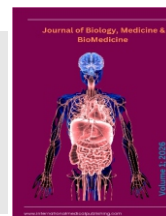




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Review

Section: Zoology

A Review on Dysregulation of Lipid Metabolism & Ketogenesis in Type 2 Diabetes Mellitus

Jyoti Thakre², Durgesh Agase^{1*}, Vaishali Thakur², Karan Singh Saini²

¹Department of Zoology, PMCOE Government Post Graduate College, Sheopur, Madhya Pradesh, India

²Department of Zoology, JataShankar Trivedi Post Graduate College, Balaghat, Madhya Pradesh, India

HIGHLIGHTS

- Ketones regulate metabolic signalling
- Immune metabolism drives inflammation
- Acylcarnitines indicate metabolic dysfunction
- β -Hydroxybutyrate modulates immunity
- Multi-omics improves diabetes biomarkers

Key Words:

Diabetes mellitus;
Metabolomics;
Immunometabolism;
Ketogenic metabolism;
Ketone bodies;
 β -hydroxybutyrate;
Acylcarnitines;
Insulin resistance;
Metaflammation;
Immune cell metabolic
Reprogramming;
Multi-omics biomarkers;
Type 2 diabetes;
Diabetic kidney disease

ABSTRACT

Introduction: Diabetes mellitus (DM) is a metabolic disorder characterised by chronic hyperglycaemia resulting from impaired insulin–glucagon regulation. Type 1 diabetes involves autoimmune β -cell destruction, whereas type 2 diabetes mellitus (T2DM) is primarily associated with insulin resistance and relative insulin deficiency. Advances in metabolomics and immunometabolism have identified metabolites that participate in insulin resistance, inflammation, and metabolic dysregulation. **Aim & Objective:** To review the roles of ketogenic and immune metabolism in DM and evaluate their potential as biomarkers for early diagnosis, patient stratification, and personalised therapeutic monitoring. **Materials & Methods:** A narrative review of current evidence was undertaken, focusing on metabolomic and immunometabolic studies involving ketone bodies, acylcarnitines, branched-chain amino acids, ceramides, glycine, glutamine, lactate, NAD⁺, immune-cell metabolic pathways, and inflammatory mediators in DM. **Results:** Ketone bodies, particularly β -hydroxybutyrate, act as metabolic substrates and signalling molecules influencing oxidative stress, histone deacetylation, and immune-cell function. Alterations in acylcarnitine and other metabolite profiles are associated with insulin resistance and metabolic dysfunction. Immune-cell metabolic reprogramming contributes to chronic low-grade inflammation (metaflammation), particularly in obesity and T2DM. However, clinical translation is limited by insufficient longitudinal human studies, heterogeneous diabetes phenotypes, non-standardised measurement protocols, incomplete multi-omics integration, and limited validation of metabolite-based assays. **Conclusion:** Integration of ketogenic and immune-metabolic pathways may provide a systems-level approach to understanding DM pathogenesis. Combined assessment of ketone bodies, acylcarnitines, immune-derived enzymes, and inflammatory mediators may improve early detection, disease stratification, and personalised monitoring beyond conventional glycaemic indices.

* Corresponding Author: Dr. Durgesh Agase, e-mail: sbtdurgesh@gmail.com

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INTRODUCTION

Diabetes was first described by the ancient Egyptians, who recognised it as a condition characterised by excessive urination and weight loss. The term *diabetes* was later introduced by the Greek physician Aretaeus, deriving from the Greek word *diabainein*, meaning “to pass through,” in reference to excessive urination. The Latin term *mellitus*, meaning “honey-sweet,” was added later to distinguish the condition by the presence of sweet-tasting urine. Blood glucose homeostasis is maintained through a tightly regulated negative feedback mechanism involving two key pancreatic hormones, insulin and glucagon [1].

