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New Vistas in Diabetes Management: New Age Early Detection Markers, Diet, Nutrition and Herbal Supplements

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Abstract: ***With the number of people with diabetes and pre-diabetes increasing at an alarming rate, diabetes has become a major global concern. Although the pathophysiology and long-term effects of diabetes-related complications, such as diabetic retinopathy, diabetic kidney disease, and cardio-metabolic changes, are better understood, more knowledge is still required for a goal-directed management program that aims to stop the progression of these complications. Catching diabetics while they are still in their pre-diabetic stage would be the obvious course of action (1) . While the fasting blood glucose (FBG), post-prandial blood glucose (PBG) and HbA1c have been the mainstay of diabetes diagnosis and management, there are several challenges with these biomarkers which have been illustrated in several researches over time. HbA1c is particularly prone to issues related to Hb variants, hepatic disorders and any disorder that shortens the lifespan of red blood cells, iron deficiency anemia (2). The challenges of standardization and interference with HbA1c assays are another challenge that makes it difficult to totally trust the values (3) (4). There is a need to explore new age markers to catch the diabetics early and several candidates like fructosamine, glycated albumin and 1,5 anhydroglucitol have shown promise. The two main theories put forth to explain the sharp increase in diabetes rates globally are aging and urbanization, which result in sedentary lifestyles. Switching to a Western diet has been proposed as a substitute motivator (5). The prevalence of diabetes may be significantly influenced by the consumption of sugar and similar sweeteners rather than merely total joules. According to new research on the insulin-modifying qualities of refined sugars, sugar and similar sweeteners have a statistically significant impact on diabetes that is separate from the impact of weight on diabetes. The associations between diabetes and increasing incomes and urbanization statistically vanish when the impacts of sugar and similar sweeteners are considered, suggesting that sugar intake could be a contributing factor to urbanization. With the rise in diabetes and increasingly larger numbers and earlier onset put a huge burden on economies. This is especially important for emerging economies as the rapid development, changing diet and lifestyle and sedentary living conditions pose a bigger disease burden without the infrastructure and per capita spending on health as in developed economies (6). This calls for newer markers for earlier detection of diabetes and catching more people in their prediabetes stage. Medication may not always be the best option in such a stage and the role of diet, nutrition, supplements and herbs can play a major role in the addressing the ever-increasing burden of diabetes.***

Keywords: Diabetes, Nutrition, Herbal Supplements, Diet, diabetic retinopathy

1. Introduction

Over the past few decades diabetes mellitus or non-insulin dependent, type 2 diabetes has become more prevalent. Due to shifting lifestyles, the typical presentation is characterized by a comparatively earlier onset, impacting the world's young and productive population. Higher Body Mass Index (BMI), sedentary lifestyles, and consumption of processed foods high in carbohydrates and different syrups that cause insulin resistance are characteristics of Type 2 diabetes's clinical presentation. The long-term metabolic consequences of insulin resistance, including retinopathy, hypertension, cardio-metabolic complications, diabetic foot, diabetic kidney disease, and numerous others, are now recognized by the scientific and medical community(7). Since HbA1c values have been established and are now more widely accepted worldwide, people frequently wonder if the search for diabetes markers is over. After insulin binds to its receptor, glycogenesis takes place (8). As a result, too much cytosolic glucose is converted to glycogen, and too much cytosolic acetyl-COA starts the lipogenesis process. An antagonist of these mechanisms is the hormone glucagon. Blood glucose levels that are normal or lower do not easily enter cells and stay in the blood. The DCCT/EDIC study provided more precise and convincing evidence of links between glycated proteins, including glycated albumin, and diabetic complications (9).

Non-insulin dependent type 2 diabetes mellitus, which is characterized by peripheral tissue insulin resistance that impairs blood glucose absorption, accounts for the great majority of the burden (10). Compensatory hypersecretion of insulin from the pancreatic islets may occur prior to the actual decline in the islet of Langerhans' capacity to secrete insulin. All of the organs that actively participate in the uptake or metabolism of glucose, such as the liver, skeletal muscles, and adipose tissue, are significantly impacted by this (10). Proinflammatory cytokines and elevated fatty acid levels set off a series of events that lead to insulin resistance, which in turn impairs glucose transport and increases lipid breakdown. It's interesting to note that inadequate insulin production

causes glucagon levels to rise leading to a further rise in blood glucose levels. (11).

