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Review Article

Pharmacy for better health

Biomarkers: An Important Tool for Diagnosing and Treating Diabetes Mellitus

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Abstract: Diabetes mellitus is a group of metabolic disease caused by an abnormal increase in blood glucose levels due to abnormal activity of pancreatic beta cells. Elevated blood glucose levels causes a variety of cell damage, including endothelial cells, neurons, renal cells, keratinocytes, and fibroblasts. Chronic diabetes mellitus causes several diabetic manifestations such as diabetic neuropathy, diabetic nephropathy, diabetic myopathy, and diabetic dermopathy. There are many causes and risks of diabetes mellitus, including type 1 diabetes caused by bacterial infections, chemical poisoning with food, and self-resistance; Type 2 diabetes is caused by obesity, weight gain, prediabetes and family history, and type 3 is caused by Cushing's syndrome. Diabetes mellitus treatment has encountered a few progressions in the previous decades with the revelation of explicit prescient prognostic biomarkers that make conceivable the use of individualized treatments. Various hypoglycemic oral and parenteral dosage formulations are used to treat diabetes mellitus, but insulin therapy is one of the most effective treatments for type 1 and type 2 diabetes and its complications. Various conventional diagnosing and treating methods of diabetes mellitus are available but there are limitations of resistance and, accuracy. For that reason now a day's various biomarkers like Autoantibodies, C-reactive protein (CRP), Fibrinogen, Interleukin-1 receptor antagonist (IL-1RA), Plasminogen activator inhibitor (PAI-1), etc. are used for diagnosis; Adiponectin, microRNA, Acylcarnitine, Haemoglobin A1c, etc. are used for treatment, and 1,5-anhydroglucitol are used for both diagnosis and treatment of diabetes mellitus. In this review, we discussed the functions, application and limitations of diabetes biomarkers in their use as diagnostic and treatment. These biomarkers are of paramount importance in the assessment and diagnosis process, leading to better care and protection of patients. Due to its various advantages, biomarkers are considered as an innovative tool in the advancement of diagnosis and treatment of diabetes mellitus.

Keywords: Diabetes mellitus; biomarkers; 1,5-anhydroglucitol; C-reactive protein; microRNA; Haemoglobin A1C.

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1. INTRODUCTION

Diabetes mellitus is a heterogeneous group of metabolic diseases characterized by abnormally high blood sugar levels, resulting in defects in insulin secretion, insulin action, or both[1,2]. Patients with diabetes mellitus are characterized clinically by hyperglycemia which in turn leads to the production of protein kinase C, advanced glycation end-products (AGE), and significant reactive species oxygen (RSS) such as polyols[3–5]. Around 346 million people worldwide have diabetes. India has more than 50 million cases compared to other countries[6]. There are six types of diabetes Type 1, Type 2, gestational diabetes patients, latent autoimmune diabetes, Maturity onset diabetes (MODY), and Neonatal diabetic (NDM)[7-9]. There are many causes and risk factors of diabetes mellitus and among them is type1 diabetes that are caused by a bacterial infection, chemical poisoning of Food, unknown components causing an autoimmune reaction. Type 2 is caused by obesity, weight gain, wrong diet, type 3 caused by Cushing's syndrome, and glucagonoma, polycystic ovary syndrome[10–14].There are several diagnostic tests for diagnosing diabetes, including blood glucose levels and hemoglobinA1c. If the blood glucose level is 128 mg/dL or more is called prediabetes, and 200 mg/dL or more is called diabetes. On the other hand, 5.7%-6.4% of haemoglobin A1c levels are called prediabetes, and 6.5% or more is called diabetes. Oral hypoglycemic agent and insulin therapy is available for the treatment of diabetes mellitus[15]. Various conventional methods of diagnosis and treatment of diabetes mellitus are available but there are limitations in prevention, accuracy, and treatment because most of these are not compatible with each other, show serious adverse effects and high cost[2]. - Various biomarkers such as Autoantibodies, C-reactive protein (CRP), Fibrinogen, Interleukin-1 receptor antagonist (IL-1RA), Plasminogen activator inhibitor (PAI-1), and Leptin are used for diagnosis; Adiponectin, Fetuin-A, Fructosamine, microRNA, Acylcarnitine, and Haemoglobin A1c are used for treatment; and 1,5-anhydroglucitol is used both to diagnose and treat diabetes mellitus[3,16–22]. These biomarkers are of great importance in the diagnosis and treatment process which leads to better patient care and protection of the patients.