When blood glucose levels rise, β -cells within the pancreatic islets of Langerhans secrete insulin, a 51-amino acid peptide hormone composed of two polypeptide chains (A and B) linked by disulfide bonds. Insulin is synthesised as the precursor molecule proinsulin and is processed through enzymatic cleavage by the prohormone convertases PC1/3 and PC2, followed by carboxypeptidase E, to generate mature insulin and C-peptide in equimolar amounts. Upon secretion, insulin binds to the insulin receptor, a transmembrane receptor tyrosine kinase consisting of two extracellular α -subunits and two transmembrane β -subunits joined by disulfide bonds. Receptor binding induces autophosphorylation of the β -subunits and initiates intracellular signalling cascades that promote glucose uptake, glycogen synthesis, and other anabolic processes. In skeletal muscle and adipose tissue, insulin stimulates glucose uptake through the translocation of GLUT4 transporters to the plasma membrane, whereas in the liver it promotes glycogen synthesis and suppresses hepatic glucose production, thereby restoring

blood glucose homeostasis. Conversely, when blood glucose levels decline, pancreatic α -cells secrete glucagon, which stimulates hepatic glycogenolysis and gluconeogenesis, thereby increasing glucose release into the bloodstream and maintaining normoglycaemia [2].

In diabetes mellitus, this finely tuned regulatory system is disrupted. Type 1 diabetes results from autoimmune destruction or dysfunction of pancreatic β -cells, leading to insulin deficiency. Type 2 diabetes involves insulin resistance, where body tissues fail to respond adequately to insulin or insulin production is insufficient. Both forms result in chronic hyperglycaemia and impaired glucose regulation [3].

Cardiometabolic diseases, including type 2 diabetes mellitus (T2DM) and obesity, are major contributors to global morbidity and mortality. The advent of metabolomics, defined as the comprehensive profiling of metabolites in biological systems, has transformed our understanding of the metabolic dysregulation underlying these conditions. Metabolomic studies have revealed that specific metabolites serve not only as biomarkers but also as active mediators of insulin resistance, a central pathological hallmark of T2DM [4].

Among these, branched-chain amino acids (BCAAs), ceramides, glycine, and glutamine play crucial roles. Elevated levels of BCAAs and ceramides are consistently linked to impaired insulin signalling and increased risk of T2DM [5,6]. In contrast, glycine exhibits an inverse association with insulin resistance, suggesting its potential protective role in glucose metabolism [7]. This indicates that glycine supplementation may offer therapeutic benefits by improving insulin sensitivity and restoring metabolic

