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New Biomarkers in Diagnosis of Diabetes Mellitus: A Review

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ABSTRACT

Millions of individuals worldwide suffer from diabetes mellitus, a chronic metabolic condition caused by either insulin resistance or insufficiency. Accordingly, it is divided into Types 1 and 2 diabetes mellitus, and Gestational Diabetes (diabetes related to pregnancy). Insulin injections are used to treat diabetes type 1, which is caused by lack of insulin as a result of the autoimmune destroy of β-cells in pancreas. Insulin resistance (lack of insulin function) and impaired insulin secretion combine to cause diabetes type 2, which is the most common type. Consequently, there are anomalies in the metabolism of proteins, fats, and carbohydrates. By altering the endocrine glands' ability to produce hormones, diabetes mellitus also contributes to the emergence of secondary metabolic disorders. Diabetes mellitus is a serious health issue because of increased Incidence and mortality rate, increased cost of treatment, and considerable impact on people's lives owing to lost productivity. Furthermore, research conducted globally indicates that a large number of people have undiagnosed diabetes and prediabetes. Newly identified Important indicators for glucose regulation and the reason of metabolic diseases like diabetes mellitus have been brought to light by recent research. Presenting recently discovered Prognostic and diagnostic biomarkers of diabetes mellitus with recent advancements is the goal of this review. It has been suggested that employing novel Diabetes biomarkers as indicators of risk and associated information could help clinical evaluations by enabling the early detection of diabetic complications.

الواسمات الحيوية الجديدة في تشخيص داء السكري: مراجعة علمية

صبـأ إبراهيم صالح

الخلاصة

يُعَدّ داء السكري من الأمراض الاستقلابية المزمنة التي يعاني منها ملايين الأشخاص حول العالم، وينتج عن مقاومة الإنسولين أو عدم كفايته. وبناءً على ذلك، يُقسَّم إلى ثلاثة أنواع رئيسية: السكري من النوع الأول، والسكري من النوع الثاني، وسكري الحمل (المرتبط بفترة الحمل).
يُعالَج السكري من النوع الأول باستخدام حقن الإنسولين، وذلك بسبب نقص الإنسولين الناتج عن التدمير المناعي الذاتي لخلايا **β**في البنكرياس. أما السكري من النوع الثاني – وهو الأكثر شيوعاً – فينتج عن مزيج من مقاومة الإنسولين (ضعف وظيفته) وضعف إفراز الإنسولين. ونتيجة لذلك، تحدث اضطرابات في استقلاب البروتينات والدهون والكربوهيدرات.
يُسهِم داء السكري أيضاً في ظهور اضطرابات استقلابية ثانوية من خلال تأثيره على قدرة الغدد الصمّاء على إنتاج الهرمونات. ويُعدّ داء السكري مشكلة صحية خطيرة بسبب ارتفاع معدلات الإصابة والوفيات، وارتفاع تكلفة العلاج، وتأثيره الكبير على حياة الأفراد نتيجة انخفاض الإنتاجية. إضافة إلى ذلك، تُشير الدراسات العالمية إلى أن أعداداً كبيرة من الأشخاص يعانون من السكري غير المُشخَّص ومقدمات السكري.
وقد سلطت الأبحاث الحديثة الضوء على مؤشرات جديدة مهمة لتنظيم الغلوكوز وأسباب الأمراض الاستقلابية مثل داء السكري. يهدف هذا الاستعراض إلى عرض أحدث المؤشرات التنبؤية والتشخيصية المكتشفة حديثاً لداء السكري، مع التطورات العلمية المرتبطة بها. وقد اقتُرح أن استخدام الواسمات الحيوية الجديدة للسكري كمؤشرات خطورة أو معلومات مساندة قد يساهم في تحسين التقييمات السريرية من خلال تمكين الكشف المبكر عن مضاعفات السكري.

