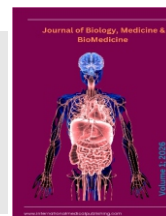




JBMB

Journal of Biology, Medicine & Biomedicine

www.internationalmedicalpublishing.com



Review

Section: Zoology

A Review on Metabolic Dysregulation & Cutaneous Pigmentation: Elucidating the Role of Diabetes Mellitus in Melanogenic Pathways

Vaishali Thakur¹, Durgesh Agase^{1*}, Harsh Tiwari³, Karan Singh Saini² & Jyoti Thakre¹

¹Department of Zoology, Jata Shankar Trivedi Post Graduate College, Balaghat, Madhya Pradesh, India

²Department of Zoology, PMCOE Government Post Graduate College, Sheopur, Madhya Pradesh, India

³Department of Zoology, Biospark Research Institute & Laboratories Private Limited Balaghat, Madhya Pradesh, India

HIGHLIGHTS

- Diabetes alters skin physiology
- Diabetes affects melanin metabolism
- Reduced melanin in type 1 diabetes
- Metformin inhibits melanin synthesis
- Voglibose shows therapeutic potential

Key Words:

Diabetes mellitus
Voglibose
Metformin
Pigmentation disorder
Melanin synthesis

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

Article History: Received 06 August 2026; Received in Revised form 23 September 2026; Accepted 30 September 2026

How To Cite: Vaishali Thakur, Durgesh Agase, Harsh Tiwari, Karan Singh Saini & Jyoti Thakre. A Review on Metabolic Dysregulation & Cutaneous Pigmentation: Elucidating the Role of Diabetes Mellitus in Melanogenic Pathways *JBMB: Journal of Biology, Medicine & Biomedicine*. 2026;1(1):1-8. DOI: <https://doi.org/10.71393/2ehfxb88>

This publication is licensed under CC-BY 4.0. Copyright © 2026 The Authors. Published by International Medical Publishing Group.

INTRODUCTION

Melanogenesis, the process of melanin production, is a complex biological process primarily regulated by specialized dendritic cells known as melanocytes. Melanocytes synthesize melanin from tyrosine and transfer it to keratinocytes within melanosomes [33]. The process of synthesizing melanin from tyrosine occurs through a series of enzymatic reactions culminating in the production of two distinct types of melanin, eumelanin and pheomelanin, through the Raper-Mason pathway [19]. The synthesis of these two forms of melanin occurs within melanosomes through a cascade of enzymatic reactions catalyzed by melanogenic enzymes, whose expression is primarily regulated by the microphthalmia-associated transcription factor (MITF) [7]. The relative proportion of eumelanin, which imparts brown-black pigmentation, and pheomelanin, which imparts yellow to reddish-brown pigmentation, determines an individual's overall pigmentation phenotype [13]. The genetically programmed level of melanin responsible for an individual's baseline skin color is referred to as constitutive pigmentation and can be modified by numerous intrinsic and extrinsic factors [37].

Diabetes mellitus (DM), a prevalent metabolic disorder, is associated with numerous systemic complications, including disturbances in skin homeostasis and alterations in cutaneous pigmentation [34]. Diabetes mellitus is characterized by chronic hyperglycemia resulting from insufficient insulin secretion, impaired insulin action, or both. Its global prevalence continues to increase, largely due to changes in diet, sedentary lifestyles, and rising obesity rates. According to the World Health Organization, diabetes-related deaths increased by approximately 70% between 2000 and 2019, making diabetes one of the

leading causes of mortality worldwide. Clinical diagnosis is based on measurements of glycated hemoglobin (HbA1c), fasting plasma glucose, and oral glucose tolerance tests, which are widely used for the diagnosis and monitoring of diabetes [11].

The goal of this review is to examine the metabolic dysregulation associated with diabetes mellitus and its effect on the complex mechanisms of melanogenesis and cutaneous pigmentation. Understanding the relationship between diabetes-induced metabolic dysregulation and melanogenesis is essential for improving early diagnosis, preventing pigmentary complications, and developing novel therapeutic strategies [32]. In addition, this review examines the underlying cellular mechanisms, signaling pathways, and possible therapeutic targets involved in diabetes-related pigmentary alterations. Particular emphasis is placed on the effects of glycemic variability, insulin resistance, and oxidative stress on melanocyte proliferation, differentiation, and the enzymatic pathways regulating melanin synthesis. Metabolic Dysregulation and Cutaneous Pigmentation (Figure 1).