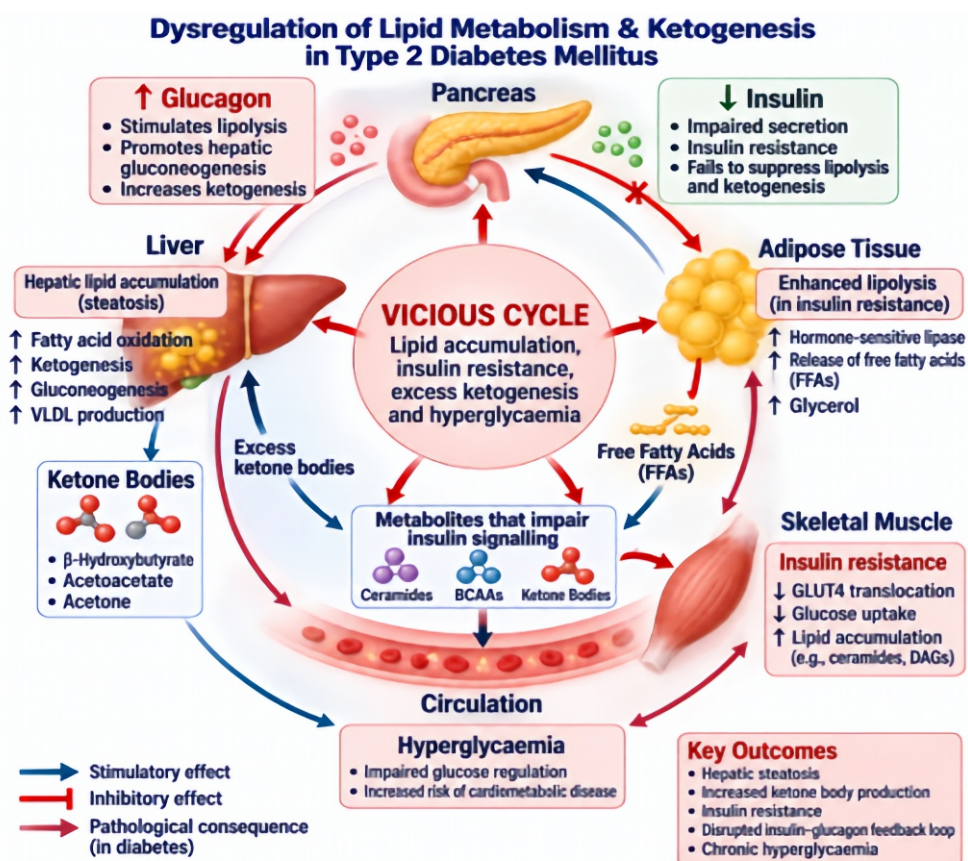


Figure 1: Dysregulation of lipid metabolism and ketogenesis in type 2 diabetes mellitus

balance. Beyond amino acid and lipid metabolites, molecules associated with cellular energy metabolism, including ketone bodies, lactate, and nicotinamide adenine dinucleotide (NAD⁺), also modulate insulin sensitivity and mitochondrial function. Ketogenic diets and supplementation with NAD⁺ precursors have been reported to improve insulin sensitivity and overall metabolic health [8]. Furthermore, the identification of *N*-lactoyl-phenylalanine (Lac-Phe) as a novel exercise-induced metabolite involved in energy homeostasis underscores the expanding landscape of metabolic biomarkers [9]. Collectively, these findings highlight the potential of metabolite-based diagnostics and therapeutic interventions for the early detection, risk stratification, and precision management of metabolic disorders. In recent years, the emerging field of immunometabolism, the intersection of metabolism and immune function, has become a major area of focus. Once considered peripheral to immunology, metabolic pathways are now recognised as central regulators of immune cell activation, differentiation, and survival. Metabolites and metabolic intermediates not only supply energy and biosynthetic precursors but also influence signalling, transcriptional, and epigenetic programs within immune cells [10]. Voss and colleagues proposed a systematic framework for investigating cellular metabolism in the immune system, emphasising the integration of biochemical, metabolomic, and genetic approaches to support hypothesis-driven research. These methodologies, including metabolomics, stable isotope tracing, and genetic manipulation, have enabled the precise mapping of metabolic fluxes within immune cells. Such advances have provided critical insights into how metabolic reprogramming regulates immune cell effector functions and inflammatory responses [11]. **Figure 1.** Lipid metabolism and ketogenesis in type 2 diabetes mellitus.

Metabolites can also act as signalling molecules that modulate cytokine production, transcription factors, and epigenetic remodelling, thereby influencing immune responses in both health and disease [12]. The incorporation of metabolic analysis into immunology has transformed understanding of how immune cells adapt to energetic and environmental challenges. By merging classical biochemistry with cutting-edge metabolomic and genetic tools, modern immunology now explores the dynamic interplay between cellular metabolism and immunity with unprecedented depth and translational potential.

The pathogenesis of diabetes mellitus (DM) is increasingly recognised as involving a complex interplay between metabolic dysregulation and immune processes. Traditional biomarkers, such as glycated haemoglobin (HbA_{1c}) and fasting plasma glucose, primarily reflect glycaemic status; however, emerging evidence suggests that metabolic-immune crosstalk represents a promising avenue for the discovery of novel biomarkers. This review focuses on two intersecting axes: ketogenic metabolism, which reflects ketone body production and utilisation during altered energy metabolism, and immune metabolism, encompassing metabolic reprogramming of immune cells & inflammatory mediators. By integrating these complementary pathways, this

review highlights their potential for identifying sensitive and clinically relevant biomarkers for diabetes mellitus.