1. Introduction

Hyperglycemia and glucose intolerance are the hallmarks of diabetes mellitus, which is recognized as a syndrome, a group of illnesses caused by either an insufficient amount of insulin, a reduction in the efficiency of insulin's action, or a combination of both (Mir et al., 2025). The typical physiological processes that take place during and after a meal must be understood in order to comprehend diabetes. Food travels via the digestive tract, where the bloodstream absorbs nutrients, such as proteins, fats, and carbs. An endocrine pancreas is triggered to release the hormone insulin when sugar, a carbohydrate, is present. Almost every type of tissue in the body, but particularly the liver, muscles, and fat tissues, absorbs and stores sugar as a result of insulin (Yang et al., 2024). Although there is currently no treatment for diabetes, the chance of developing long-term problems from the disease can be reduced by managing blood sugar levels with medication, exercise, and a nutritious diet (Chatterjee & Davies, 2015). Long-term complications that can be experienced are (Amsalu et al., 2024) :

-Eye conditions that can cause blindness include cataracts and retinopathy, which are gradual damage to the eye.

-Kidneys: renal failure and kidney disease

-Nerves - neuropathy (slow nerve damage)

-Feet: gangrene, ulcers, infections, etc.

-Heart disease, stroke, and arterial stiffening in the cardiovascular system.

1.1. Classification of Diabetes Mellitus

Appropriate classification is a key prerequisite for systematic epidemiologic and clinical research on diabetes mellitus and for its therapy. Additionally, the ability to recognize and distinguish between a disease's numerous forms and arrange them within a logical etiopathologic framework is a necessary component of comprehending the etiology of a disease and researching its natural history. In Western nations, there are two main types of diabetes: Type II diabetes, or non-insulin dependent diabetes mellitus, and type I diabetes, or insulin-dependent diabetic mellitus (Ivan, 2024; Zhou et al., 2025). The body is unable to manufacture insulin in T1D due to an autoimmune breakdown of the beta-cells in the pancreas. As a result, the body cannot efficiently reduce blood sugar. About 5–10% of diabetes cases are of this kind, which often appears in childhood and early adulthood. In T2D, however, the body cannot respond appropriately to insulin. Here, insulin-resistant cells are unable to absorb glucose in response to insulin stimulation, which results in glucose remaining in the blood and raising blood glucose levels. T2D accounts for about 85% of all instances of diabetes and is frequently associated with the metabolic syndrome, which is characterized by dyslipidemia, hypertension, and adipositas (Forbes & Cooper, 2013; Harjutsalo et al., 2008). In addition to these reasons, gestational diabetes is another way that chronic hyperglycemia can appear during pregnancy, as a result of drugs (like steroids) may result from genetic abnormalities, such diabetes mellitus in newborns or Diabetes of the Young with Maturity Onset. Any portion of the body might be affected by diabetes. Excessively elevated blood glucose levels have the potential to either quickly upset the body's balance through hyperosmolarity or ketoacidosis, alternatively they could gradually harm any tissue by compromising its circulatory system (Anyanwagu et al., 2016; Banday et al., 2020; Mittal et al., 2025).

1.2. Complications and Diagnosis Of DM

Nonketotic hyperosmolar condition, diabetic ketoacidosis, Lactic acidosis, and hypoglycemia are some of consequences of diabetes mellitus, on the other hand, microvascular complications, such as nephropathy, coronary artery disease, retinopathy, neuropathy, hypertension and macrovascular complications, such as peripheral vascular disease and cerebrovascular disease, are the two types of chronic problems. Diabetes-related complications are more likely to occur as the disease's incidence rises, which poses a serious morbidity and mortality issue for public health. These days, tests including the oral glucose tolerance test (OGTT), glycosylated hemoglobin A1c (HbA1c), postprandial postprandial glucose (PPG), and fasting plasma glucose (FPG) are utilized to identify DM. These four criteria can be used to diagnose apparent diabetes mellitus (Cloete, 2022; Tegegne et al., 2024; TEMD Diabetes Mellitus Çalışma ve Eğitim Grubu, 2022). American Diabetes Association defined diabetes mellitus (DM) as FPG, or fasting plasma glucose more than 126 mg/dL (≥ 8 hours with no food), 75 g of glucose for the oral glucose tolerance test (OGTT), postprandial glucose more than 200 mg/dL, Measured using the High-performance liquid chromatography method (HPLC), glycosylated hemoglobin (HbA1c) ≥ 6.5% in the presence of diabetes symptoms ("Glycemic Targets: Standards of Medical Care in Diabetes−2021," 2021).

