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Role of novel biomarkers in early detection of diabetes mellitus: The Ethiopian Context

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Abstract

Background

Identification of individuals at an early stage through reliable biological indicators is crucial to prevent complications. The conventional biomarkers have their drawbacks, including only moderate accuracy; person to person variability, and vulnerability to physiologic fluctuations, and reduced reliability in certain medical conditions. Therefore, this review has investigated the role of novel biomarkers in the early detection of diabetes in the Ethiopian context.

Methods: Narrative literature review design was used to synthesize and summarize existing evidence

Main findings: Novel biomarkers have demonstrated that they offer additional benefits in detecting diabetes early. Their serum level depends on tissue function and physical properties, not molecular alterations that makes them preferable over the conventional markers, which depend on blood glucose level alterations.

Conclusion: Despite the advancements, some challenges remain related to high costs and need for more validation for clinical use. Therefore, strong sectoral collaboration is crucial to validate and integrate novel biomarkers in Ethiopian diabetes diagnosis practices.

Keywords: Diabetes mellitus (DM), early detection, emerging biomarkers, novel biomarkers, pre diabetes, undiagnosed diabetes mellitus (UDM)

Introduction

The name "diabetes mellitus" was first introduced in 1674 by Thomas Willis(1). It is a long-term metabolic condition that affects multiple body systems and is characterized by an elevated blood sugar level(2). It has become a major global public health issue, with its prevalence rising dramatically around the world(3). It affected about 537 million adults worldwide aged 20 to 79, in 2021 and the number is expected to keep rising, reaching 643 million by 2030, and climbing further to 783 million by 2045(4). In Ethiopia, approximately 2.3 million adults aged 20 to 79 are living with diabetes, making it the country with fifth highest number of diabetes in Africa(5).

However, a great proportion of people living with diabetes, especially those with type 2 diabetes mellitus (T2DM) remain unaware of their condition, with many only being diagnosed after serious complications have developed(6). In 2021, 537 million adults aged between 20-79 were living with diabetes; however, 44.7% of them were unaware of their status.

Surprisingly, 75% of adults who were unaware of their diabetes status are from low and middle income countries (7, 8).

Africa has the greatest occurrence of undetected diabetes mellitus, and 2% to 6.5% in Ethiopia(6, 9). Although undiagnosed type 1 diabetes can occur, it typically lasts for a short period because the signs and symptoms appear suddenly and it is likely to be captured in population based research needed to assess undiagnosed diabetes(10).

Pre-diabetes a stage at which the blood glucose level is elevated and biomarkers such as blood glucose and glycated hemoglobin exceed the normal levels but do not meet the diagnostic requirements for diabetes(11). This condition carries a substantial risk for the development of diabetes and its related complications(11). Therefore, identifying the disease early is essential to slow the growing number of cases or prevent its related complications from increasing(8). When blood glucose levels are not well managed, it can lead to long term damage to both small and large blood vessels, causing severe complications such as kidney disease, eye problems, nerve damage, and heart disease(12). Due to a mix of several factors such as inefficient health systems, limited awareness among the public and healthcare providers and the frequently gradual onset of symptoms or advancement of type 2 diabetes, the condition can go unnoticed for many years, during which uncontrolled high glucose causes severe and permanent progression of micro and macro-vascular issues allowing complications to rise (11).

It is known that certain lifestyle modifications such as diet control and physical exercise can improve insulin sensitivity along with certain medication such as α-glucosidase and metformin (1). Nevertheless, this can only be achieved if individuals have been identified at an early stage through reliable biological indicators(Biomarkers)(13).

The Biomarkers Definitions Working Group described a biomarker as "a feature that is objectively assessed and measured as a sign of normal biological processes, disease processes, or pharmacological responses to a treatment intervention"(14).

Therefore the presence and concentration of certain biomarkers have a beneficial use in detecting and monitoring chronic diseases such as diabetes(14). In the case of diabetes, using the right biomarkers at the right time and with accurate measurement can greatly improve early detection and management, highlighting the crucial role these diagnostic markers play(15, 16), and the greatest therapeutic significance of biomarker is the potential application of markers in early detection and effective treatment to track cognitive decline caused by diabetes(17). Currently, the biomarkers used in diabetes detection are categorized into 3 main classes *(Figure 1)*.

The traditional biomarkers currently used, such as Blood sugar levels, HbA1C , fructosamine, and glycated albumin, each have their drawbacks, including only moderate accuracy and reduced reliability in certain medical conditions(15, 16). Consequently, discovering new biomarkers that can identify individuals at high risk of diabetes and its complications has become a key priority for enabling more targeted and efficient preventive strategies(18).

Researchers have been striving to clinically confirm new biomarkers that can reflect short and medium term blood sugar control across different populations. However, the clinical applications of novel diabetic biomarkers in Ethiopia have not been studied. Accordingly, this review will investigate the types, diagnostic mechanisms and the clinical applications of novel diabetes biomarkers in Ethiopia.

1. Methodology

Narrative literature review design was used. A Comprehensive literature review was conducted across databases such as PubMed, Google scholar, and the Cochrane library, and data was synthesized and analyzed from 18 relevant studies. Combinations of keywords and Boolean operators have been employed to retrieve important literature.