REVIEW OF LITERATURE

Ketogenesis, the hepatic production of ketone bodies (e.g., β -hydroxybutyrate, acetoacetate) in states of low carbohydrate availability, has historically been associated with starvation or diabetic ketoacidosis. More recently, ketogenic metabolism has been studied as a modifiable metabolic state (e.g., via ketogenic diet) with relevance to insulin resistance and type 2 DM (T2DM). A meta-analysis demonstrated that ketogenic dietary interventions significantly lowered fasting glucose, HbA_{1c}, triglycerides and BMI in T2DM patients, supporting the notion that ketone-rich states influence metabolic homeostasis [13]. Further, advanced metabolomics reviews identify ketone bodies among the metabolites that regulate insulin sensitivity and metabolic flexibility [14,15]. Therefore, ketone bodies and associated acylcarnitines, fatty-acid oxidation intermediates, and the enzymes/regulators of ketogenesis may serve as biomarkers of an altered metabolic state relevant to DM onset or progression.

Immune metabolism, which lies at the intersection of immunology and cellular metabolism, is now recognised as a central regulator of metabolic disease. Chronic low-grade inflammation, termed *metaflammation*, in obesity and type 2 diabetes mellitus (T2DM) is characterised by metabolic reprogramming of immune cells, whereby macrophages, T cells, and other immune cell subsets undergo shifts in metabolic fuel utilisation from oxidative phosphorylation to glycolysis or vice versa. These metabolic adaptations profoundly influence immune cell phenotype, inflammatory responses, and systemic insulin sensitivity [11]. In DM research, proteomic reviews in type 1 DM (T1DM) show that circulating protein biomarkers enriched in complement, lipid metabolism, and immune response pathways are altered in disease development [16]. Thus, biomarkers reflecting immune cell activation, cytokine/chemokine profiles, complement components, and immunometabolic regulators hold promise.

The novel frontier lies in identifying biomarkers that link ketogenic metabolism with immune metabolism in the diabetic context. Ketone bodies such as β -hydroxybutyrate (β HB) are not only energy substrates but also signalling molecules: β HB can modulate histone deacetylation, oxidative stress, and immune-cell function [17,18].

For example, recent work shows that a ketogenic diet remodels the immune transcriptome in murine models of autoimmune uveitis, suggesting that ketone-driven metabolic states influence immune cell phenotype [19]. In DM, the hypothesis is that altered ketone metabolism may influence immune cell activation and inflammatory pathways, thereby generating biomarkers that reflect both metabolic and immune dysregulation.

Possible candidate biomarkers include elevated ketone body levels (β HB, acetoacetate), acylcarnitines indicating incomplete fatty acid oxidation, and immune-metabolic proteins (complement C3, C4, lipoproteins, cytokines) that have shown consistent

dysregulation in DM proteomic screens [16,20]. Integrative metabolomic reviews in cardiometabolic disease highlight ketone bodies, NAD⁺/NADH ratios, ceramides, branched-chain amino acids and metabolite networks linking metabolism to insulin resistance [14].

Key challenges include establishing causal relationships between alterations in ketogenic and immune metabolism and the progression of diabetes mellitus (DM), rather than merely identifying associations; validating candidate biomarkers in large, longitudinal human cohorts; and developing clinically applicable and analytically robust assays. Furthermore, the heterogeneity of DM, including differences between type 1 and type 2 diabetes, diverse dietary and metabolic states, and inter-individual variability in immune responses, complicates the generalisability of potential biomarkers. Future studies should integrate multi-omics approaches, including metabolomics, proteomics, transcriptomics, and immunophenotyping, to identify robust biomarker panels that comprehensively capture the ketogenic–immune metabolic axis.

