eISSN : 2810 – 0204
Available Online at : http://journal.scientic.id/index.php/sciena/issue/view/31

Emerging Biomarkers for Prediabetes : A Review

Dinda Aprilia[1,2*], Eva Decroli[1,2], Alexander Kam[1,2], Putri Deas Hadilofyani[3]

[1.] Metabolic Endocrinology and Diabetes Division, Internal Medicine Department, Medical Faculty, Universitas Andalas, Padang, West Sumatera, Indonesia
[2.] Metabolic Endocrinology and Diabetes Division, Internal Medicine Department, M. Djamil General Hospital, Padang, West Sumatera, Indonesia
[3.] Internal Medicine Department, Medical Faculty, Universitas Andalas, Padang, Indonesia
Email: dindaaprilia.sppd@gmail.com

Abstract

Prediabetes is a global health concern marked by elevated blood glucose levels that do not yet meet the threshold for type 2 diabetes mellitus (T2DM). It is often underdiagnosed despite being associated with insulin resistance, beta-cell dysfunction, and increased cardiovascular risk. Improved strategies for early detection are crucial to prevent disease progression. This review aims to explore novel biomarkers associated with prediabetes and evaluate their potential clinical applications in early diagnosis and risk stratification. A literature search was conducted on English and Indonesian language publications, including original research, case reports, and expert guidelines, focusing on emerging molecular and metabolic biomarkers related to prediabetes. Several promising biomarkers have been identified, including adiponectin, microRNAs, fetuin A, alpha-hydroxybutyrate (α-HB), and Protein Z. Adiponectin demonstrates an inverse relationship with insulin resistance. Specific microRNAs, such as miR-192 and miR-193b, are implicated in glucose metabolism and beta-cell function. Elevated fetuin A levels are linked to hepatic insulin resistance, while increased α-HB levels reflect early metabolic shifts in glucose utilization. Additionally, altered Protein Z concentrations may contribute to prothrombotic states in individuals with prediabetes. In conclusion, these biomarkers offer valuable insight into the pathophysiology of prediabetes and hold potential for enhancing early detection and prevention strategies. However, further validation through large-scale studies is needed before their integration into clinical practice.

Keywords: Prediabetes, recent biomarkers.

Abstrak

Pradiabetes merupakan masalah kesehatan global yang ditandai dengan peningkatan kadar glukosa darah yang belum memenuhi ambang batas diabetes melitus tipe 2 (DMT2). Kondisi ini seringkali kurang terdiagnosis meskipun berkaitan dengan resistensi insulin, disfungsi sel beta, dan peningkatan risiko kardiovaskular. Strategi deteksi dini yang lebih baik sangat penting untuk mencegah progresi penyakit. Tinjauan ini bertujuan untuk mengeksplorasi biomarker baru yang terkait dengan pradiabetes dan mengevaluasi potensi aplikasi klinisnya dalam diagnosis dini dan stratifikasi risiko. Penelusuran literatur dilakukan terhadap publikasi berbahasa Inggris dan Indonesia, termasuk penelitian asli, laporan kasus, dan panduan ahli, dengan fokus pada biomarker molekuler dan metabolik yang baru muncul terkait dengan pradiabetes. Beberapa biomarker yang menjanjikan telah diidentifikasi, termasuk adiponektin, microRNA, fetuin A, alfa-hidroksibutirat (α-HB), dan Protein Z. Adiponektin menunjukkan hubungan terbalik dengan resistensi insulin. MikroRNA spesifik, seperti miR-192 dan miR-193b, berperan dalam metabolisme glukosa dan fungsi sel beta. Peningkatan kadar fetuin A berkaitan dengan resistensi insulin hepatik, sementara peningkatan kadar α-HB mencerminkan pergeseran metabolik dini dalam pemanfaatan glukosa. Selain itu, perubahan konsentrasi Protein Z dapat berkontribusi terhadap kondisi protrombotik pada individu dengan pradiabetes. Kesimpulannya, biomarker ini menawarkan wawasan berharga tentang patofisiologi pradiabetes dan berpotensi meningkatkan strategi deteksi dini dan pencegahan. Namun, validasi lebih lanjut melalui studi skala besar diperlukan sebelum integrasinya ke dalam praktik klinis.