Recent studies that were written in English language were included. On the other hand, articles without full information and those with very old outdated data were excluded. Additionally, studies on only animals were excluded due to non-relevance. Thematic data retrieval and summary were employed.

The keywords used included "novel biomarkers," "diabetic biomarkers," "diabetes," "early detection," 'adiponectin," "fetuin-A," "netrin-1," "linoleoyl-glycerophosphocholine," "lipoprotein (a)," "ceramides," "α-Hydroxybutyrate," "acyl carnitine," and "micro RNAs (miRNAs)."

2. Overview of conventional biomarkers recommended by the American Diabetes Association (ADA)

Traditional biomarkers are the ones most often used, represent the standard, and well established approaches. They can be classified in to glucose based markers and Auto-antibodies(15).

3.1 Glucose based markers

1. The oral glucose tolerance test (OGTT)

This test involves taking multiple blood samples over about two hour period. It begins with fasting sample, and the exact time is recorded. The patient then takes a measured amount of glucose, based on body weight, up to 75g, within five minutes. Then blood glucose levels are then measured at both the start and again after two hours. Increased glucose levels after two hours are associated with pre-diabetes and diabetes (19, 20). Type 1 diabetes, type 2 diabetes, and pregnancy related diabetes(GDM) can all be identified with this test, and it reveals a significant association with Insulin resistance and release than HbA1C(21). A 2- hour glucose concentration of 140-199mg/dL indicates impaired glucose tolerance (Pre-diabetes) and >200mg/dL indicates diabetes mellitus(22).

2. Glycated hemoglobin (HbA1C)

It is a commonly used biomarker to identify individuals with diabetes and pre-diabetes(23). The major mechanism of its formation is through non-enzymatic binding of a glucose molecule to the amino terminal of a globin sub-unit of hemoglobin, therefore it reflects average blood glucose levels over a lifespan of red blood cells, unlike blood sugar levels, which show fluctuations in short time(23, 24).

HbA1C offers multiple benefits compared to FPG and OGTT, for instance, it has increased convenience since fasting is not required before measurement, better pre-analytical stability, and reduced variability on a daily basis during times of stress and illness(23). It is measured by different laboratory methods such as High performance liquid chromatography(HPLC), immunoassay, enzymatic assays and point of care testing(POCT), and its normal range is <6.5%(48mmol/mol)(15, 25).

3. Fructosamine(FA)

Fructosamine is a keto-amine formed by glycosylation of serum proteins, mostly albumin, by a process that involves enzymatic

modification(15). It reflects the blood glucose concentration over weeks, and useful in situations where hemoglobin levels are altered or when red blood cell turnover is abnormal, which makes it more reliable indicator, than HbA1C. It is usually measured by chemical methods such as Nitroblue Tetrazolium(NBT) Colorimetric assay, Kinetic colorimetric assay and by enzymatic methods in manual and automated methods. It normal range in healthy individuals ranges from 200 to 285µmol/L (26, 27, 28).

4. Glycated albumin(GA)

Glycation albumin is a compound formed by glycation of a plasma protein albumin, which is usually expressed as the proportion(percentage) of the total serum albumin(27). In clinical conditions such as hemolytic anemia, renal failure, recent blood donations, it has superior reliability than HbA1C(27). It is also preferred over fructosamine in clinical situations involving significant protein loss, including nephrotic syndrome, liver disease, and thyroid disorders(27, 29). It is mostly analyzed in the laboratory by enzymatic assays, High performance liquid chromatography, Immunoassays, and Boronate affinity chromatography, and its normal reference range varies from 11% to 16% of the total serum albumin (15, 27, 30, 31).

3.2 Immune markers (Auto-antibodies)

Auto-antibodies are immune mediators that are produced against insulin producing β-cells of the pancreas, rather than directly causing damage(32). These biomarkers that aid in the prediction of the development of Type 1 diabetes are especially valuable for understanding the early, symptomless phase of diabetes before the disease clinically manifests(33). During this stage, the destruction of β-cells occurs at a varying rates, offering important insights into how the disease starts and progresses(34).

Common antibodies such as ICA, GADA, IAA, IA-2A, and ZnT8A are well known for their high sensitivity and specificity in both diagnosing and predicting T1DM(33).The presence of two or more of these auto-antibodies greatly increases the risk of progressing varies depending on factors such as age, genetic makeup, and the specific types of auto-antibodies involved.

As such, children with multiple auto-antibodies are at a much higher risk of T1DM development compared to those with only one(35).The common laboratory methods applied in detection and measurement of auto-antibodies are Radio Immunoassay(RIA), Enzyme-Linked Immunosorbent Assay(ELISA), Electro-Chemiluminesce(ECL) assay, and Fouresent Immunoassat(FIA)(33, 35).

3.3 Drawbacks of conventional biomarkers for diabetes

It was reported by the Centers for Disease control(CDC), that approximately one third of adults globally have pre-diabetes, unfortunately, 90% of them don't even know that they have the condition(36). Common biomarkers currently used for diabetes are fasting and post-prandial glucose levels, HbA1C, fructosamine, and glycated albumin.

However, these traditional biomarkers have certain drawbacks; for instance, fasting plasma glucose (FPG) is quite sensitive to many factors that can affect its accuracy even before analysis. These include recent food intake, sample storage condition, natural physiological fluctuations within the same person, short term stress, and changes throughout the day. In addition to this, several therapeutic drugs such as corticosteroids, fibrates, beta-blockers, cyclosporine, sulfamethoxazole, diuretics and thyroid hormones, among others, can also have an influence on glucose metabolism(27, 37).