Despite encouraging evidence linking ketogenic and immune metabolism to diabetes mellitus, several important research gaps remain that currently limit clinical translation. Most studies conducted to date are cross-sectional, providing only a snapshot of metabolic–immune interactions at a single time point. There is a clear lack of longitudinal human studies that monitor ketogenic and immune biomarkers over extended periods from pre-diabetes through disease onset and progression. Such prospective investigations are essential to determine whether specific biomarkers, such as β -hydroxybutyrate (β HB), acylcarnitines, or immune metabolic enzymes, can serve as early predictors rather than mere correlates of disease.

Another critical gap lies in the standardisation of biomarker measurement and interpretation. Ketone body concentrations fluctuate widely depending on diet, fasting duration, circadian rhythm, and individual metabolic flexibility. Currently, there are no universally accepted protocols for blood or urine sampling, nor are there validated clinical cut-offs to define “ketogenic states” in the context of diabetes. Likewise, many immune-metabolic biomarkers—such as BDH1 expression in T cells or GAPDH malonylation in macrophages—are typically measured under controlled laboratory conditions or in animal models rather than human clinical samples. Without harmonised methods and reproducible assays, it remains difficult to compare findings across studies or translate them into clinical diagnostics. A further conceptual challenge is distinguishing causality from association. Existing research largely demonstrates correlations between ketone metabolism, immune activation, and diabetes outcomes, but causal mechanisms remain uncertain. Whether ketone body signalling actively drives immune dysregulation leading to insulin resistance or whether altered immunity secondarily perturbs ketone pathways is yet to be clarified. Mechanistic human studies, especially those employing stable isotope tracers or cell-specific metabolic flux analysis, are needed to unravel these causal relationships. In addition, the heterogeneity of diabetes phenotypes complicates biomarker

discovery. Although most investigations focus separately on Type 1 (autoimmune) and Type 2 (metabolic) diabetes, many patients exhibit overlapping characteristics, such as latent autoimmune diabetes in adults (LADA) or ketosis-prone Type 2 diabetes. These mixed forms may display distinct immune–ketogenic biomarker patterns, yet few studies have addressed this complexity. Stratified analyses across diabetes subtypes, age groups, and ethnic populations will be crucial for developing robust and generalisable biomarker panels. Another major limitation is the limited integration of multi-omics approaches. The dynamic interplay between ketogenic and immune metabolism is inherently multi-layered, involving metabolites (ketone bodies, acylcarnitines), proteins (complement factors, cytokines), and gene-expression networks (BDH1, CPT1A, NLRP3). However, most studies examine these layers in isolation. Comprehensive multi-omics studies that integrate metabolomics, proteomics, and transcriptomics within the same cohort could yield powerful composite biomarkers and clarify functional links between metabolic and immune pathways in diabetes. Translational progress is also hindered by the absence of clinically validated assays. Many candidate biomarkers identified in research, such as malonylated GAPDH or immune-cell BDH1 expression, lack scalable, cost-effective testing platforms suitable for hospital laboratories. Developing robust, reproducible, and affordable diagnostic assays with established reference ranges is essential for moving this field from experimental observation to clinical utility.