Discovering novel biomarkers to identify people High-risk individuals for diabetes and its consequences are now given priority in focusing on preventative care because of the existing circumstances, this calls for prompt diagnosis and the development of a safe and efficient treatment plan. To aid in the prediction, prevention, and treatment of diabetes mellitus, for a subset of individuals with different underlying pathophysiologies and differences in the rate at which the disease progresses, more accurate biomarkers need to be discovered ("Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020," 2020; Tegegne et al., 2024; TEMD Diabetes Mellitus Çalışma ve Eğitim Grubu, 2022). In the clinical context, combining biomarkers may increase the sensitivity and specificity of illness prediction and prevention. Finding new DM biomarkers is essential to creating non-invasive, painless, and incredibly sensitive screening methods. These new biomarkers have the potential to supplement or perhaps replace traditional DM markers with additional confirmation. The goal of the review is to identify new biomarkers in kinds of diabetes mellitus and their present capacity to evaluate risk for improved clinical results ("Glycemic Targets: Standards of Medical Care in Diabetes−2021," 2021; Ortiz-Martínez et al., 2022).

1.3.Afamin

The glycoprotein Afamin with a molecular weight (87 kDa) and its amino acid sequence is 55% similar to that of albumin. However, it differs from albumin in that it is glycosylated in a complicated manner. The liver is where afamin is mostly expressed and released into the blood stream. Although afamin's physiological role is unclear, it is believed to play a role in the transport of tiny, hydrophobic molecules (Dieplinger & Dieplinger, 2015; H. & B., 2015). Vitamin E has been demonstrated to be transported across the blood-brain barrier via afamin, hence believed to act as an antioxidant to protect neurons from oxidative damage. Patients with sepsis or pneumonia have been found to have lower plasma afamin levels (Kratzer et al., 2009). Regardless of the main metabolic risk variables or characteristics, afamin is substantially linked to the prevalence, insulin resistance, and incidence of type 2 diabetes, according to a meta-analysis research including almost 20,000 people. Additionally, it has been announced that Afamin may serve as a promising novel biomarker for identifying those at elevated risk of acquiring type 2 diabetes. Children with type

1 diabetes have a condition where their bodies are unable to manufacture insulin. Serum afamin levels in 138 children with T1D, ages 5 to 18, were examined by Polkowska et al. The study found that serum afamin levels were lower in all subgroups than in the control group (B. et al., 2017; Kollerits et al., 2017). According to a recent study, pregnant women with gestational diabetes mellitus had higher plasma afamin levels in the first trimester, but the findings were reversed in the second and third trimesters. Other study posits that Afamin ought to be a standard diagnostic test for women diagnosed with gestational diabetes mellitus. Urinary afamin levels have been linked to the advancement of diabetic nephropathy (DN), according to Kaburagi et al. (B. et al., 2017; Yuan et al., 2023).

1.4.Cartonectin (CTRP-3)

Karducin is another name for cartonectin. is a newly discovered adipokine that is a member of the C1q/TNF superfamily that released from human adipose tissue. It plays a part of energy metabolism and immunological control and is released from visceral and subcutaneous adipose tissue (27). CTRP3's physiological function operates through endocrine pathways, also, Vascular calcification, fibrosis, ischemia damage, inflammation, proliferation, apoptosis, and metabolism are all impacted by CTRP3. According to a study by Ban et al,2014, levels of CTRP-3 are reduced in obese and hypertensive individuals. They also exhibited a positive link with insulin, HOMAIR, and leptin levels, and a negative correlation with insulin resistance, glucose, and CRP. Additionally, other study indicates that CTRP-3 may be utilized for early diagnosis of T2DM. In another study by Yakar et al., 2020, who found that women with gestational diabetes (GDM) had lower serum levels of CTRP-3, and it is thought that CTRP-3 plays a part in the etiology of GDM (Guo et al., 2020). In retinal cells produced by high glucose, overexpression of CTRP3 has been shown to promote cell survival and apoptosis while lowering oxidative stress. CTRP3 may be a novel indicator for retinopathy caused by Diabetes Mellites and a novel therapy option for the condition, according to both historical and contemporary research. According to Soha et al., adolescents with T1D had noticeably increased serum CTRP-3 concentrations. In the cross-sectional investigation, CTRP-3 significantly correlated negatively with HDL and negatively with total cholesterol/HDL, and triglyceride/HDL. Additionally, they suggested that CTRP-3 might serve as an indicator for lipid disorder in T1DM. Additionally, Moradi et al. showed that individuals with T2D and diabetic nephropathy had much lower serum CTRP-3 levels than healthy controls (Abd El Dayem et al., 2018; Zhang & He, 2019).