1.1 BIOMARKERS

The biomarker is a substance used as an indicator of disease status and a property that is expected and evaluated for general, pathological, and pharmacological responses to therapeutic interventions. These are biological molecules found in blood, other bodily fluids or tissues that may have clinical value and maybe elements of interest in medical practice and represent a general or abnormal process or an indication of a condition or disease[3,16].

1.2 DIABETES BIOMARKERS ARE CLASSIFIED INTO FOUR TYPES

1. Traditional biomarkers[17],
2. Novel biomarkers[6],
3. Inflammatory biomarkers[18],
4. Protein biomarkers[19].

1.2.1 TRADITIONAL BIOMARKERS

Traditional biomarkers are often well embedded in clinical practice and research, usually in proximity to a pathological event of interest. These are generally limited in analytical complexity and can range from qualitative to quantitative[17]. Example - HemoglobinA1c[20–22].

1.2.2 NOVEL BIOMARKER

Novel biomarkers are measured and evaluated as indicators of general biological processes, pathological processes, or pharmacological responses to therapeutic interventions[6]. Example- Adiponectin[21,23].

1.2.3 INFLAMMATORY BIOMARKERS

Inflammatory biomarkers are specific proteins released into the bloodstream during inflammation; if the concentration increases by at least 25%, these are used as systemic inflammatory markers[18].Example-C-reactive protein (CRP)[21].

1.2.4 PROTEIN BIOMARKER

Protein molecular biomarkers are particularly popular due to the availability of a large range of analytical instrumentation, which can identify and quantify proteins in complex biological samples[19]. Example-Leptin[19].

Table:1. Biomarkers used for diagnosing and treating diabetes mellitus

Types Of Diabetes	Biomarker Used For Diagnosis	Biomarker Used For Treatment
Type 1	**A.** Autoantibodies[24] **B.** 1,5-anhydroglucitol[21,25]	**A.** Adiponectin[21,23] **B.** Fetuin-A[6,26] **C.** microRNA[27] **D.** Acylcarnitine[21]
Type 2	**A.** C-reactive protein (CRP) [21] **B.** Fibrinogen[21] **C.** Interleukin-1 receptor antagonist (IL-1RA)[21] **D.** Plasminogen activator inhibitor (PAI-1)[21] **E.** Leptin[19, 28] **F.** 1,5-anhydroglucitol[21,25]	**A.** Haemoglobin A1c [20,22] **B.** Fructosamine[20,29] **C.** 1,5-anhydroglucitol[20,25]GA [21]
Type 3	**A.** Autoantibodies[24] **B.** 1,5anhydroglucitol[21,25]	**A.** Haemoglobin A1c[20,22] **B.** Fructosamine[20,29] **C.** 1,5-anhydroglucitol[20,25] **D.** Glycated albumin **(**GA)[21]

A group list of biomarkers used for diagnosing and treating diabetes mellitus

A. AUTOANTIBODIES[24].

Year of discovery: 1974.
Invented by:Gian Franco Bottazzo.
Function
1. AAB is developed as a result of cell death and subsequent risk of autoantigens to the immune system.
2. The development of excess abs may represent an autoimmune response or even epilation and diffuse epitope of antigen specific responses.
3. AABs are useful in predicting the development of disease in at-risk relatives of patients with T1D.
4. Constant concentrations and longer half-lives are expected due to the limited concentration and clearance of autoantibodies.
5. Large-scale production despite the presence of relatively small amounts of related antigens.

Application
1. Used for diagnosis of Type 1 and Type 3 diabetes mellitus, it was listed in Table-1.

Limitation
1. Self-response of autoantibodies can be harmful to host tissue.

B. 1,5-ANHYDROGLUCITOL[20,21,25]

Year of discovery:1981.
Invented by:Akan Uma.
Function
1. Plasma concentrations are inversely correlated with plasma glucose.
2. Plasma 1, 5 AG levels were reduced in subjects with prediabetes and diabetes compared with those with normosia.
3. 1.5 AG is a useful biomarker because it shows glucose levels in the last 10-15 days.
4. It is stable, replicable and less expensive than other glycemic diagnostic tests.