Furthermore, few interventional studies have examined how therapies that modify metabolism, such as ketogenic diets, exogenous ketone supplements, or immune-modulating drugs, affect these biomarkers in diabetic individuals. Measuring both metabolic and immune endpoints in the same trial would offer critical insights into mechanistic pathways and therapeutic efficacy. Similarly, the influence of co-morbidities and medications such as metformin, SGLT2 inhibitors, insulin therapy, obesity, or cardiovascular disease on ketogenic-immune biomarker levels remains poorly characterised. Understanding these confounding factors is vital for accurate biomarker interpretation in real-world patient populations. The interface between ketogenic and immune metabolism represents an emerging area for biomarker discovery in diabetes mellitus. Integrative measurement of ketone bodies, their metabolic intermediates, immune-cell enzymes, and inflammatory mediators could yield sensitive, systems-level markers of metabolic–immune dysregulation that complement conventional glycaemic indices such as fasting glucose or HbA_{1c}. However, to translate these insights into clinical application, future research must prioritise longitudinal cohort studies, standardised biomarker protocols, multi-omics integration, and interventional trials with clearly defined biomarker outcomes. Equally important is the development of clinically validated assays and consideration of disease heterogeneity and treatment effects. Addressing these gaps will be fundamental to evaluating the potential of ketogenic–immune metabolic biomarkers for early detection, patient stratification, and personalised therapeutic monitoring in diabetes care.

LIPID PROFILE AND DIABETES

In multivariable logistic regression, a set of 38 lipids differed significantly between people with type 2 diabetes (T2DM) and controls in both the discovery and validation cohorts. These results remained significant after adjusting for potential confounders including age, sex, BMI, fasting plasma glucose (FPG), smoking and drinking status, education, physical activity, family history of diabetes, and systolic blood pressure (SBP), with false discovery rate (FDR) and *P*-values both below 0.05. Notably, this lipid panel contained 34 triacylglycerols (TAGs) covering a broad spectrum of total carbon numbers (C44–C58) and degrees of unsaturation (number of double bonds, $n[C=C]=0-8$). Across these ranges, the TAGs were consistently linked with higher risk of developing T2DM. Among the other lipid classes, short-chain cholesteryl ester (CE14:0), di-unsaturated phosphatidylcholines (PC34:3), and lyso-phosphatidylinositol (LPI16:1) were also associated with increased diabetes risk. In contrast, polyunsaturated plasmalogen phosphatidylethanolamine (for example, PE38:4p with 18:0p/20:4) showed a protective association, being negatively related to incident diabetes.

The study further explored whether diabetes risk depended on specific structural features of lipids—specifically carbon-chain length and double-bond content—using lipid patterns across different lipid classes. Overall, statistically significant effects of carbon number and unsaturation were observed only for TAGs. Because the discovery cohort provided the most complete coverage of the serum lipidome across both carbon numbers and double bonds, the structural analysis focused on that cohort [21].

LIPID ACCUMULATION-INDUCED ADIPOSE TISSUE IMMUNE DYSREGULATION

Saturated free fatty acids (FFAs) act as potent signalling molecules that activate the inflammasome, thereby promoting the maturation and secretion of the pro-inflammatory cytokines interleukin (IL)-1 β and IL-18. These cytokines are released by immune cells infiltrating adipose tissue in individuals with obesity, thereby amplifying both local and systemic inflammation. As lipid overload persists, adipose tissue progressively expands, immune cell infiltration increases, and chronic low-grade inflammation becomes established, characterised by dysregulated immune responses involving macrophages, T cells, B cells, and other immune cell subsets [22].

ADIPOKINES AND LIPID-RELATED MARKERS

Lipid homeostasis requires coordinated signalling among the liver, pancreas, and adipose tissue, with adipose tissue-derived hormones now recognised as key regulators of metabolic homeostasis. Leptin, the circulating concentration of which correlates with adipose mass and is higher in women than in men at an equivalent body mass index (BMI), regulates appetite, energy expenditure, and lipid and glucose metabolism. In contrast, adiponectin exerts insulin-sensitising, anti-inflammatory, and anti-atherogenic effects, and its circulating levels decline with increasing adiposity. Consequently, the leptin-to-