***Kata Kunci**: Pradiabetes, biomarker terbaru*

I. INTRODUCTION

Prediabetes is a growing global health issue, characterized by elevated blood glucose levels that have not yet reached the threshold for diabetes diagnosis.[1] It is a metabolic disorder marked by insulin resistance and/or pancreatic beta-cell dysfunction. Initially, as blood glucose levels rise, the body compensates by increasing insulin production to enhance glucose uptake. However, as insulin resistance and/or beta-cell dysfunction progresses, the capacity to absorb glucose diminishes, leading to further elevation of blood glucose levels.[2]

This condition encompasses two primary disorders: Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG). According to the American Diabetes Association (ADA), prediabetes is diagnosed when Hemoglobin A1C (HbA1c) levels are between 5.7% and 6.4%, fasting plasma glucose levels range from 100 to 125 mg/dL, or a two-hour oral glucose tolerance test (OGTT) results in glucose levels between 140 and 199 mg/dL.[3] In 2019, the International Diabetes Federation (IDF) estimated that 373.9 million adults worldwide lived with prediabetes, a number expected to increase significantly in the coming decades.[4]

Prediabetes is driven by insulin resistance, beta-cell dysfunction, increased lipolysis, inflammation, and excessive hepatic glucose production. These metabolic abnormalities contribute to endothelial dysfunction and impaired fibrinolysis, which elevate the risk of macrovascular complications such as atherosclerosis. Although often considered a precursor to type 2 diabetes mellitus (T2DM), prediabetes itself carries a significant cardiovascular risk, with studies indicating that many patients may develop coronary artery disease or heart failure before progressing to diabetes.[3]

Given that up to 37% of individuals with prediabetes may develop diabetes within four years if untreated, early identification is crucial. Current strategies emphasize lifestyle interventions, which can reduce the progression to diabetes by up to 20%.[4,5] Biomarkers play a critical role in early detection. Traditional biomarkers, such as fasting glucose and HbA1c, have limitations, prompting research into new biomarkers that may enhance diagnostic accuracy.

Recent studies have identified promising biomarkers in the fields of metabolomics and microRNA research. Key candidates include adiponectin, fetuin-A, alpha-hydroxybutyrate, 1,5-anhydroglucitol and specific microRNAs associated with prediabetes. These findings offer the potential for earlier and more accurate diagnosis, ultimately improving intervention outcomes.[6] This review aims to summarize recent research on new biomarkers for prediabetes, focusing on their clinical implications and potential for future studies. By enhancing early detection, these new biomarkers could help prevent the progression to type 2 diabetes and its associated complications.

II. PREDIABETES: DEFINITION, EPIDEMIOLOGY, AND DIAGNOSIS

Prediabetes is an intermediate metabolic condition characterized by elevated blood glucose levels that are below the diagnostic threshold for diabetes.[1] It serves as a critical warning for the potential development of type 2 diabetes mellitus (T2DM), often without clear symptoms. Prediabetes was first recognized in the late 1970s as a phase between normal glucose tolerance and diabetes, defined by plasma glucose levels that do not meet the criteria for diabetes. Thus, it provides a valuable window for early intervention.[3]

Global epidemiological data indicate that prediabetes affects a significant portion of

the population. The International Diabetes Federation (IDF) estimates that approximately 7.5% of adults aged 20–79 years, equivalent to about 374 million individuals, have impaired glucose tolerance (IGT), with a notably high prevalence in North America and the Caribbean.[4] In the United States alone, more than 96 million adults are affected by prediabetes, with nearly 80% undiagnosed, highlighting an urgent need for improved screening methods.[6] Data from the National Health and Nutrition Examination Survey (NHANES) 2015–2016 show that the prevalence of prediabetes varies widely depending on the diagnostic criteria applied, ranging from 4.3% to 43.5%.[5]