In order to guarantee early detection and reduce patients' risk of developing life-threatening disease complications, it is essential to implement efficient and economical strategies for systematic screening of diabetes mellitus. Therefore, it is crucial to find new diabetes mellitus biomarkers and assay techniques in order to create reliable, painless, non-invasive, highly sensitive, and accurate screening methods.

2. Challenges with Current Paradigm of Early Diagnosis of Diabetes

Diabetes falls into one of the following broad categories:

1) Type 1 diabetes, which includes latent autoimmune diabetes of adulthood, is caused by autoimmune β-cell destruction and typically results in complete insulin insufficiency.
2) Type 2 diabetes, often accompanied by insulin resistance, is caused by a progressive loss of adequate β-cell insulin secretion.
3) Other causes of diabetes include diseases of the exocrine pancreas (like cystic fibrosis and pancreatitis), monogenic diabetes syndromes (like neonatal diabetes and maturity-onset diabetes of the young), and drug- or chemical-induced diabetes (like after organ transplantation, when using glucocorticoids, or during HIV/AIDS treatment).
4) Diabetes that was not obviously evident before pregnancy but was discovered in the second or third trimester is known as gestational diabetes mellitus.

Current criterion for diabetes is as follows (12).

Table 1: Diagnostic criteria for diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
OR
A patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

There are currently a number of issues with T2DM management that require attention. Technically speaking, new, more thorough approaches are required for the best possible screening, prompt diagnosis, and effective treatment of type 2 diabetes. Strategies that combine the use of risk assessment tools, with more potent biomarkers for T2DM screening and progression are more likely to be successful in controlling the global diabetes epidemic. By lowering the underdiagnosis and undertreatment of diabetes, it will also have a beneficial effect on preventing complications from hyperglycemic episodes in people with diabetes and prediabetes (13).

Oral Glucose Tolerance Test

Compared to FPG and HbA1c, OGTT is a more sensitive way to diagnose prediabetes and diabetes because it is a marker of early impaired glucose homeostasis (14). An established marker of prediabetes and diabetes is an abnormally elevated plasma glucose concentration in the OGTT(15). However, in certain situations, OGTT has low reproducibility, can be complicated, and is rather expensive. OGTT involves blood draws over a two-hour period and an oral load of 75g of glucose. Analytical and logistical limitations result from the requirement for timed samples(16).

Challenges with HbA1c

Although HbA1c testing is recognized as a biomarker for long-term glycemic control, measuring HbA1c presents some difficulties. Interference from different hemoglobin types, including HbC, HbS, HbE, HbD, elevated HbF, and carbamoylated Hb, in various assay methodologies is one of the difficulties (17) (18). For both the diabetic patient and the caregiver, these factors are challenging to clinically evaluate and normalize in routine diabetes management. Cross-reactions with chemically altered hemoglobin species or genetically determined hemoglobin variants are always possible (2). Common issues encountered with HbA1c assays routinely are illustrated below.

1) Iron deficiency Anemias: Treatment leads to lowering of HbA1c. (19)(20).
2) Commonly encountered Vitamin B12 and Folate deficiency leads to decreased red cell turnover leading falsely elevated HbA1c values. (21)
3) Alcoholism: Several studies have shown that alcoholism leads to elevated HbA1c (22).
4) Pregnancy: Reduced Erythrocyte lifespan may lead to falsely lower values of HbA1c. Besides this Gestational Diabetes commonly encountered may not be accurately diagnosed using HbA1c as a marker.
5) Anemia from Hemolytic causes will lead to falsely lower HbA1c values.
6) Hepatic disorders leading to Hyperbilirubinemia will lead to falsely elevated HbA1c values.