It has been proved that the oral-glucose tolerance test shows a better reliability in indicating insulin resistance that HbA1C and fasting blood sugar measurements and also preferable for identifying different forms of diabetes; However, it has some drawbacks such as personal variability and invasiveness. Additionally it can also be inconvenient, as it requires fasting beforehand and may show day to day fluctuations, especially during periods of stress or illness (15, 38, 39).

HbA1C testing has a limitation in catching people with pre-diabetes, even when results are below 5.5%. The usual cutoff value used to define pre-diabetes overlooks essential factors such as ethnicity, body mass index, and age, all of which can significantly affect HbA1C readings(21).

Glycated hemoglobin levels also show racial variability, for instance, African Americans, Asian/pacific islander groups, Hispanic and non-hispanic white populations have a higher HbA1C levels (8, 40). Additionally, in situations that will cause an alteration in red blood cell longevity will affect its levels and measurement result, since HbA1C reflects average blood sugar over lifespan of red blood cells(41).

When there is faster RBC turnover, cells spend less time exposed to high glucose levels, which falsely decreases its result, and when red cell production is slowed, older cells will dominate and HbA1C concentration will be elevated. Certain medical conditions such as Iron deficiency anemia, Splenectomy, vitB12 or folate deficiency, severe hypertriglyceridemia and uremia will make HbA1C appear higher than it is. So it is prone to false results in the presence of these clinical conditions(41, 42).

On the other hand, it can read falsely low in cases such as hemolytic anemia, blood loss, an enlarged spleen, and end stage renal disease. Because of these limitations, relying only on HbA1C may not be sufficient to diagnose pre-diabetes accurately and early.(43).

Another traditional biomarker Fructosamine (FA) can serve as a useful additional marker in certain clinical situations, especially when HbA1C doesn't provide reliable results (27, 44). However, FA has limitations; its value can vary significantly within individuals, and it may show falsely low results in some cases, such as in young children, who naturally have lower serum protein levels than adults, or in conditions involving rapid albumin turnover, including nephrotic syndrome, severe liver disease, and protein-losing enteropathy.

Additionally, it has a high variation among subjects and rapid albumin turnover can lead to falsely low levels and its concentration in the blood can be affected in conditions where there is severe protein loss, in cases such as nephrotic syndrome, or produce less protein, as seen in liver cirrhosis. Thyroid disorders can also influence the clinical applicability of fructosamine for the detection of diabetes(15, 27).

Glycated albumin tends to provide more reliable marker of diabetes development in people with conditions such as kidney failure, hemolytic anemia, or those who have recently received blood transfusions(27). However, GA can reveal misleading results in situations where albumin turnover is altered. It may also appear falsely low in individuals with higher Body mass index, increased body fat, or greater visceral fat accumulation(27, 44).

4. Novel biomarkers for diabetes mellitus

Brief History

In the past, diabetes management has mainly depended on standard markers such as blood glucose levels and HbA1C to monitor blood sugar control and guide the diabetes management choices(38). The earliest biomarkers for diabetes were blood glucose and urine glucose levels. Since Samuel Rahbar and his colleagues identified in 1969 that patients with diabetes have a higher levels of glycted hemoglobin than those without the disease, HbA1C has become the gold standard method for monitoring and managing blood glucose in individuals with diabetes(45).

In 1976, studies revealed that HbA1C reflects the average blood glucose level over several months, making it a reliable marker for diabetes and it use in glycemic control assessment was validated by Larsen and associates in 1990 (14) and in 2009, a global experts panel suggested HbA1C as an accurate method for long term glycemic levels, which the WHO later adopted(46, 47).

However, starting from late 1990's, the diagnostic pitfalls of HbA1C has become clear as a result of its wide application, such as its vulnerability to influences by several factors such as how much glucose enters the blood cells, how quickly glycation occurs, and how long the red blood cells live, which was found to alter the level of HbA1C(48). Emerging technologies such as metabolomics, proteomics and genomics were opened up in late 1990's and early 2000's, and new approaches has made it possible to develop biomarkers based on tissue function or physical properties, rather than just molecular alterations.

A detailed understanding that diabetes is highly complex condition that impacts nearly every organ and tissue in the body, which effects go beyond problems in glucose metabolism has led to the development of new biomarkers for glycation and oxidative stress including the advanced glycation end products(AGEs) as potential biomarkers, and novel targets for the identification of additional, more effective markers have been identified(14, 48).

More recently, advances in research methods from other disciplines, particularly oncology, are helping shape more effective methods for identifying novel biomarkers. Using a systems biology perspective, researchers can look at the bigger picture and explore how genes and body processes interact, revealing the complex links between diabetes, metabolic syndrome, and ischemic cardiovascular disease(14, 49).