adiponectin ratio has emerged as a biomarker of cardiometabolic risk and a marker of atherogenicity in type 2 diabetes mellitus (T2DM). Adipose tissue expansion promotes chronic low-grade inflammation and alters the composition of bioactive lipids, including C16:0 ceramide, which has been implicated in insulin resistance and β -cell dysfunction. Furthermore, saturated fatty acids can induce endoplasmic reticulum stress independently of classical inflammatory pathways. Elevated circulating branched-chain amino acids (BCAAs) in obesity and T2DM may further exacerbate insulin resistance through activation of the mechanistic target of rapamycin complex 1 (mTORC1) and suppression of autophagy. Emerging metabolic regulators, including growth differentiation factor 15 (GDF15) and fibroblast growth factor 21 (FGF21), integrate nutritional stress, adipose tissue browning, and lipid metabolism; however, their biological roles and clinical utility as biomarkers of β -cell stress, dysfunction, or recovery in humans remain to be fully established [23].

LIPID METABOLISM ABNORMALITIES IN DIABETIC KIDNEY DISEASE (DKD)

In healthy kidneys, lipids make up about 3% of the tissue's wet weight. Most of these lipids are phospholipids, which are important building blocks of cell membranes, while smaller portions consist of triglycerides and free fatty acids. Growing evidence shows that abnormal lipid levels in the blood and excessive fat buildup in kidney tissue are closely linked to kidney disease, especially diabetic kidney disease (DKD). Importantly, kidney damage caused by lipid overload depends not only on how much fat accumulates, but also on the specific type of lipid involved.

A Mendelian randomization study found that triglycerides increase the risk of DKD and a higher urinary albumin-to-creatinine ratio, while HDL-C appears to have a protective effect against both. The same study suggested that apolipoprotein A1 may help protect against DKD, whereas apolipoprotein B may increase the risk of albuminuria.

It is now increasingly clear that changes in fatty acid and cholesterol metabolism play a major role in renal lipid buildup, inflammation, oxidative stress, and fibrosis. In DKD, several lipid types—including cholesterol, phospholipids, triglycerides, fatty acids, and sphingolipids—become dysregulated and accumulate abnormally in the kidney, contributing directly to disease progression. **Figure 2.** Abnormal lipid metabolism and associated diseases. High blood glucose makes this process worse by driving a harmful cycle known as glucolipotoxicity. Increased glucose inside cells activates ChREBP and increases SREBP-1c expression, which together stimulate new lipid production and further fat accumulation in the kidney. At the same time, hyperglycaemia increases oxidative stress and advanced glycation end products, both of which worsen lipid peroxidation and intensify cellular injury [24].

CONCLUSION

This review underscores that the interface between ketogenic & immune metabolism represents a promising frontier for bio-

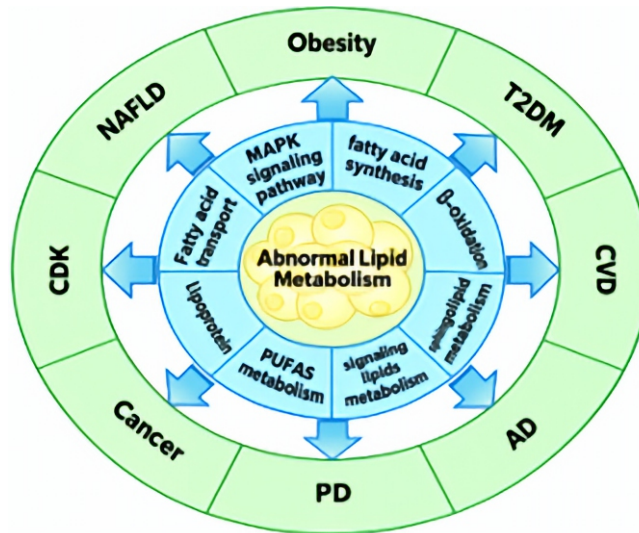


Figure 2. Schematic representation of abnormal lipid metabolism and its association with metabolic pathways and diseases.