1.5.Fibulin

Is a protein of a class of secretory glycoproteins present in membranes, basement elastic fibers, and other extracellular matrix proteins? Fibulin family proteins have a C-terminal structure and epidermal growth factor (EGF) like units. There are two subgroups of fibulins. Fibulin type1 (100 kDa) and Fibulin type 2 (200 kDa) make up the first group. Forms 3, 4, 5, 6, and 7 of the fibulin are included in the second category (34). Fibulin-1 is a protein found in the extracellular matrix that covers the elastic artery lamina and vascular smooth muscle cells. According to a study by Scarinci et al., 2019, it may interact with other ECM components to influence cell adhesion, migration, and proliferation (Scarinci et al., 2019). Fibulin type 1 may play a role in forecasting damage of endothelia in death of patients with DM and cardiovascular disease, according to Cangemi et al 2011, They also came to the conclusion that fibulin-1 appears to be a factor linked to alterations in the arterial extracellular matrix in T2DM and it builds up in the diabetic person's plasma and artery wall (C. et al., 2011; Cangemi et al., 2011). Increased plasma fibulin type 1 was linked to DM and poor renal function, according to another study. Fibulin-1 and angiogenesis are strongly connected.

Serum and vitreous fibulin-1 concentrations were found to be higher in diabetic retinopathy (DR) patients, according to a study that examined these levels. Diabetic nephropathy's (DN) pathophysiological mechanisms are complex and multidimensional. The mesenchymal transition (EMT) of excess extracellular matrix (ECM) proteins and epithelial accumulation in the tubulointerstitium are the defining characteristics of DN, and they also play a role in the latter stages of renal fibrosis. According to another study, autocrine exosomal fibulin type 1 causes the proximal tubule in DN to undergo an epithelial-mesenchymal transition (C. et al., 2011; Cangemi et al., 2011; Scholze et al., 2013; Tian et al., 2016).

1.6.Subfatin

Adipocytes produce the newly identified hormone subfatin, which is involved in controlling glucose metabolism. A particular gene known as MERTRNL (similer of meteorin) codes for the protein subfatin, a tiny cytokine that is around 27 kDa in size. It is extensively expressed in activated macrophages, mucosal tissues, and skin (Onalan et al., 2020). Subfatin improves adipose function, which in turn inhibits inflammation, activates metabolism, and promotes adipocyte differentiation, so counteracting the effects of obesity-induced insulin resistance. Patients with diabetes type 2 have low concentration of subfatin, which contributes significantly to the pathophysiology and increases insulin resistance. Elevated subfatin levels play a crucial part in halting the release of inflammatory mediators. Increased levels of subfatin improved glucose tolerance and the intercellular insulin signal (Hassan et al., 2023; Yilmaz et al., 2022). In macrophages, adipocytes, cardiomyocytes, and myocytes, it may initiate and activate many intracellular signaling pathways. Subfatin's impacts on cardiometabolic disorders such type 2 diabetes, obesity and coronary heart disease are hypothesized to contribute to the metabolic syndrome disorders. Subfatin may therefore be a promising target for metabolic syndrome treatment (Alizadeh, 2022; Yilmaz et al., 2022). Subfatin uses the PPARγ (peroxisome proliferator activated receptor-γ) pathway to regulate insulin sensitivity with local autocrine/paracrine activity. Yavuzkir et al. looked into the subfatin levels in the blood of mothers and umbilical cords in GDM patients. Blood samples obtained at baseline from moms with GDM in the study showed a significantly higher level of subfatin. Similar findings were noted in maternal and cord blood samples at the end of pregnancy (Alizadeh, 2022; Li et al., 2015; Yavuzkir et al., 2020). Another study found that, in comparison to those without diabetes, the T2DM and prediabetes groups had decreased serum subfatin levels. In a recent investigation, plasma and aqueous subfatin levels were measured in patients with diabetic retinopathy (DR).. DR patients had greater amounts of plasma and aqueous subfatin than controls. Compared to the other T2D categories, the macroalbuminuria group's T2D patients (DN) had considerably lower serum subfatin concentrations. Additionally, the study demonstrated a link between serum subfatin and a lower incidence of DN and T2D (Fadaei et al., 2020; Güngör Kobat et al., 2023; Yavuzkir et al., 2020).