4.1 Protein biomarkers

1. Adiponectin

Adiponectin is adipose tissue specific 30kDa plasma protein mainly produced by mature fat cells, but can also be found in tissues such as heart, bones, and the mammary and salivary glands(50). This hormone has anti-atherogenic and anti-inflammatory properties and found to and it also helps inhibit the formation of new blood vessels and may also have potential protective effects against cancer and increase insulin sensitivity and associated with lower risk of diabetes(51)

It acts as an insulin sensitizer, signaling the liver and skeletal muscles to breakdown fatty acids and utilizes glucose(52, 53). This adipokine has anti-diabetic properties and interacts with AdipoR1 and AdipoR2 receptors, which are part of a superfamily of rhodopsin like receptors and pumps that are associated with the progesterone adipoQ receptor(PAQR) family(54)

A certain review study on 31 novel biomarkers pointed that adiponectin in circulation are linked to tumor advancement through their influence on apoptosis and suppression of β-catenin signaling(55). In prevention studies, lower levels are commonly associated with obesity and insulin resistance, whereas higher levels are seen in individuals who adopt healthy lifestyle changes(50, 56).

Additionally, studies which involve hyperinsulinemic-euglycemic clamp and intravenous glucose tolerance tests revealed that levels of serum adiponectin have positive association with insulin sensitivity and have inverse relationship to insulin secretion(51, 56). Insulin therapy has also been found to raise circulating adiponectin levels and further enhance insulin sensitivity(51). Additionally, its specificity and sensitivity has also been well studied (*Table 1*).

However, it has also been pointed that its use in day-to-day clinical settings is still challenging, mainly due to a large differences between testing methods and variations in normal ranges across different populations, and absence of widely agreed up on cut off values(13, 51)

2. Fetuin-A

Fetuin-A is one of protein based novel biomarkers identified as helpful in early diagnosis of type 2 diabetes mellitus. This glycoprotein is also named as alpha-2-Heremans Schmid glycoprotein, with a molecular weight of 64kDa and encoded by the AHSG gene in humans. It is primarily produced and released by the liver(57). It has been known that this glycoprotein has been linked to the development of insulin resistance and type 2 diabetes mellitus by its inhibitory action on insulin receptor tyrosine kinase(57).

Reports from the Health, Ageing and Body Composition study(Health ABC) and the European Prospective Investigation into Cancer and Nutrition(EPIC)-Postdam Study showed that people with high fetuin-A levels had a greater risk of developing diabetes(58), which is supported by a comparative study reported that elevated concentrations are also often detected even before clear signs of high blood sugar appear, pointing its use as early indicator of metabolic risk(59).

A multiethnic cohort study involving adults who are middle aged to older, without overt cardiovascular disease(CVD) at the start revealed that elevated fetuin-A levels were notably linked to a higher diabetes risk in women(60). Some studies also identified that it will interact with toll like receptor 4(TLR 4), activating inflammatory signaling pathways that lead to the release of cytokines and contribute to lipid induced insulin resistance(39).

Interventional studies also reported that lifestyle modifications, medications and bariatric surgery can lower Fetuin-A levels, sometimes even before improvements are seen in traditional biomarkers (59, 61, 62).

This role of fetuin-A has also been supported by studies in knockout mice, as these animals possess increased insulin activity, stronger glucose tolerance, and enhanced insulin sensitivity(63).Additionally, fetuin-A has also been implicated as an independent influencing factor for the development of insulin resistance by measurements using homeostatic model assessment(HOMA-IR)*(Table 2)*.

Generally, fetuin-A was reported to act as a natural ligand of TLR 4, triggering insulin resistance. Because of this role it is indicated that fetuin-A may represent a new target for detecting and treating insulin resistance(39, 64). Several studies have also identified that this biomarker has a relationship with diabetic complications *(Table 2).*

3. Netrin-1

Netrins are extracellular protein groups which are closely associated to laminin. Netrin-1, netrin-3 and netrin-4 are extracellular forms, while netrin G1 and G2 are membrane bound. They are known to be widely expressed in body tissues such as the central nervous system, liver, spleen, intestines, kidneys and the vascular endothelium(39, 65).

It has been reported that netrin-1 is associated with different pathological processes and being recognized as potential diagnostic and prognostic biomarkers for various chronic disease conditions such as cardiovascular diseases, cancer, acute kidney injury and sub-arachinoid hemorrhage(65). Netrin-1 has also been reported to play a role in the development of the pancreatic cell, movement of islet cells, and tissue regeneration, which suggests a possible link to diabetes (66).

A histochemical examination revealed that among the two established Netri-1 receptors, neogenin was significantly present in pancreas, suggesting a role for Netrin-1 in pancreatic development, tissue regeneration and renewal of islet cells(67). Recent studies reported that levels of serum netrin-1 are higher in patients with impaired glucose or type 2 diabetes as compared to controls who are free from these conditions, which reveals that netrin-1 could serve as useful analyte to detect T2DM and IGT early(67, 68).

Additionally, a statistically inverse relationship was identified between Netrin-1 and levels of High density lipoprotein(HDL) cholesterol and estimated glomerular filtration rate(eGFR) and serum Netrin-1 levels exhibited a notable positive correlation with fasting blood glucose, HbA1C, HOMA-IR, Aspartate transaminase(AST), and Alanine transaminase(ALT)(69).

Lower amounts in the bloodstream have been found in patients with cardiovascular disease, diabetic neuropathy, and retinopathy. In contrast, higher levels in urine may appear before the development of albuminuria in diabetic nephropathy, pointing to early kidney damage (70). Its level have shown a shift with treatment, suggesting that it could be helpful for tracking disease progression(71, 72).