Newer Markers of Glycemic Control

With the challenges of OGGT deployment on a widespread basis and the issues related to variability in HbA1c results, the quest for newer more sensitive and less troublesome markers of glycemic control is an ongoing quest (13). Several candidates have generated interest and shown potential. The new approach is also directed towards looking at diabetes in a more syndromic manner and covering all aspect of the disease presentation. A brief illustration of the syndromic nature and the variety of complications that poor long term glycemic control can cause as provided in the Figure 1: Newage markers in Diabetes and their role

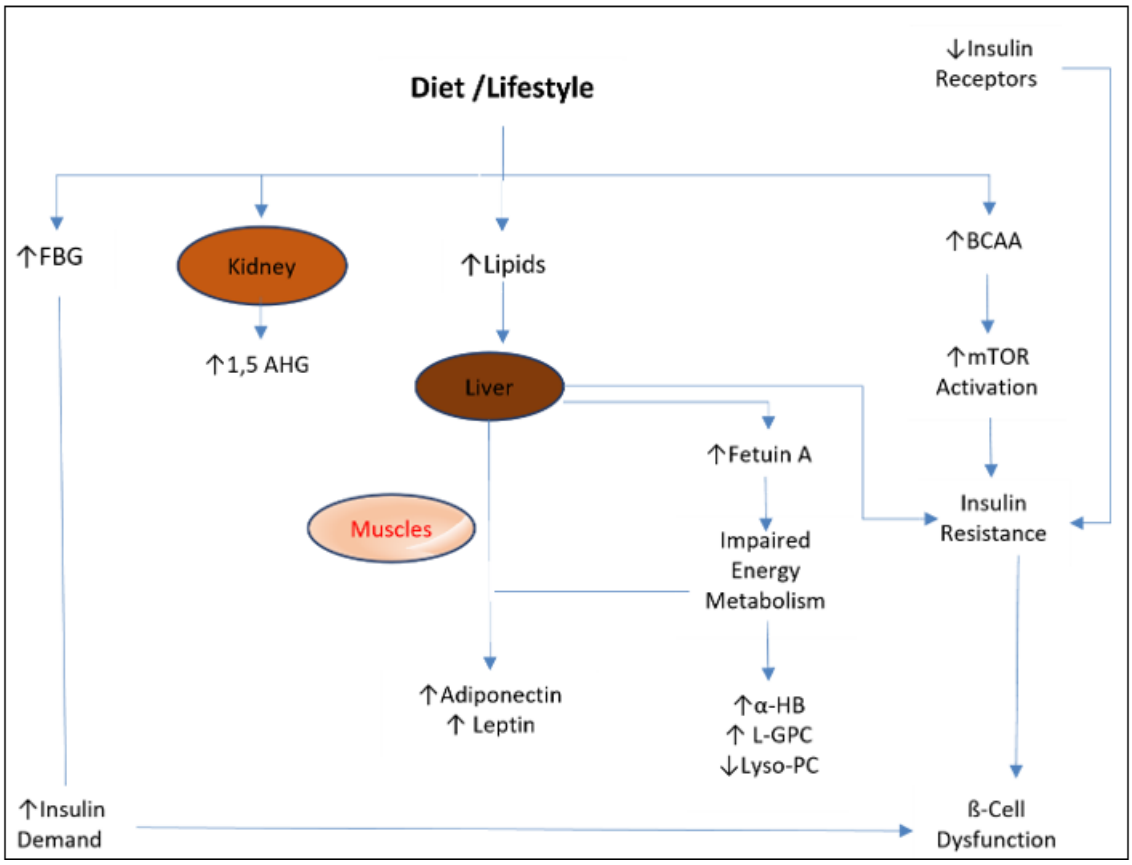

Figure 1: Newage markers in Diabetes and their role

While lot of work is still ongoing and yet the consensus on the newer markers eludes and so far none of them have been adjudicated to replace or adjunct the current diagnostic criteria. Of the lot the three which have shown most promise are Fructosamine, Glycated Albumin and 1,5 Anhydroglucitol. A brief comparison of all three are given in the table below. Ref