marker discovery in diabetes mellitus (DM). Ketone bodies and related metabolites, together with immune cell metabolic reprogramming and inflammatory mediators, reflect systems-level metabolic dysregulation that extends beyond conventional measures of glycaemic control, such as blood glucose and glycated haemoglobin (HbA_{1c}). Accumulating evidence indicates that ketone bodies, particularly β -hydroxybutyrate, modulate immune function, oxidative stress, and inflammatory signalling, whereas lipid accumulation, adipokine imbalance, and chronic low-grade inflammation contribute to insulin resistance, β -cell dysfunction, and diabetic kidney disease. However, translating these insights into clinical practice requires addressing several key challenges, including conducting large, longitudinal, multi-ethnic cohort studies; establishing standardised protocols for sample collection, processing, and metabolomic analysis; distinguishing causal mechanisms from associative relationships through mechanistic investigations and stable isotope-tracing studies; accounting for the heterogeneity of diabetes subtypes, disease stage, and medication use; integrating multi-omics approaches, including metabolomics, proteomics, transcriptomics, and immunophenotyping; and developing robust, cost-effective, and clinically validated diagnostic assays. Addressing these challenges will facilitate the development of composite immunometabolic biomarker panels that integrate ketogenic and immune metabolic signatures, thereby improving the early detection of diabetes, patient stratification, personalised therapeutic monitoring, and disease prognosis beyond the capabilities of conventional glycaemic markers alone.

LIMITATIONS & FUTURE PERSPECTIVES

The study's limitations include a single-centre setting, a relatively small sample size, and a short study duration, which may limit the broader applicability of the results. Future studies should incorporate multicentre designs with larger populations to enhance validity, assess long-term outcomes, and investigate advanced diagnostic & management approaches. Such efforts will improve overall patient care & help minimize complications.

CLINICAL SIGNIFICANCE

The clinical significance of this study lies in its potential to bridge the gap between research findings and practical health-care, diagnosis, and treatment outcomes. By highlighting real-care applications. It emphasizes the importance of translating scientific observations into meaningful improvements in patient world relevance, the study contributes to evidence based medical practice and supports informed clinical decision making. Ultimately, the findings aim to enhance patient quality of life, optimize therapeutic strategies, and promote better disease management in clinical settings.

ABBREVIATIONS

DM: Diabetes mellitus

T1DM: Type 1 diabetes mellitus

T2DM: Type 2 diabetes mellitus

BHB: β -Hydroxybutyrate

NAD⁺: Nicotinamide adenine dinucleotide

BCAA: Branched-chain amino acids

HDAC: Histone deacetylase

AUTHOR INFORMATION

Dr. Jyoti Thakre: Research Scholar

Dr. Durgesh Agase: Assistant Professor,

<https://orcid.org/0000-0002-5874-3232>

Dr. Vaishali Thakur: Research Scholar

Dr. Karan Singh Saini: Assistant Professor

AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation. They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to the current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work. Additionally, all authors meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) guidelines.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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All necessary consent & approval was obtained by authors.

CONSENT FOR PUBLICATION

All necessary consent for publication was obtained by authors.

DATA AVAILABILITY

All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a reasonable request.

USE OF ARTIFICIAL INTELLIGENCE (AI) & LARGE LANGUAGE MODEL (LLM)

The authors confirm that no AI & LLM tools were used in the writing or editing of the manuscript, and no images were altered or manipulated using AI & LLM.

AUTHOR'S NOTE

This article serves as an important educational tool for the scientific community, offering insights that may inspire future research directions. However, they should not be relied upon independently when making treatment decisions or developing public health policies.

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MANAGING & PUBLISHING EDITOR

Dr. Pooja Gaur^{1,2}

Ph.D. & National Post-Doctoral Fellow in Medicinal Chemistry

¹CSIR-Central Institute of Medicinal & Aromatic Plants, Lucknow, India

²CSIR-National Botanical Research Institute, Lucknow, India

HANDLING EDITOR

Dr. Dinesh Kumar Verma

Research Assistant Professor, School of Allied Health Sciences, Boise State University, Boise, Indiana, USA

e-mail: dineshkumarverma@boisestate.edu

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