It has also been reported that Netrin-1 aids in corneal epithelial wound healing, reduce inflammation and promote nerve fiber regeneration in diabetic mice, which indicates that it could be useful in the treatment of diabetic keratopathy and has also been implicated to help in the treatment of diabetic nephropathy(39, 73).Although these mechanistic understandings are present, clinical studies assessing circulating netrin 1 levels in individuals with T2DM has produced variable outcomes.

Certain studies reported higher levels in those with diabetes, possibly as a compensatory anti-inflammatory reaction(68, 74), whereas others show decreased levels, suggesting a potential lack of internal protection(75, 76).

4.2 Metabolic intermediates

1. α- Hydroxybutyrate (α- HB)

Recent research has highlighted α- Hydroxybutyrate (α- HB), which is associated with insulin resistance and derangement in glucose metabolism. Elevated levels of α-HB, an organic acid, have been found to indicate decreased insulin sensitivity and impaired glucose tolerance, which conventional biomarkers cannot measure directly, showing that it can help predict the development of dysglycemia, even among people whose blood glucose levels are still normal(77, 78)

This was observed on non-diabetic study participants from the relationship between insulin sensitivity and cardiovascular disease study using the euglycemic hyper-insulinemic clamp technique(39, 77).Random forest statistical analysis also identified this biomarker as the highest ranked biomarker for distinguishing insulin resistant individuals from insulin sensitive individuals with accuracy of 76%(77).

Additionally, it is pointed that it can be measured using non-invasive blood tests such as mass spectrometry techniques(77). Despite these advantages, its broader use is still constrained due to high costs and limited standardization of testing methods(1).Ongoing studies are examining α-HB to make its use practical by adapting it for point of care testing and tailoring it to aid personalized prevention approaches(78).

α- Hydroxybutyrate is produced during metabolism of amino acids such as threonine and methionine, as well as the production of glutathione in the liver, which produce it as a by-product. Increased oxidative stress and enhanced fat oxidation can interfere with normal glutathione synthesis, leading to a rise in α- HB levels, especially in individuals with insulin resistance(77).

An excess of tricarboxylic acid (TCA) cycle from high free fatty acid levels, along with increased glycolytic activity from elevated glucose due to insulin resistance, leads to a heightened NADH/NAD ratio, subsequently causing oxidative stress and the buildup of α-HB generation precursors. For this reason, α-HB is considered a promising early indicator that may help predict the onset of type 2 diabetes and positively associated with the progression of type 2 diabetes(39, 79), and has good sensitivity and specificity in detecting insulin resistance and impaired glucose tolerance*(Table 1).*

2. Acyl carnitine

It is a small, water soluble compound formed from fatty acids (acyl group) and carnitine (quaternary ammonium compound) (80). Its main function is a transport of long chain fatty acids from the cytosol to the mitochondria, where they are cleaved through beta oxidation process to generate an energy(80). Additionally, this compound is essential in the regulation of balance between acyl-CoA and CoA ratio and also promotes storage of energy in the form of acetylcarnitine and has antioxidant and anti-inflammatory effects and contributes in improved insulin sensitivity, improved lipid balance and stability of cell membranes(81).

Clinical data has revealed that levels of acylcarnitines in the blood are elevated in individuals with pre-diabetes and diabetes (82, 83, 84). When there is an excess supply of lipids, fatty acids may not be fully metabolized in the mitochondria, leading to what is known as “mitochondrial stress”, which can contribute to insulin resistance (82, 83, 85). It has also been suggested that long chain acyl-CoA molecules serve as precursors for ceramides, which are already recognized for their role in promoting insulin resistance(77).

An alternative mechanism proposes that intermediate compounds such as acylcarnitine begin to accumulate when the rate of fatty acid oxidation exceeds the capacity of tricarboxylic acid cycle, and this buildup may counteract insulin sensitivity(81, 86).This is supported by a recent Canadian study, which found that increased levels of circulating medium chain acyl-carnitines are associated with gestational diabetes and the early stages of type 2 diabetes, and may directly impair pancreatic β -cell function (87).

Additional study also demonstrated that specific acyl-carnitine

patterns, particularly involving short and long chain forms, are strongly linked to a higher risk of developing type 2 diabetes in individuals already at increased cardiovascular risk(88), which is supported by a German study that reported a significant variations in acylcarnitine profiles among individuals with normal glucose tolerance, pre-diabetes, or type 2 diabetes(89).

4.3 Lipids and lipid derivatives

1. Linoleoglyceroposphocoline (L-GPC)

L-GPC is produced through the activity of enzymes such as hepatic phospholipase-A2 and lecithin cholesterol acyl-transferase in circulation (92). The biochemical properties of cell membranes, including their reaction to hormone, are largely influenced by the composition of phospholipids. Elevated plasma levels of L-GPC have been linked to a higher risk of developing impaired glucose tolerance or type 2 diabetes mellitus(T2DM)(77, 90, 91).

In an observational study, L-GPC showed a notable negative relationship with how well glucose was cleared during the clamp test (Spearman r= -0.56, P= 0.029)(92).

Even though the participants weren't diabetic, those with higher levels of plasma L-GPC experienced much larger increases in plasma glucose levels after the glucose challenge in the 5-point oral glucose tolerance test` and indicates a negative association(92).