Table 2: Comparison of Fructosamine, Glycated Albumin and 1,5 Anhydroglucitol

Table 2: Comparison of Fructosamine, Glycated Albumin and 1,5 Anhydroglucitol

	Fructosamine (FA)	Glycated albumin (GA)	1,5-Anhydroglucitol (1,5-AHG)
Duration of Change	1–2 weeks	1–2 weeks	24–72 h
Duration of Glycemic Change	2–3 weeks	2–3 weeks	1–2 weeks
Correlations to FBG and PBG	Yes	Yes	Yes
Correlation to Long term complications	Yes	Yes	Yes
Determination by enzymatic methods	Available	Available	Available
Application on standard Lab Chemistry Analyzers	Yes	Yes	Yes
Erroneous Low Values	Hypothyroidism, Cirrhosis		Chronic kidney disease stages 4–5
Erroneous High Values	Hypoalbuminemia, Hyperthyroidism, Hypertriglyceridemia, Nonalcoholic fatty liver disease		Pregnancy, Chronic liver disease, Maturity-onset diabetes of the young (MODY)

Glycated albumin testing is more sensitive and specific than HbA1c and fasting blood glucose alone in identifying pre-diabetes and has shown more promise in various independent studies (23). When HbA1c and GA were used together, the sensitivity was higher (78%) than when HbA1c was used alone (50%), and almost 80% of African prediabetics were successfully identified. Furthermore, the majority of undiagnosed diabetics could be identified with a GA level of 17.1% or greater (24). Compared to using fasting glucose alone, the rate of false positives was decreased by 33.75% when fasting glucose was measured in conjunction with glycated albumin (25).

More research on the use of new-age biomarkers in the diagnosis and surveillance of diabetes is the need of the hour in some populations, particularly in regions like India where iron deficiency anemia is common, particularly in females and renders HbA1c as unreliable. As fructosamine, glycated albumin and 1,5 AHG are unaffected by erythrocyte turnover, it likewise exhibits less fluctuations.

Impact of diet and nutrition on glycemic control

Any diet that promotes or preserves general health is considered healthy. The body needs hydration, micronutrients, macronutrients, and enough calories, all of which are provided by a healthy diet (26). Nutrition and overall well-being depend on eating a balanced diet. It shields a person from several chronic noncommunicable diseases, including cancer, heart disease, and diabetes, particularly type 2 (27). A balanced diet must include a range of foods and reduce consumption of sweets, saturated and industrially generated trans fats, and salt. Whole grains, fruits, and vegetables, along with little to no processed meals and sugar-sweetened beverages, can all be found in a balanced diet. Numerous plant-based and animal-based meals can satisfy the requirements for a balanced diet. Nevertheless, vegans must obtain their vitamin B12 from a non-animal source. Governmental, medical, and nutritional organizations produce a variety of nutrition guidelines to inform the public about what they should eat to be healthy. In many countries, nutrition data labels are also required so that people can choose foods based on health-related factors rather than just what they want to eat. Regarding both individuals and populations, the World Health Organization recommends the following five measures:

1) Consume 400 g or more of fruits and vegetables per day; starchy root crops such as sweet potatoes, cassava, and potatoes are not included. Nuts, whole grains, and legumes (such beans and lentils) are also components of a nutritious diet.
2) Limited fat consumption. Fats should constitute less than 30% of total calories. Unsaturated fats should be preferred over saturated fats. Totally shun trans fats.
3) Limited simple sugars consumption, preferably below 10% of calorie (below 25 grams or below 5% of calories per day may even be better).
4) Limited sodium. Ensure that only iodized salt is consumed below 5g/day. This has been shown to reduce the risks of cardiovascular diseases.
5) Maintain healthy weight by consuming approximately the same number of calories the body is expending.

Diet strategies for diabetes.