Diagnostic criteria for prediabetes generally refer to impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). According to the World Health Organization (WHO), IFG is defined as fasting plasma glucose levels between 100–125 mg/dL, while IGT is diagnosed when plasma glucose levels range from 140–199 mg/dL two hours after an oral glucose tolerance test (OGTT). The American Diabetes Association (ADA) uses similar criteria and includes glycated hemoglobin (HbA1c) as an additional diagnostic tool, with HbA1c levels between 5.7% and 6.4% indicating prediabetes.[7] In Indonesia, diagnostic guidelines reflect this definition, incorporating HbA1c along with IFG and IGT for a more comprehensive assessment.[1,8]

III. EMERGING BIOMARKERS IN PREDIABETES

Biomarkers are crucial for improving the early detection and understanding of prediabetes. Recent advances have identified several biomarkers with the potential to enhance clinical screening and provide deeper insights into the mechanisms underlying the progression to T2DM. Among these biomarkers, adiponectin, microRNA (miRNA), fetuin A, alpha-hydroxybutyrate (α-HB), Protein Z and 1,5-anhydroglucitol have emerged as promising candidates.

ADIPONECTIN

Adiponectin, first identified in 1995, plays a crucial role in glucose metabolism and insulin sensitivity. It is secreted by adipose tissue and circulates in three forms: low, medium, and high molecular weight (HMW), with HMW being the most active in glucose uptake.[9-11] Adiponectin enhances insulin sensitivity through the activation of key pathways such as AMPK and PPAR-α, which regulate glucose uptake and fatty acid oxidation. It binds to two receptors: AdipoR1 in skeletal muscle and AdipoR2 in the liver, affecting glucose metabolism, hepatic glucose production, and insulin sensitivity.[10]

In obesity and metabolic syndrome, inflammatory cytokines like TNF-α and IL-6 reduce adiponectin levels, contributing to insulin resistance.[12] Conversely, higher adiponectin levels are associated with lower fasting glucose levels and a reduced risk of developing prediabetes. Adiponectin's anti-inflammatory properties are crucial in reducing insulin resistance and preventing vascular complications, particularly in women.[13] Studies indicate that individuals with higher initial adiponectin levels have a 40% lower risk of developing prediabetes over a 2.5-year observation period.[13]

MICRORNA (MIRNA)

miRNA are small non-coding RNAs that regulate gene expression post-transcriptionally, affecting processes like glucose metabolism and insulin signaling.[14,15] Research shows that several miRNAs are associated with diabetes development, including specific miRNAs such as miR-15a, miR-375, and miR-126, linked to the risk of T2DM and prediabetes. For instance, miR-126, which is specific to

endothelial cells, has been proposed as a biomarker for early prediabetes detection.[15]

Recent studies indicate that miR-192 and miR-193b levels are elevated in individuals with impaired fasting glucose and impaired glucose tolerance, correlating with increased triglycerides and liver fat accumulation.[14] These miRNAs are also influenced by physical activity, which significantly reduces their levels. This suggests that miRNAs are useful not only as biomarkers for prediabetes but also for monitoring responses to lifestyle interventions.[15,16]

FETUIN A

Fetuin A is a multifunctional hepatokine involved in glucose homeostasis. It inhibits insulin receptor function, contributing to insulin resistance by promoting inflammation and activating TLR4 (Figure 1). High fetuin A levels have been linked to metabolic disorders such as T2DM, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD).[17,18]

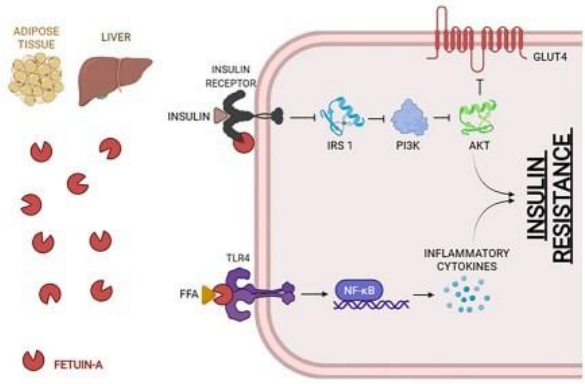

Figure 1. Mechanism of fetuin-a in enhancing insulin resistance.