It also showed a negative relationship with dysglycemia even after controlling for significant known T2DM risk factors in two groups of Caucasian participants(79). A different study investigated the concentrations of total plasma lysophosphatidylcholines in individuals with obesity and diabetes, both of which demonstrated notably lower levels in comparison to lean individuals(93).

In sub-analysis of a clinical trial involving omega-3 poly-unsaturated fatty acids(PUFA), obese individuals exhibited lower plasma L-GPC levels compared to participants with normal weight, both at the beginning and after supplementation with omega-3 PUFAs(94). This finding reveals the association of L-GPC with obesity and metabolic disorders, but it does not confirm it as an actual biomarker for insulin resistance.

Although many other research works have investigated the possible involvement of various complex phospholipids, such as lipo-polysaccharides, in the development of IR via pro-inflammatory mechanisms(95, 96), there is a significant scarcity of studies regarding the connection between plasma L-GPC and direct assessment of IR(92). Additionally, it has been indicated that it will be helpful to use L-GPC with α-HB together in predictive models to identify individuals at high risk for type 2 diabetes, which enables to minimize invasive procedures such as OGTT(79, 97).

2. Ceramides

Ceramides are lipid molecules from sphingolipid group consisting of long chain fatty acids of different lengths, and they serve as essential building blocks of cell membranes(98). In the body, they are formed through several pathways, including the de-novo pathway, the salvage pathway, and the breakdown of sphingomyelin (13).

Their accumulation in tissues can increase when there is extremely high supply of fatty acids, particularly due to heightened activity of the salvage pathway(99). Recent studies have indicated a causal link between ceramide production and β-cell impairment an insulin resistance (17).

They interfere with the phosphatidylinositol-3 kinase pathway and block the activation of Protein kinase B9Akt/PKB), an important enzyme involved in the metabolism. Moreover, they also stimulate several enzymes such as caspases, protein kinase C, serine/threonine protein phosphatases, and cathepsin D(79). Due to this, they will decrease glucose uptake and inhibit the storage of energy in forms such as triglyceride and glycogen and also trigger inflammatory responses through pro-inflammatory cytokines, disrupt a cell metabolism and even promote cell death(100).

Elevated ceramide concentration has been reported to be linked to insulin resistance and obesity and studies indicated that ratio of certain ceramides such as Cer(d18:1/18:0) to Cer(d18:1/16:0) can act as independent predictors of development of diabetes in the future(101). Extensive evidence suggested that extended exposure to free fatty acids (FFA) negatively impact pancreatic β-cells. Ceramide is suggested to act as a mediator of β-cell toxicity caused by FFA, palmitate, a precursor of ceramide, has been shown to trigger islet cell apoptosis in both diabetic rat models and healthy rats, as well as in human β-cells (102, 103).

Recent studies also reported a causal relationship between ceramide synthesis and β-cell impairment, alongside insulin. Elevated circulating ceramide levels correlate with mitochondrial dysfunction, consequently resulting in increased free radical production(104), and has also been reported that ceramides stimulate poly(ADP-ribose) polymerase-1(PARP-1) activity, leading to free radical production and oxidative harm in neuronal cells(104).

Although there is no evidence for direct ceramide-induced oxidative damage in β-cells, indirect evidence suggests that oxidative stress from ceramide buildup may significantly contribute to islet dysfunction, reduced insulin secretion, and the progression of diabetes(105). Ceramides can be detected in easily obtainable body fluids, they exhibit excellent potential as convenient biomarkers for early detection of metabolic disorders such as diabetes(101), and they are consistently expressed in tissues, utilizing ceramide inhibitors might offer novel therapeutic paths for diabetes and associated complications(105).

3. Lipoprotein(a)

Lipoprotein(a) is a plasma lipoprotein that resembles LDL but contains an additional protein component called apolipoprotein (a), which is linked to apolipoprotein B100 through a disulphide bond and is produced in the liver (77, 106). Its serum level depends on genetics, particularly the variations in the LPA gene and number of Kringle IV-2 repeats, which explain much of the difference in Lp(a) levels among individuals(39, 106).

Studies reported that elevated levels of Lp(a) have been established as an independent risk factor for cardiovascular disease, and reported to have an inverse relationship between its levels and conditions such as T2DM, pre-diabetes, insulin resistance and hyper-insulinemia(107, 108)*(Table2)*.

A study reported that serum Lp(a), when considered independently, had a significant inverse relationship with all measures of glucose metabolism, including fasting plasma glucose, 2-hour plasma glucose(2h-PG), HbA1C and fasting serum insulin(FSI)(109), which is supported by another studies(110, 111), but it is uncertain if the inverse relationship between LP(a) levels and T2DM is causal(112).

Clinical evidence also shows that treatments such as rosiglitazone, extended release niacin/laropiprant (ERN/LRPT), and certain combinations of anti-hypertensive drugs can significantly lower LP(a) levels, while also improving oxidative stress, lipid balance, and blood glucose control(110, 113).

In addition, higher levels of Lp (a) were associated with a lower prevalence of pre-diabetes, insulin resistance, and hyperinsulinemia. In a case control study, a low level of Lp(a) in the blood was linked to high risk of developing type 2 diabetes in a way that depended on the amount present(dose)(107). Although Lp(a) is linked to a higher risk of micro and macro vascular complications in diabetes, there is limited understanding of how diabetes influences Lp(a) levels and cause of inverse association are still not fully understood(77, 108, 114).