Various diet strategies have been considered globally with mixed results. While some have some scientific evidence albeit with risks others are more of pseudoscience. A summary of the different strategies and fads which caught the attention over time. Ref

Table 3: Diet Strategies

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Diet Strategy	Brief Description
Low Fat Diet	A low-fat diet is a diet that restricts fats, and often cholesterol and saturated fat as well. Low-fat foods are intended to reduce occurrence of conditions such as heart diseases and obesity, which increases the risks of diabetes and can worsen diabetes in already diabetic patients. For weight loss, low-fat diets perform similarly to low carbohydrate diets, since macronutrients compositions do not determine weight loss success(28). Fat provides 9 calories/g while carbohydrates and protein each provide 4 calories/g. The Institute of Medicine recommends restricting fat intake to 35% or less of total calories to control the intake of saturated fat (29). Although low fats may affect the functional properties of foods, restricting fats intake within the recommended limit is required for healthy living and managing diabetes.
Very-low-calorie Diet	A fad diet with exceedingly or very low daily food energy consumption is known as a very-low-calorie diet (VLCD), sometimes referred to as a crash diet or semistarvation diet (30). A diet with 800 kcal (3,300 kJ) or less per day is considered VLCD (31). With a regulated formulation in Europe and Canada, modern medically supervised very-low-calorie diets (VLCDs) use total meal replacement and include the recommended daily requirements for electrolyte balance, protein, vitamins, minerals, fatty acids, and trace elements. Protein can be partially or entirely replaced with carbohydrates; this decision has a big impact on metabolism. Very-low-calorie diets under medical supervision have a specialized therapeutic use for quick weight loss, such as prior to bariatric surgery or in cases of severe obesity. (32)
Raw Foodism	Diets that consist primarily or exclusively of uncooked or low-temperature cooked food are known as raw food diets. Many starch molecules are more likely to be difficult for the body to digest when they are undercooked, which lowers blood glucose levels. Nutrient digestibility is enhanced by cooking. Raw foodism is considered a fad diet by medical experts. Iron, calcium, and protein are among the vital minerals and nutrients that are not included in raw food diets, namely raw veganism. The arguments for raw foods are not wholly supported by science.(33)
Ketogenic Diet	The ketogenic diet is a low-carb, high-fat, and sufficient-protein diet that is mostly used in medicine to treat children with refractory epilepsy (34). The body is forced to burn fats rather than carbs when following a ketogenic diet. Glucose, which is carried throughout the body and primarily serves to power brain function, is typically produced from the carbs found in diet. On the other hand, the liver turns fat into fatty acids and ketone bodies if there are little or no carbohydrates left in the meal. As an energy source, the ketone bodies enter the brain and take the place of glucose. The ketogenic diet, which is high in fat and low in carbohydrates, may alter how the body utilizes and stores energy, so reducing the symptoms of diabetes. When following a ketogenic diet, the body produces energy from fat instead of sugar. In 1924, the ketogenic diet was developed as a means of treating epilepsy. Diabetes type 2 is another condition for which the consequences of this eating pattern are being investigated. In diabetics, the ketogenic diet may lower insulin requirements while simultaneously raising blood glucose levels. But there are hazards associated with the diet.(35)

Dietary Interventions for Glycemic Control

The source reviews various dietary interventions and their effectiveness in improving glycemic control in individuals with prediabetes (26). It highlights the following:

- **Carrageenan-free diet:** Carrageenans are sulfated polysaccharides derived from red seaweed, commonly used as a food additive. Studies suggest that carrageenan can induce inflammation and impair insulin signaling, contributing to glucose intolerance in animals. **Adopting a carrageenan-free diet may potentially improve glucose tolerance and lower blood glucose levels.** A pilot clinical trial found that a carrageenan-free diet led to

improvements in HbA1c levels among participants with prediabetes. However, more research is needed to confirm these findings and establish the long-term effects.