Research indicates that fetuin A can serve as a predictor of prediabetes, with higher levels associated with increased insulin resistance, higher body mass index (BMI), and elevated fasting glucose levels.[19,20] Studies also demonstrate that individuals with elevated fetuin A levels have a significantly greater risk of developing type 2 diabetes mellitus (T2DM). Furthermore, interventions such as the use of PPAR-γ agonists, dietary changes, and physical activity can reduce fetuin A levels, highlighting its potential as both a biomarker and therapeutic target in managing prediabetes and insulin resistance.[21]

ALPHA-HYDROXYBUTYRATE (α-HB)

α-Hydroxybutyrate (α-HB) is a byproduct of amino acid metabolism and glutathione synthesis, primarily produced in the liver. α-HB is a promising biomarker for prediabetes due to its role in reflecting liver stress and lipid oxidation.[22,23] Studies have shown that α-HB levels are elevated in individuals with impaired glucose tolerance (IGT), with this increase associated with decreased β-cell function and delayed insulin secretion during the oral glucose tolerance test (OGTT).[24,25]

In a cohort study, α-HB demonstrated an 80% sensitivity in identifying individuals with IGT, suggesting its utility in screening for prediabetes without the need for OGTT. Additionally, elevated α-HB levels have been linked to reduced β-cell function and delayed insulin kinetics, making it a valuable early marker for the progression to T2DM.[24,25]

PROTEIN Z

Protein Z is a vitamin K-dependent glycoprotein involved in regulating blood coagulation by inhibiting factor Xa, thereby reducing the risk of thrombosis. Recent studies indicate that decreased levels of Protein Z are associated with prediabetes, with lower levels also linked to an increased risk of cardiovascular and thrombotic diseases.[26-29]

In a study comparing normoglycemic, prediabetic, and T2DM individuals, Protein Z levels were found to be significantly lower in prediabetic patients. Moreover, Protein Z demonstrated higher sensitivity (62.9%) and specificity (80.3%) for predicting prediabetes

compared to HbA1c, which has lower sensitivity in detecting this condition. This suggests that Protein Z may be a more reliable biomarker for early detection of prediabetes and related vascular complications.[27,34-37]

1,5 ANHYDROGLUCITOL

1,5-Anhydroglucitol (1,5-AG) is a monosaccharide found in foods like rice, bread, and beef. It plays a key role in glucose regulation by being absorbed in the intestines and reabsorbed in the kidneys. In hyperglycemic conditions, its reabsorption is impaired, causing increased urinary excretion and lower blood levels. Clinically, 1,5-AG is used to monitor glycemic control, particularly for diagnosing and managing prediabetes and diabetes. It is more sensitive than glucose testing in detecting fluctuations in blood glucose and postprandial hyperglycemia. Serum levels typically range from 14-29 μg/ml, with levels below 10 μg/ml indicating diabetes and 11-14 μg/ml suggesting prediabetes. 1,5-AG remains unaffected by factors like hemoglobin, bilirubin, or lipid levels, making it a reliable diagnostic marker. It is especially useful for detecting short-term blood glucose irregularities and assessing overall glycemic control. Combining 1,5-AG with other tests, such as GD2PP, can improve diagnostic accuracy for diabetes.[28-33]

IV. CONCLUSION

Biomarker assessment is crucial for the early identification and management of prediabetes. Low adiponectin levels are associated with obesity, hypertension, dyslipidemia, elevated blood glucose levels, and insulin resistance, all of which are major risk factors for prediabetes and type 2 diabetes mellitus (T2DM). Among the new biomarkers, microRNAs, particularly miR-192 and miR-193b, exhibit high specificity and sensitivity in detecting prediabetes, with elevated levels observed in individuals with impaired fasting glucose and glucose tolerance. Additionally, fetuin A levels positively correlate with fasting glucose and insulin resistance, while serum alpha-hydroxybutyrate (α-HB) levels increase under insulin resistance conditions. These biomarkers provide valuable insights for early intervention in prediabetes, improving patient outcomes and preventing progression to T2DM.