Application
1.Used for diagnosis of Type 1, Type 2 and Type 3 diabetes mellitus as well as treatment of Type 2 and type 3 diabetes mellitus, it was listed in Table-1.

Limitation
1. Plasma 1, 5 AG levels may vary depending on dietary habits, gender and colour.
2. Levels are also affected by treatment with renal hemodynamics or SGLT2 inhibitors.

C. ADIPONECTIN[21,23]

Year of discovery:1995.
Invented by:Scherer PE, Williams S, Fogliano M, Baldini G, and Lodish HF.
Function
1. Adiponectin is derived from adipose tissue and exhibits insulin sensitive, anti-inflammatory and anti-atherogenic properties.
2. Low levels of adiponectin are associated with increased IR and obesity, while higher levels are associated with lifestyle intervention groups in diabetic patients.
3. The occurrence of adiponectin levels is inversely related to the risk of pre-diabetes, apart from racial or sexual differences.
4. Immediate glucose lowering effect.
5. Applied in humans as an adjuvant to insulin therapy.

Application
1.Used for the treatment of Type 1 diabetes mellitus, it was listed in Table-1.

Limitation
1. Difficulty in administration.
2. Does not eliminate the need for insulin.

D. FETUIN-A[21,26]

Year of discovery:Early 1900.
Invented by: J. R. Army M. Corps.
Function
1. Feta is a liver secretory glycoprotein that was proposed to promote lipid-induced IR via the TLR4-inflammatory signaling pathway, resulting in the production of inflammatory cytokines.
2. Feta is associated with an increased risk of developing T2DM and related complications.
3. It plays a role in insulin resistance with increased levels seen in second diabetic patients.
4. Fetuin-A also plays a role in macrophage inhibition and inflammation.

Application
1. Used for the treatment of Type 1 diabetes mellitus, it was listed in Table-1.

Limitation
1. It is difficult to validate and require different levels of validation depending on their intended use.

E. MICRORNA[21,27]

Year of discovery:1993.
Invented by:Ambros, Lee and Feinbaum.
Function
1. miRNAs are involved in cell growth, differentiation, proliferation, and death.
2. Several miRNAs have been shown to improve in individuals with prediabetes.
3. miRNAs are considered a novel class of signalling molecules that mediate intercellular communication.
4. miRNA plasma levels added to HbA1c can become a valuable new tool for assessing the early risk of type 2 diabetes in clinical practice to prevent disease progression.

Application
1.Used for the treatment of Type 1 diabetes mellitus, it was listed in Table-1.

Limitation
1. Difficult to implement.

F. ACYLCARNITINE[21]

Year of discovery:1952.
Invented by: Friedman and Fraenkel.
Function
1. Acylcarnitines interact with NF-K which promotes inflammation and IR.
2. Acylcarnitine is essential in fatty acid metabolic pathways.
3. A recent study found that high levels of acylcarnitine may act as a useful biomarker for early detection of HCC in patients with Steatohepatitis (SH).
4. High levels of acylcarnitine are found in individuals with prediabetes.

Application

1.Used for the treatment of Type 1 diabetes mellitus, it was listed in Table-1.

Limitation

1. Difficult to implement.

G. C-REACTIVE PROTEIN (CRP)[21]

Year of discovery: 1930.
Invented by:Tillett and Thomas Francis.
Function

1. CRP was found to be more elevated in subjects who had pre-diabetes and IR than those with pre diabetes and insulin sensitive.
2. Found to be associated with pre-diabetes.
3. C-reactive protein (CRP) plays an important role in protecting against infection, clearance of damaged tissues, prevention of autoimmunity, and regulation of the inflammatory response.
4. It has both pro- and anti-inflammatory effects *in vitro* and *in vivo*.
5. Primary marker of acute phase response.

Application

1.Used for diagnosis of Type 2 diabetes mellitus, it was listed in Table-1.

Limitation

1. Cross reactivity with serum proteins.
2. Minimization and lack of on-site analysis.

H. FIBRINOGEN[21]

Year of discovery:1905.
Invented by:PaulMorawitz.
Function

1. Essential component of platelet aggregation.
2. Increases plasma viscosity.
3. Fibrinogen reactions affect blood viscosity, platelet aggregation, and fibrin formation.
4. Fibrinogen is associated with pre-diabetes and is poorly associated with diabetes.