1.7.Fructosamine

Fructosamine (1-amino-1-deoxy fructose) is a term refers to all glycated plasma proteins. It is a ketoamine resulting from the irreversible nonenzymatic binding of glucose to plasma proteins through a process known as glycation. Glycation is a nonenzymatic process in which glucose covalently binds to the lysine, arginine, and cysteine amino-group residues in protein molecules, forming a labile Schiff base (aldimine) early on and then rearranging it to a stable Amadori product (ketoamine).When glycated hemoglobin (HbA1c) is not recommended for this reason, fructosamine serves as an alternate biomarker of glycemic control since its values represent blood glucose levels over a period of

two to three weeks (Andrade et al., 2023; de Oliveira Andrade LJ et al., 2023; Krhač & Lovrenčić, 2019). Fructosamine is better suited for tracking therapy response since it represents the average glucose over a period of two to three weeks, allowing for more precise glycemic control and better therapeutic adjustment, particularly in patients with unstable diabetes mellitus (Andrade et al., 2023; de Oliveira Andrade LJ et al., 2023). Blood levels of Fructosamine change more than those of HbA1c, allowing for the prompt detection of sharp variations in blood glucose. Therefore, Fructosamine measurement is useful for detecting impaired glycaemic control before apparent rises in HbA1c, as well as for use as a secondary glycaemic control indicator in situations when HbA1c is inconsistent. It is especially helpful for pregnant women with diabetes whose short-term variations need to be addressed, as well as for first-degree non-diabetic relatives of diabetics (Payot et al., 2024; Yadav et al., 2023). Study by John et al 2023 found that there was a significant increase in the level of Fructoseamine in the group of diabetics when compared to the control group, and a positive relationship was found between the levels of fructoseamine and the level of HbA1c levels. Additionally, Phadake et al 2025 found that Fructosamine was a powerful predictor of HbA1c, confirming its use in assessing short-term glycemic management (John Buckley et al., 2023; John et al., 2023; Mohammed Iqbal et al., 2023). Also, one measurement of Fructosamine significantly and alone predicts incident of retinopathy in people with HbA1c less than 7.0% (53 mmol/mol), according to another study by Iqbal et al., 2023. Even in patients with diabetes, cancer, anemia, hypoproteinemia, or chemotherapy, fructosamine and HbA1c can be employed as glycemic indicators, this result is found in research by Toyoshima et al ,2023. Study by Asorose et al, 2023 has demonstrated a strong association between serum fructosamine and FBG in T2DM patients, even showing a somewhat stronger correlation than HbA. As a result, it can be used to monitor blood glucose levels in T2DM patients who need a shorter follow-up duration and have limited financial resources (John Buckley et al., 2023; Mohammed Iqbal et al., 2023; Toyoshima et al., 2023).

2. Conclusion

Even though the researches have achieved great strides, further work is required to find novel DM biomarkers. Advances in this area are crucial for lowering the prevalence of DM and enhancing the disease's prognosis and they contribute significantly to the diagnosis and treatment of diabetes. More research are need for elucidate the complete potential of subfatin, fibulin, afamin, cartonectin and Fructosamine for DM illness.

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