REFERENCE

[1]. Decroli E. Prediabetes. Padang: Andalas University Press; 2022. 146 p. ISBN: 978-623-172-002-3.
[2]. Decroli E, Efendi YP, Kam A, Manaf A, Syahbuddin S. Description of Insulin Resistance and Beta-Cell Pancreas Dysfunction in Prediabetic Patients. ICOMHER. 2018
[3]. Echouffo-Tcheugui JB, Selvin E. Prediabetes and What It Means: The Epidemiological Evidence. *Annu Rev Public Health*. 2021;42:59-77
[4]. International Diabetes Federation. *IDF Diabetes Atlas*, 9th edition. Brussels, Belgium, International Diabetes Federation. 2019
[5]. Center for Disease Control and Prevention. Prevalence prediabetes of among adults. 2022
[6]. Dorcely B, Katz K, Jagannathan R. Novel biomarkers for prediabetes, diabetes, and associated complications. *Diabetes Metab Syndr Obes*. 2017;10:345-361
[7]. Díaz-Redondo A, Giráldez-García C, Carrillo L, et al. Modifiable risk factors associated with prediabetes in men and women: a cross-sectional analysis of the cohort study in primary health care on the evolution of patients with prediabetes *BMC Fam Pract*. 2015;16:5
[8]. Persatuan Diabetes Indonesia. Pengelolaan dan pencegahan prediabetes di Indonesia. 2019
[9]. Abdella NA, Mojiminiyi OA. Clinical applications of adiponectin measurements in type 2 diabetes mellitus: Screening, diagnosis, and marker of diabetes control. Dis Markers. 2018.
[10]. Khoramipour K, Chamari K, Hekmatikar AA, Ziyaiyan A, Taherkhani S, Elguindy NM, et al. Adiponectin: Structure, Physiological Functions, Role in Diseases, and Effects of Nutrition. Nutrients. 2021;13(4):1180.
[11]. Ganesh V, M M, Palem SP. Adiponectin Can Be an Early Predictable Marker for Type 2 Diabetes Mellitus and Nephropathy. Cureus. 2022;14(7).
[12]. Lin D, Hong X, Sun K, Zhang X, Lian H, Wang J, et al. Galectin-3/adiponectin as a new biological indicator for assessing the risk of type 2 diabetes: a cross-sectional study in a