Pathophysiology of Diabetes Mellitus

In individuals with diabetes mellitus, advanced glycation end products (AGEs) accumulate in various tissues and significantly alter the biological properties of the skin. Diabetic skin exhibits unique biophysical properties, including reduced elasticity, lower water content in the stratum corneum, and increased incidence of pruritus and sweating irregularities [23]. Diabetes mellitus, characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both, exerts profound effects on multiple physiological systems, including the

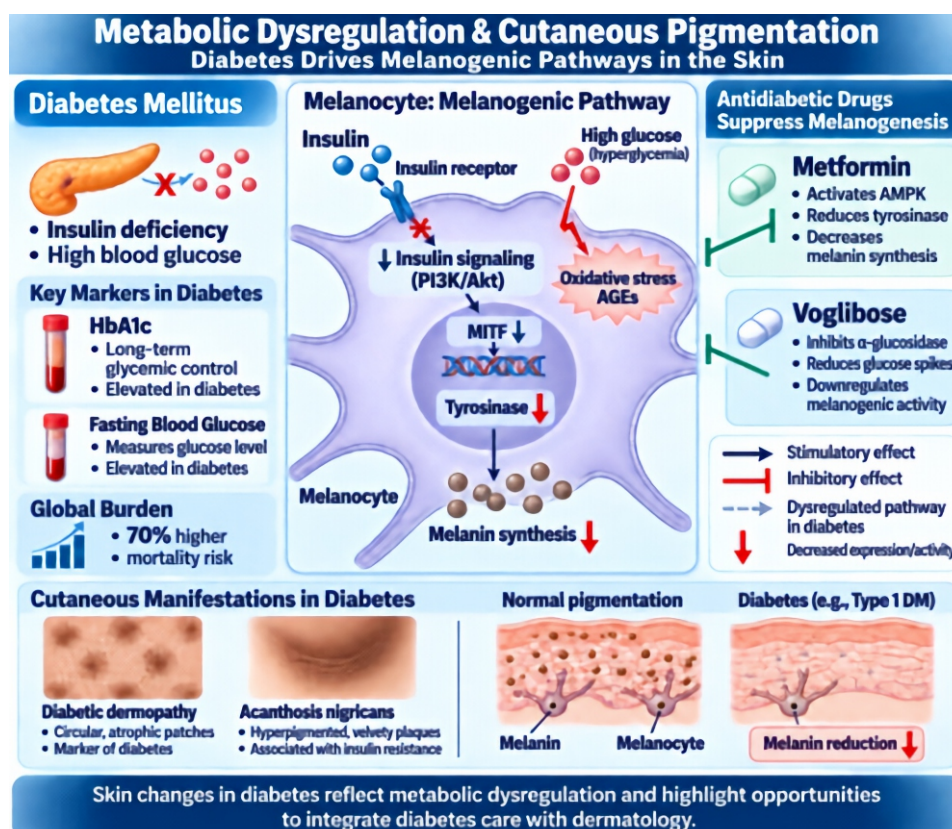


Figure 1: Metabolic Dysregulation & Cutaneous Pigmentation

integumentary system [16]. These dermatological manifestations range from mild cosmetic alterations to severe complications and may serve as clinical indicators of metabolic status and glycemic control [18]. Chronic hyperglycemia and hyperinsulinemia are associated with a variety of cutaneous manifestations, including acanthosis nigricans, diabetic dermopathy, and ichthyosiform skin changes [35]. Beyond these dermatological manifestations, diabetes mellitus is increasingly recognized for its effects on melanogenic pathways, resulting in alterations in cutaneous pigmentation [29]. These pigmentary changes encompass both hyperpigmentation, exemplified by conditions such as melasma, and hypopigmentation, such as vitiligo, underscoring the interplay between metabolic dysregulation and melanocyte function [15].

Skin Biology and Melanogenesis

The basal layer, located between the epidermis and dermis, contains melanocytes. Melanocytes synthesize melanin to protect the skin against environmental insults, particularly ultraviolet (UV) radiation [40].

Molecular link between Diabetes and Melanogenesis

In dermatology and cosmetic science, post-inflammatory hyperpigmentation (PIH) and post-inflammatory hypopigmentation (PIHp) are common clinical conditions. Prevention and treatment remain challenging because the precise mechanisms underlying their development are not yet fully understood. α -Melanocyte-stimulating hormone (α -MSH), stem cell factor (SCF), and other regulatory molecules promote the expression of melanogenesis-related genes through activation of multiple signaling pathways. Recent studies have demonstrated that numerous inflammatory mediators also play important roles in regulating melanogenesis in melanocytes. Previous studies have shown that interleukin (IL)-1, IL-4, IL-6, IL-17, and tumor necrosis factor (TNF)- α inhibit melanogenesis, whereas IL-18, IL-33, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)- γ , and prostaglandin E2 (PGE2) promote melanogenesis. These inflammatory mediators exert their effects by binding to their respective receptors and activating or inhibiting melanogenesis-related signaling pathways, including the protein kinase A (PKA) and mitogen-activated protein kinase (MAPK) pathways. This suggests that therapeutic approaches targeting inflammatory pathways may provide new strategies for the management of pigmented dermatoses [8].