- **Yogurt with *Lactobacillus plantarum* OLL2712:** *Lactobacillus plantarum* OLL2712 is a probiotic strain found in yogurt. Research indicates that **consuming yogurt enriched with L. plantarum OLL2712 can potentially reduce HbA1c levels in individuals with prediabetes**. Probiotics, in general, are believed to have beneficial effects on gut health, which may indirectly influence glucose metabolism.
- **Allium hookeri extract (AHE):** *Allium hookeri*, a traditional herb from the Liliaceae family, has demonstrated anti-diabetic effects in previous studies. Consumption of AHE has been shown to significantly reduce HbA1c situations compared to a placebo group.
- **Delta- tocotrienol**: Delta- tocotrienol is a form of vitamin E that has shown pledge in perfecting glycemic control. A randomized controlled study set up that delta- tocotrienol supplementation significantly bettered fasting tube glucose (FPG) and HbA1c situations in individualities with prediabetes.

The source also mentions salutary interventions that didn't show significant advancements in HbA1c situations, including salmon consumption, zinc supplementation, and balanced deep- ocean water (BDSW). still, it acknowledges the limited exploration in these areas and suggests farther disquisition is warranted (7).

Indian Herbal medicines for Diabetes

Due to growing exploration in traditional drug, factory-grounded specifics that are eco-friendly, bio-friendly, affordable, and generally safe have surfaced from the borderline to the mainstream in recent decades. Atta-ar-Rahman listed further than 300 factory species known for their rates in glycemic control. 21,000 shops that are used medicinally worldwide have been listed by the WHO. Of the 2500 species set up in India, 150 are exploited for marketable purposes. India leads the pack in terms of presence of largest species of herbal shops, their knowledge and understanding as well as commercialization of these herbal and traditional drugs (36).

Another source focuses on Indian medicinal shops and herbal medicines traditionally used in diabetes treatment. It emphasizes the growing acceptance of herbal drugs due to their natural origin and perceived lower threat of side goods.

The source acknowledges the lack of scientific and clinical data supporting the efficacity and safety of numerous herbal remedies. It calls for farther exploration to establish their effectiveness, regularize tablets, and understand implicit relations with conventional specifics.

The source provides a detailed list of Indian medicinal shops with purported antidiabetic parcels, including

- **Acacia arabica (Babhul):** Mostly found throughout India, Acacia arabica has been traditionally used to treat diabetes. Studies suggest its implicit hypoglycemic goods, but further exploration is demanded to confirm its efficacity and safety.
- **Allium cepa (Onion):** A common culinary component, Allium cepa has shown anti-hyperglycemic exertion in beast studies. It's also known for its antioxidant and hypolipidemic parcels.
- **Allium sativum (Garlic):** Allium sativum contains allicin, a sulfur- containing emulsion, which has been linked to bettered glucose metabolism and reduced oxidative stress.
- **Eugenia jambolana (Jamun)**: This fruit is believed to retain hypoglycemic parcels, particularly the seeds and pulp.
- **Momordica charantia (Bitter gourd):** Momordica charantia is a popular vegetable in India, known for its bitter taste and traditional use in diabetes operation.
- **Ocimum sanctum (Tulsi)**: Deified in Ayurveda, Ocimum sanctum has demonstrated hypoglycemic, antioxidant, and anti-stress properties in studies.
- **Phyllanthus amarus (Bhuiaml):** Phyllanthus amarus has been used in Ayurvedic drug for several conditions, including diabetes. Studies suggest its implicit hepatoprotective and hypoglycemic parcels.
- **Pterocarpus marsupium (Bijasal)**: The dinghy of this tree is believed to have antidiabetic parcels.
- **Tinospora cordifolia (Guduchi):** A crucial condiment in Ayurveda, Tinospora cordifolia is known for its immunomodulatory, antioxidant, andanti-diabetic goods.
- **Trigonella foenum graecum (Fenugreek):** Trigonella foenum graecum seeds are a common spice in Indian cookery. They're also a traditional remedy for diabetes, with studies indicating their capability to ameliorate glucose forbearance and insulin perceptivity.
- **Withania somnifera (Ashwagandha)**: Withania somnifera is an adaptogenic condiment known for its stress- reducing andanti-inflammatory parcels. It has also shown implicit hypoglycemic goods in studies.