4.4 Nucleic Acids

Micro RNAs (miRNAs)

These are small Ribonucleic acid(RNA)molecules that don't code for any protein and with a length of 20-22 nucleotides, that participate in regulation of target gene expression, preventing the translation of target mRNAs(18), by binding to the 3' end of target messenger RNAs and blocking their translation, which ultimately lowers gene expression(115). They do this by constituting RNA induced silencing complex(RISC), and this complex directly inhibits the translation of mRNAs into proteins(116, 117).

It is estimated that more than 30% of human genes are controlled by miRNAs(77). They are released freely or packaged from cells within micro vesicles under different physiological and pathological conditions, allowing them to be taken by other cells(118). In this way, extracellular miRNAs act as important messengers in cell to cell communication, aiding in regulation of processes such as angiogenesis, tumor invasion, and immune responses(18, 118).

Recent studies on circulating miRNAs have emphasized their potential as valuable disease biomarkers (18, 118, 119). Advances in technologies for nucleic acid amplification, sequencing, and data analysis have made it possible to detect miRNAs released from pancreatic islets, especially under stress conditions. Micro RNAs are considered reliable biomarkers because they are highly stable in circulation and resistant to degradation and can be detected in different body fluids, therefore they have attracted attention as promising biomarkers for T2DM(120, 121).

Additionally, their tissue specific expression patterns can help identify the origin of circulating miRNAs further enhancing their clinical relevance(118). Numerous miRNAs have been demonstrated to be variably expressed in the insulin-producing pancreatic beta cells(122). For instance, miR-103 and miR-143 are thought to play a role in regulating subcutaneous fat tissue and the development of diabetes in animal models, while miR-103 additionally contribute to adipose tissue function and glucose metabolism in humans(115, 123).

A recent report indicates that miR-7 is the most prevalent miRNA in rat and human pancreatic islets when compared to acinar cells, whereas miR-375 seems to be more abundant within the islets(124). In a cohort of non-diabetic individuals from the Han Chinese population, lower levels of miR-126 were found to predict the future development of type 2 diabetes(125).

In another study involving healthy participants, several microRNAs showed important relationships with metabolic markers: mi-126 and mi-375 were negatively associated with glucose area under the curve values, while miR291 and miR-21 showed positive correlations with insulin resistance as measured by HOMA-IR. Moreover, miR-29a was positively linked to β-cell function based on Homeostatic assessment of beta cell(HOMA-B) values(126).

Several miRNAs, such as miR-375 and mi-R124, have been linked to the regulation of insulin secretion and the development of pancreatic beta cells; however, the precise functions of many miRNAs discovered in pancreatic islets are still unclear(70). Long term follow up studies over 15 years revealed that individuals with higher baseline levels of miR-122 has an increased risk of developing metabolic syndrome or type 2 diabetes(119).

Generally, findings from multiple studies implicated that several circulating mRNAs, including miR-28-3p, miR-142, miR-486, miR-122, miR-15a, miR320a, miR-126, and miR-375 show a consistent variations even before appearance of any clinical symptoms, highlighting their potential role as early biomarkers for metabolic disorders, including diabetes(119, 127).

4.8 Challenges and opportunities in Ethiopian context

4.8.1 Challenges

Despite a heavy burden of communicable and non-communicable disease in developing countries such as Ethiopia, most biomarker-focused research is still concentrated in the developed countries, with only 10% of global research efforts directed toward addressing needs of growing nations(149). Challenges in Ethiopia are as follows:

1. Resource constraints

A key challenge in research and application of novel biomarkers for diabetes in Ethiopia is an expensive reagents and specialized equipment that novel biomarker detection methods require (ELISA, PCR amplification, Metabolomics tools) are unaffordable for public health systems(150, 151). The whole process of biomarker development, validation, trial and approval requires cost in terms of money, time and human resources, which will be additional burden to the already weak health system in the country(152, 153).

2. Lack of an experienced personnel

There is an extremely small number of well-trained laboratory staff (Endocrinologists, well trained laboratory specialists, and trained professionals on biomarker analysis) to utilize a new detection and diagnostic methods and interpretation of the results using advanced and novel biomarkers, which causes dependence on the traditional methods for result interpretation and service delivery(150, 151).

3. Awareness gaps

There is a large gap among the population in the understanding of the chronic diseases, including diabetes and its diagnostic methods and, health professionals are also not familiar with new emerging diabetes early detection tools, which pose an obstacle to integration of novel biomarkers in diabetic screening and diagnostic protocols of healthcare system of the country. Moreover, there are no clear strategies devised for researches on novel biomarkers and their clinical applications (150, 154).

4. Socio-cultural barriers

A long standing dependence of the population on the traditional treatments an healing activities have an enormous effect on the acceptance of new screening mechanism and diagnostic biomarkers. Insufficient patient engagement and poor follow up will affect the effectiveness of diabetes screening activities(150, 151). Additionally, a large proportion of people that attends to healthcare comes from low income backgrounds, where there is a poor hygiene, and irregular daily routines, which causes a poor follow up, stress or denial and impacts how individuals manage their condition and their permission to participate in researches concerning development and applications of novel

biomarkers(150, 155).