Cutaneous manifestations of diabetes

1. Diabetic Dermopathy

Diabetic dermopathy (DD) was first described by Hans Melin in 1964, and the term *diabetic dermopathy* was subsequently introduced by Binkley in 1965 [21,2]. Diabetic dermopathy is also referred to as "shin spots," "pigmented pretibial patches," "diabetic dermangiopathy," and "spotted leg syndrome." The reported prevalence of diabetic dermopathy ranges from 0.2% to 55% among individuals with diabetes [2,26].

An Indian study involving 500 individuals with diabetes reported a low prevalence of diabetic dermopathy, whereas a study conducted in the western Himalayan region reported a prevalence of 36%, highlighting regional variability [2,26]. Melin described DD as small, well-circumscribed, brownish, atrophic cutaneous lesions that typically occur on the pretibial surfaces of the lower extremities [21]. These lesions are generally asymptomatic, non-contagious, and may appear as solitary lesions or clusters, frequently displaying asymmetry and bilateral distribution. Although initially considered strongly associated with diabetes mellitus, similar lesions have also been reported in individuals without diabetes [4]. In elderly patients with a long history of diabetes, diabetic dermopathy is frequently associated with microvascular disease [31]. The preference for type 1 versus type 2 diabetes remains unclear [24], and no significant difference in prevalence between males and females has been observed [25].

2. Acanthosis Nigricans

Acanthosis nigricans (AN) is a characteristic dermatological manifestation associated with diabetes mellitus and insulin resistance. It is more prevalent in individuals with type 2 diabetes mellitus and occurs more frequently in populations with darker skin pigmentation [6]. AN is also associated with a range of endocrinopathies characterized by insulin resistance, including acromegaly, Cushing syndrome, obesity, polycystic ovary syndrome, and thyroid dysfunction [6,3,9].

Acanthosis nigricans is a complex and multifactorial condition associated with diabetes and insulin resistance. Under hyperinsulinemic conditions, elevated circulating insulin levels can aberrantly activate insulin-like growth factor-1 receptors (IGF-1R) expressed on keratinocytes and dermal fibroblasts. This receptor activation initiates downstream mitogenic signaling pathways, promoting cellular proliferation, epidermal hyperplasia, and the characteristic epidermal and dermal alterations observed in AN [3,14].

Hyperinsulinemia also indirectly enhances insulin-like growth factor-1 (IGF-1) activity by suppressing the hepatic synthesis of insulin-like growth factor-binding proteins (IGFBP-1 and IGFBP-2). Reduced concentrations of IGFBP-1 and IGFBP-2 increase circulating free IGF-1 levels, thereby enhancing IGF-1R-mediated signaling in keratinocytes and dermal fibroblasts [14]. At supraphysiological concentrations, insulin can directly activate IGF-1R because of structural homology between insulin and IGF-1. Simultaneously, suppression of IGFBP-1 and IGFBP-2 increases the availability of free IGF-1, further amplifying IGF-1R signaling. These mechanisms promote keratinocyte and fibroblast proliferation, contributing to the velvety hyperpigmented plaques characteristic of AN [14,37].

3. Other Manifestations

Skin tags, or acrochordons, are another common cutaneous manifestation associated with diabetes and insulin resistance. These small, flesh-colored papules occur more frequently in

individuals with diabetes, particularly those with obesity and insulin resistance [6].

Pigmentary alterations in diabetes

1. Hypopigmentation (Type 1DM)

Type 1 diabetes mellitus is characterized by autoimmune destruction of pancreatic β -cells. Reduced melanin content and alterations in melanocyte function have been reported in individuals with type 1 diabetes. Lower melanin content in the skin has also been associated with diabetic microangiopathy [20]. Cutaneous Manifestations Associated with Diabetes (Figure 2).