3. Discussion

The global prevalence of diabetes on supremacy, necessitating a reevaluation of current individual strategies and the disquisition of innovative labels for early discovery and intervention. While traditional labels like Fasting Blood Glucose (FBG) and Hemoglobin A1c (HbA1c) have been crucial to diabetes operation, the adding number of diabetics worldwide poses challenges that demand a more individualized approach. The intricate connections between diabetes, insulin resistance, and cardiometabolic complications have been considerably delved, emphasizing the need for a paradigm shift in individual algorithms (37). Through this review we endeavor to examine the eventuality of several new- age biomarkers and argue for their addition in routine individual algorithms.

4. Challenges in Current individual Approaches

1) Heterogeneity: Diabetes is a multifaceted syndromic condition, hence current algorithms, which constantly calculate on standardized approaches — need a critical reevaluation. It's imperative to broaden the criteria by adding further parameters and biomarkers given the lack of a widely applicable result. The complexity of diabetes necessitates a more personalized individual approach is

necessary to address the complaint's multifaceted and syndromic nature.

2) Early diagnosis in prediabetic state: In order to reduce complications related to diabetes, early intervention is essential. In order to stop a rise in complications linked to cardiometabolic pattern, prediabetic webbing becomes pivotal. By catching people who are in the prediabetic stage, preventative measures can be put in place to decelerate the progression of serious complications like Diabetic Retinopathy, Diabetic Kidney Disease, and Diabetic Foot.
3) Marker of Intermediate Glycemic Control: Beyond its part as a individual marker, Glycated Albumin proves to be a marker of intermediate glycemic control. This aspect is particularly salutary in managing diabetes in cases with associated factors, offering healthcare professionals a further holistic perspective for acclimatized treatment plans (38).
4) Diet and Nutritional strategies play a critical part in management of active diabetes and preventing prediabetics from moving towards full blown diabetes. Likewise, with enhanced emphasis on catching them early, the part of Diet and nutrition managing pre-diabetes and improving glycemic control is critical. Correct diet and nutrition strategy based on the needs of the individual under proper supervision can drastically improve the outcomes. The interesting elements in this approach is that dietary habits and foods preferences vary widely globally. In more diversified countries like India the variance nationally is steep. This implies that the dietary and nutritional strategy must translate in a variety of food options fit for the pre-diabetic and diabetic stage and vastly more work is needed in this area. A failure to follow dietary regimen can easily push a person towards poor glycemic control and a pre-diabetic can breach the diabetic threshold.
5) The role of herbs and supplements in managing and augmenting outcomes especially with a focus on glycemic control is key. These are already consumed globally in an informal manner. A more regimented strategy in a dose dependent manner with proper glycemic goals, can improve the management of diabetes in a cost-effective manner. More work on standardization of options and solutions with harmonization can make it easy for the patients to make the right choice.

5. Conclusion

Glycated Albumin emerges as a promising marker for short-term glycemic control, offering a unique perspective complementary to HbA1c. In a span of 2-3 weeks, it provides a real-time snapshot of glycemic fluctuations, filling a crucial gap where HbA1c's long-term perspective may be less responsive to recent changes. This allows for faster modification and adjustments in lifestyle with the right diet and a mix of herbs and supplements to complement the regimen. Glycated Albumin's faster rate of glycation makes it a dynamic marker, closely reflecting ongoing glycative stress and consequently, offering insights into the level of oxidative stress.

Dietary and Nutritional strategy under supervisions supplanted with the already existing and known herbs and supplements can improve outcome and may slow down the progress of active diabetes towards more critical stages of metabolic syndrome and pre-diabetics towards active diabetes. More standardization and harmonization are needed in herbs and supplements, if they are to play a palpable role in this mission. Dietary strategies suiting different patient needs like vegan. Vegetarian, egg-meat eaters serving different regional and local food preferences are critical to ensure compliance.

A concerted effort in catching them young and laying emphasis on diet, nutrition, lifestyle modification is necessary for stemming the tide of diabetes globally.

Conflict of interest
None

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