5. Policy and regulatory obstacles

In developing countries like Ethiopia, there is often a fragile cooperation between studies and policies, which means that new insights from clinical studies, including biomarker studies are not usually integrated to national health policies and strategies.

There is also no regulatory system for the evaluation, validation and standardization of novel biomarkers in the regulatory bodies of the healthcare sector of the country(156).

Additionally, urgent and widespread public health problems such as infectious diseases will consume majority of attention and resources of the healthcare system, limiting the capability to develop, validate and implement novel biomarkers for chronic diseases such as diabetes(152, 155).

4.8.2 Opportunities

1. Infrastructure Expansions

Growing investments and in tertiary hospital laboratories will offer opportunities for raising the capacity of incorporating novel biomarkers as screening and early detection approaches in addition to the conventional diagnostic methods, as well as establishment of advanced health research centers such as CDC-Africa will support the country's capacity for clinical applications of novel biomarkers(151, 157, 158).

2. Integration of digital health

Advances in health technology are reshaping delivery of medical and diagnostic tools and improving the screening and management of diseases(159). In Ethiopia, ministry of health took a significant step by launching the digital health innovation and learning center, which allows experts expand fruitful innovations to a broader scale; this will also enable laboratories in the healthcare system to improve biomarker data tracking. And addressing issues with training and infrastructure(160).

3. Sectoral collaboration

Several sectoral collaborations have been formed in the process of improving laboratory and healthcare practices in Ethiopia. Among them, the expansion of laboratory services capacity led by the Federal Ministry of Health and Ethiopian Public Health Institute under the pillar of the COVID-19 incident management system has led to strengthen collaboration and partnerships across multiple sectors in strengthening the advancements in screening and diagnosis of communicable and non-communicable diseases such as diabetes(161).

For instance, expansion of laboratories with Reverse transcriptase polymerase chain reaction (RT-PCR) capacity has been made during the time of COVID-19 pandemic, which improved the capacity of conducting advanced tests, and these can be utilized in the application of novel diabetic biomarkers such as miRNAs, which require molecular testing capability(157, 162).

4.8.3 Experience to be learned and future perspective

Most fatalities from communicable and non-communicable diseases happen in low and middle income countries, of which Ethiopia is one(149). Despite significant burden of diabetes related morbidity, biomarker focused research initiatives are confined to developed nations, with only 10% of global research targeted to address the issues faced by the growing nations like Ethiopia(163). As Ethiopia is among African countries with a large number of diabetic patients, therefore it needs to take a lesson from other nations in biomarker analysis and clinical application such as creating a standard operating procedures in biomarker analysis, development of extensive data repositories, and sharing scientific discoveries to minimize data variability and fragmentation (149). Patients' understanding of diabetes, encompassing its risk factors, prevention and management techniques, primarily corresponds with biomedical theory. Nonetheless, their capacity to turn this understanding into action will be limited by socioeconomic and environmental influences: therefore supporting the socioeconomic growth and expansion of essential infrastructure is of paramount importance(164).

Additionally, understanding community viewpoints is essential for creating effective interventions that are culturally relevant and acceptable by people in the country(165). This increases acceptance and sustainability of diagnostic and treatment outcomes(166).

Moreover, the development of bio banks will greatly aid in investigation and creating important connections in diseases, as well as to identify biological factors of diabetes or uncover new screening and diagnostic targets (149).

5. Conclusion

Drawing from the old and current clinical studies on the utilization of novel biomarkers, the literature reveals that novel biomarkers are helpful in early detection of the development of diabetes. The historical development of biomarkers that led to a use of the current traditional diabetic biomarkers, and the major conventional biomarkers used in diabetes screening, diagnosis, and prognosis were examined.

This narrative review has some limitations that deserve recognition. Being an non-systematic synthesis, the studies selected might not fully capture all existing evidence, possibly causing selection bias. The major drawbacks of traditional biomarkers such as sensitivity to storage conditions, person-to-person variation, invasiveness, vulnerability due to physiological fluctuations were implicated. The need to validate and apply novel biomarkers in Ethiopia is profound: early detection and alleviation of the complications related to diabetes is extremely important given that the healthcare costs related to diabetes may pose an additional burden on the limited resources the country has in healthcare sector.

Emphasis on strengthening multi-sectoral collaboration, policy development, training and enabling laboratory personnel on biomarker analysis, and validation is critical to apply novel biomarkers for early detection and prevention of complications and related morbidity and mortality. Provision of resources for integrating novel biomarker assessment into formal diabetes screening practices should be conducted at national, regional and zonal healthcare management level to detect diabetes early and avoid healthcare costs, and mortality related to its complications.

Training and awareness creation programs laboratory professionals on the analysis, validation and application of novel biomarkers at healthcare organizations and education and awareness creation should be carried out for Clinicians on the benefits of novel biomarkers in early detection and prevention of diabetic complications. Finally, better collaboration among academic institutions such as universities, research institutes, and health organizations should be supported to assess and apply novel biomarkers and generate local evidence on their effectiveness and efficiency to apply as formal screening tools in screening of

diabetes.

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Author contributions

All the listed authors provided intellectual contributions and made critical revisions to this narrative review; DG and AG have contributed to the conceptualization, researching the literature and drafting the first version of the manuscript; SA, MB and WC have contributed to the conceptualization and participated in the critical discussion of the review. Besides that, all authors approved the final version of the manuscript.

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