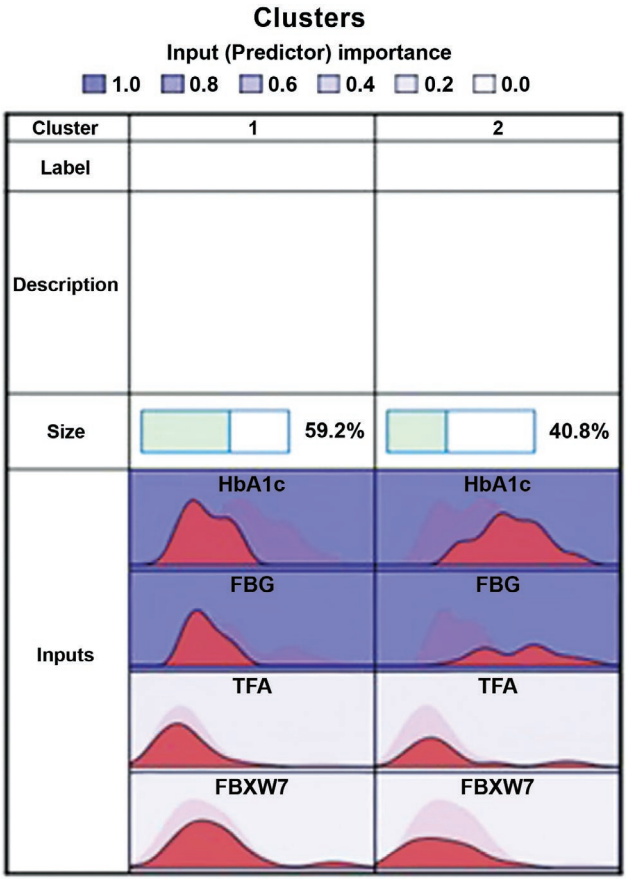

Fig. 5. Distribution of patients in to two clusters using parameters HbA1c, FBG, TFAs, and FBXW7

Notes: FBG – fasting blood glucose; TFAs – total fatty acids; FBXW7 – F-box and WD repeat domain-containing protein 7.

CONCLUSIONS

In conclusion, FBXW7 levels are elevated in the prediabetes cohort, whereas TFA levels peak in G3, exhibiting a significant reduction in both prediabetic and diabetic states. These findings highlight the possible function of FBXW7 and TFA as indicators in the transition from prediabetes to diabetes in women. The data is predominantly homogeneous, with most points conforming to a consistent pattern, although a minor subset displays diversity. Furthermore, researchers recognize TFA as a significant

predictor in diabetes, offering crucial insights for further research or therapeutic applications.

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Conflict of interest. The authors declare no conflicts of interest.

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