Application

1.Used for diagnosis of Type 2 diabetes mellitus, it was listed in Table-1.

Limitation

1) Fibrinogen concentration or decreased fibrinogen function may cause bleeding.
2) Assay standardization for fibrinogen has proven difficult.

I. INTERLEUKIN-1 RECEPTOR ANTAGONIST (IL-1RA)[21]

Year of discovery: 1984
Invented by: Charles A and Dinarello
Function

1. IL-1RA is an anti-inflammatory marker that occurs when the IL-1 pathway is stimulated by glucose and releases fatty acids during lactation.
2. Decreased insulin sensitivity.
3. Temporarily increasing Tem-cell function.
4. Advanced prediabetes and diabetes.
5. Has the ability to form a β-cell.

Application

1.Used for diagnosis of Type 2 diabetes mellitus, it was listed in Table-1.

Limitation

1) Difficulty managing within the body.

J. PLASMINOGEN ACTIVATOR INHIBITOR.(PAI-1)[21]

Year of discovery:1989.
Invented by:Lindahl and Wiman.
Function

1. PAI-1 plays an important role in the progression of fibrosis.
2. Eurokinase inhibits plasminose activator (uPA).
3. Independent predictor of diabetes**.**
4. Act as a marker of low fibrinolysis.

Application

1.Used for diagnosis of Type 2 diabetes mellitus, it was listed in Table-1.

Limitation

1. High concentrations of PAI-1 have been associated with thrombophilia.

K. LEPTIN[28]

Year of discovery: 1994.
Invented by:Jeffrey Friedman.
Function

1. Leptin is an important factor related to the regulation of food intake and also plays an important role in the pathology of obesity.
2. Leptin plays an important role in the adaptive response to starvation.
3. It controls energy balance.
4. It is found to mediate insulin secretion.
5. Leptin reaches the hypothalamus through the blood – brain barrier and acts to reduce food intake and increase metabolism.

Application

1.Used for diagnosis of Type 2 diabetes mellitus, it was listed in Table-1.

Limitation

1) Leptin responsive cells are difficult to identify.

L. HAEMOGLOBIN A1C[20–22]

Year of discovery: 1958.
Invented by:Huisman and Meyering.
Function

1. HbA1c is a reflection of chronic glycemia.
2. HbA1c is associated with more convenience. Pre-analytical stability during periods of stress and illness, and disturbances.
3. HbA1c is formed when glucose binds to the amino-terminal group of 1 subunit of haemoglobin.

Application

1.Used for the treatment of Type 2 and Type 3 diabetes mellitus, it was listed in Table-1.

Limitation

1. HbA1c has a moderate sensitivity in diagnosing diabetes compared to OGTT and FPG.
2. HbA1c polarity for predisposition does not take into account ethnicity, BMI, and age, all of which can significantly alter HbA1c levels.
3. HbA1c is not always a reliable measure for measuring the average prevalence of glucose levels.

M. FRUCTOSAMINE[21,29]

Year of discovery: 1886.
Invented by:Hermann Emil Fischer.
Function

1. FA is a ketamine composed primarily of glycosylation of total albumin serum protein.
2. This is especially useful in situations where hemoglobin status or erythrocytes affect the exchange rate.
3. FA is expensive, easy and convenient, because it does not require fasting.
4. FA increases with high glucose concentration.

Application

1.Used for the treatment of Type 2 and Type 3 diabetes mellitus, it was listed in Table-1.

Limitation

1. The FA contains a false level of conditions leading to subject variation height and rapid albumin turnover.
2. Not all studies have shown that serum FA levels are useful for prebiotic screening.

N. GLYCATED ALBUMIN (GA)[21]

Year of Discovery: 1980.
Invented by: Keeney M. and Bassette R.

Function

1. GA is a better indicator of glycemic control than HbA1c in patients with renal failure, hemolyticanemia, and circulatory system.
2. In clinical situations such as nephrotic syndrome, liver disease, and thyroid disease, protein loss is a preference for GA over FA.
3. GA can be artificially reduced in individuals with increased BMI, body fat mass and visceral fat.

Application

1.Used for the treatment of Type 3 diabetes mellitus, it was listed in Table-1.