community population.Aging. 2021;13(11):15433–43.
[13]. Nguyen TMD. Adiponectin: Role in Physiology and Pathophysiology. *Int J Prev Med*. 2020;11:136
[14]. Al-Kafaji G, Al-Muhtaresh HA, Salem AH. Expression and clinical significance of mir-1 and mir-133 in pre-diabetes. Biomed Rep. 2021;14(3):1–9.
[15]. Sidorkiewicz I, Niemira M, Maliszewska K, Erol A, Bielska A, Szalkowska A, et al. Circulating mirnas as a predictive biomarker of the progression from prediabetes to diabetes: Outcomes of a 5-year prospective observational study. J Clin Med. 2020;9(7):1– 20.
[16]. Yan LN, Zhang X, Xu F, Fan YY, Ge B, Guo H, et al. Four-microRNA signature for detection of type 2 diabetes. World J Clin Cases. 2020;8(10):1923–31.
[17]. Bodaghi A, Fattahi N, Ramazani A. Biomarkers: Promising and valuable tools towards diagnosis, prognosis and treatment of Covid-19 and other diseases. Heliyon. 2023;9(2):e13323.
[18]. Luís C, Baylina P, Soares R, Fernandes R. Metabolic dysfunction biomarkers as predictors of early diabetes. Biomolecules. 2021;11(11).
[19]. Ahn MB, Kim SK, Kim SH, Cho WK, Suh JS, Cho KS, et al. Clinical significance of the fetuin-a-to- adiponectin ratio in obese children and adolescents with diabetes mellitus. Children. 2021;8(12).
[20]. Wang Y, Koh WP, Jensen MK, Yuan JM, Pan A. Plasma fetuin-A levels and risk of type 2 diabetes mellitus in a Chinese population: A nested case-control study. Diabetes Metab J. 2019;43(4):474–86.
[21]. Susairaj P, Snehalatha C, Nanditha A, Satheesh K, Raghavan A, Vinitha R, et al. Analysis of an Indian diabetes prevention programme on association of adipokines and a hepatokine with incident diabetes. Sci Rep. 2021;11(1):1—9.
[22]. Khathi A, Dagogo-Jack S. Editorial: Prediabetes and endocrine function. Front Endocrinol (Lausanne). 2023;14(8):1–3.
[23]. Luís C, Soares R, Baylina P, Fernandes R. Underestimated Prediabetic Biomarkers: Are We Blind to Their Strategy? Front Endocrinol (Lausanne). 2022;13(3):1–7
[24]. Gall WE, Beebe K, Lawton KA, Adam KP, Mitchell MW, Nakhle PJ, et al. A-Hydroxybutyrate Is an Early Biomarker of Insulin Resistance and Glucose Intolerance in a Nondiabetic Population. PLoS One. 2010;5(5).
[25]. Cobb J, Eckhart A, Motsinger-Reif A, Carr B, Groop L, Ferrannini E. α-Hydroxybutyric acid is a selective metabolite biomarker of impaired glucose tolerance. Diabetes Care. 2016;39(6):988–95
[26]. Almawi, W. Y., Al-Shaikh, F. S., Melemedjian, O. K., Almawi, A. W. Protein Z, an anticoagulant protein with expanding role in reproductive biology. REPRODUCTION, 2013; 146(2), R73- R80
[27]. Bae YU, You JH, Cho NH. Association of Protein Z with Prediabetes and Type 2 Diabetes. Endocrinol Metab (Seoul). 2021;36(3):637-646Hazel K, O'Conor A. Emerging treatments for inflammatory bowel
[28]. Anggraini, D., Yaswir, R., Lillah, L., & Husni, H. (2017). Correlation of Advanced Glycation End Products with Urinary Albumin Creatinin Ratio in Patients with Type 2 Diabetes Mellitus. Indonesian Journal of Clinical Pathology and Medical Laboratory, 23(2), 107-110.
[29]. Anggraini, D., & Zakiyah, N. J. (2024). Risk Factors of Type 2 Diabetes Mellitus in the Elderly. Nusantara Hasana Journal, 3(10), 34-40.
[30]. Anggraini, D., Yaswir, R., Lillah, L., & Husni, H. (2017). Correlation of Advanced Glycation End Products with Urinary Albumin Creatinin Ratio in Patients with Type 2 Diabetes Mellitus. Indonesian Journal of Clinical Pathology and Medical Laboratory, 23(2), 107-110.
[31]. Anggraini, D., & Zakiyah, N. J. (2024). Risk Factors of Type 2 Diabetes Mellitus in the Elderly. Nusantara Hasana Journal, 3(10), 34-40.
[32]. Anggraini, D., Amran, R., & Adelin, P. (2023). Deteksi Dini Hiperglikemia pada Lansia Binaan Puskesmas Guguak Kabupaten 50 Kota. Jurnal Pengabdian Masyarakat Kesehatan (JURABDIKES), 1(1), 05-08.
[33]. Anggraini, D., Oktora, M. Z., & Hasni, D. (2025). Peran Indeks Aterogenik sebagai Penanda Komplikasi pada Diabetes Melitus Tipe 2: Tinjauan Pustaka. Scientific Journal, 4(2), 91-99.
[34]. Anggraini, D., Amran, R., & Adelin, P. (2023). Deteksi Dini Hiperglikemia pada Lansia Binaan Puskesmas Guguak Kabupaten 50 Kota. Jurnal Pengabdian Masyarakat Kesehatan (JURABDIKES), 1(1), 05-08.
[35]. Anggraini, D., Oktora, M. Z., & Hasni, D. (2025). Peran Indeks Aterogenik sebagai Penanda Komplikasi pada Diabetes Melitus Tipe 2: Tinjauan Pustaka. Scientific Journal, 4(2), 91-99.
[36]. Febryan R, Decroli E, Aprilia D, Kam A. Pemeriksaan 1,5-Anhydroglucitol, Suatu Hal Baru dalam Pemeriksaan Prediabetes. Maj Kedokteran Andalas. 2023 Jul;46(4):724-9.