Limitation

1. When the turnover on the album changes.
2. Lower level of obesity.

2. DISCUSSION

Different types of diabetes and its manifested diseases such as diabetic neuropathy, diabetic nephropathy, diabetic myopathy, and diabetic dermopathy are crucial for successful treatment and management. There is an urgent need for an appropriate non-invasive tool to manage diabetes mellitus and manifested diabetes mellitus. Various conventional diagnosis and treatment methods are available for diabetes mellitus, but there are limitations and justifications for prevention. Biomarkers are a great tool that can overcome the limitations of diagnosis and treatment of diabetes and diabetes manifested chronic diseases. In this review, we have noted the efficacy, application, and limitations of different biomarkers for the detection and treatment of different types of diabetes mellitus. The listed biomarkers are Autoantibodies, 1,5-anhydroglucitol C-reactive protein (CRP), Fibrinogen, Interleukin-1 receptor antagonist (IL-1RA), Plasminogen activator inhibitor (PAI-1), Leptin, Adiponectin, Fetuin-A, microRNA, Acylcarnitine, Haemoglobin A1c, Fructosamine, and Glycated albumin (GA). Among these 1,5-anhydroglucitol biomarkers is used to diagnose type 1, type 2, and type 3 diabetes and to treat type 2 and type 3 diabetes mellitus. A graphical representation of the reabsorption of 1,5-anhydroglucitol in normal and hyperglycemic states is listed below. It is crucial to continue research with biomarkers to address some of the clinical features that are missing in the management of chronic diabetic diseases such as diabetic neuropathy, diabetic nephropathy, diabetic myopathy, and diabetic dermopathy.

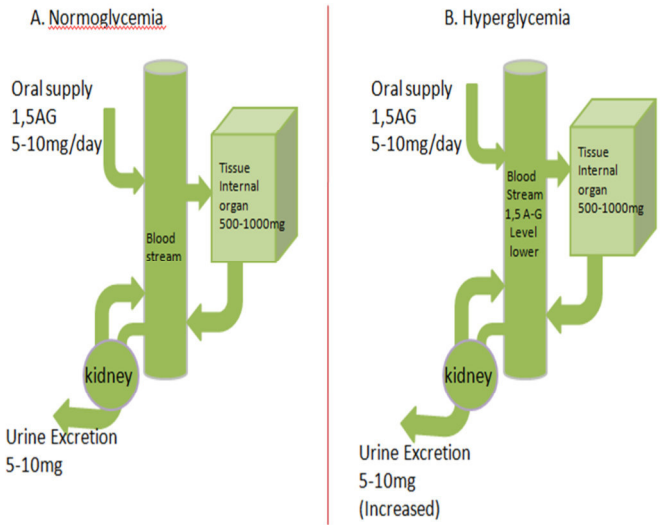

Fig 1. Effect of 1,5-anhydroglucitol(1,5-AG) in normoglycemic and hyperglycemic states. A: In normoglycemia, the orally administered content of 1,5-AG and the urinary excretion content of 1,5-AG are equilibrium with the constant level of circulating1,5-AG. B: In hyperglycemia, high levels of glucose prevent the reabsorption of 1,5-AG into the proximal tube, occurring in increased urinary excretion and decreased serum levels of 1,5-AG.[30]

3. CONCLUSION

Biomarker is a substance used as an indicator of disease status and a property that is expected and evaluated for general, pathological and pharmacological responses to therapeutic interventions. Various conventional methods of diagnosis and treatment of diabetes mellitus are available but there are limitations in accuracy and treatment. Thus, as a result of the above studies, it has been concluded that biomarkers play a crucial role in the evaluation and diagnosis process which leads to better care and protection of patients. Due to its various advantages, biomarkers are considered as an important tool in the advancement of diabetes mellitus diagnosis and treatment.

4. AUTHORS CONTRIBUTION STATEMENT

Chakraborty T conceptualized, gathered and analyzed the data with regard to this work; Dr. Gupta S and Dr.Saini V analyzed these data and necessary inputs were given towards the designing of the manuscript and Talukdar A managed the literature searches. All authors discussed and contributed to the final manuscript.

5. ACKNOWLEDGEMENT

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6. CONFLICT OF INTEREST

Conflict of interest declared none.

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