2. Hyperpigmentation

Diabetes mellitus is associated with several pigmentary and cutaneous disorders, including various forms of hyperpigmentation. Acanthosis nigricans is one of the most common pigmentary manifestations associated with diabetes mellitus and insulin resistance. Hyperinsulinemia stimulates IGF-1R signaling, promoting keratinocyte proliferation and contributing to characteristic hyperpigmentation [3,14]. Diabetic dermopathy represents another common cutaneous manifestation and is characterized by localized hyperpigmented lesions. It typically presents as well-defined, brown or reddish-brown, atrophic macules or patches on the pretibial region [21,24,25]. Skin tags (acrochordons) are another common cutaneous manifestation associated with diabetes mellitus and insulin resistance [6].

3. Cutaneous Nevi

Melanocytic nevi may function as risk indicators and potential precursors for melanoma [22,38]. People with light skin, sun sensitivity, and pigmentation are more likely to have nevi. Their formation is influenced by factors such as age, sex, and sun exposure [27]. Recent research suggests that the number of cutaneous nevi may be associated with hormonal and metabolic alterations. The relationship between nevus count and metabolic syndrome or type 2 diabetes requires further investigation [5].

Therapeutic Implications and Drug Repurposing

1. Voglibose

Drug repositioning, also known as drug repurposing, is an effective strategy for identifying new therapeutic applications for approved or existing drugs. This approach offers potential advantages by reducing the time, cost, and risk associated with conventional drug development. Voglibose is an α -glucosidase inhibitor widely used to control postprandial hyperglycemia in individuals with diabetes mellitus.

Recent evidence suggests that voglibose may also possess anti-melanogenic properties. Voglibose significantly inhibited melanin synthesis and tyrosinase activity in B16F10 melanoma cells in a dose-dependent manner. Western blot analysis further demonstrated downregulation of microphthalmia-associated transcription factor (MITF), tyrosinase-related protein-1 (TRP-1), and tyrosinase-related protein-2 (TRP-2), indicating suppression of melanogenesis [12].

Skin Manifestations Associated with Diabetes

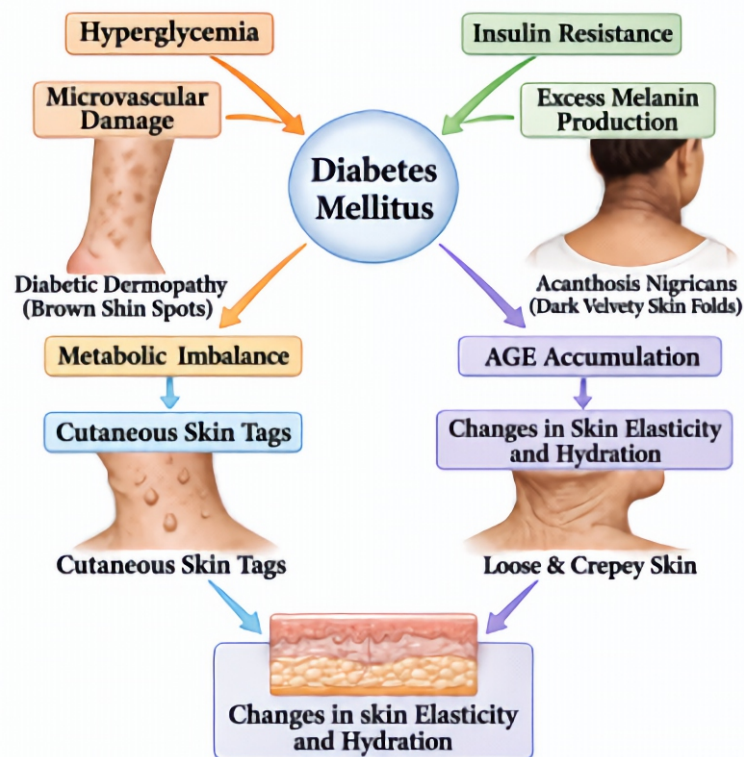


Figure 2. Skin Manifestations Associated with Diabetes.

2. Metformin

Metformin is an oral antidiabetic drug belonging to the biguanide class and is one of the most widely used antidiabetic agents worldwide. Metformin influences AMP-activated protein kinase (AMPK) signaling and mammalian target of rapamycin (mTOR)-related pathways, thereby affecting cellular metabolism, protein synthesis, and cell growth [1,28]. Several studies have demonstrated inhibitory effects of metformin on melanoma cell proliferation and invasion [36,39].

Metformin has also been investigated for its effects on melanogenesis. Evidence suggests that metformin can reduce intracellular cyclic adenosine monophosphate (cAMP), an important signaling molecule involved in melanogenesis, thereby potentially reducing melanin production [17]. Effective glycemic control with insulin or oral hypoglycemic agents can reduce the metabolic stress contributing to various cutaneous manifestations [30]. Lifestyle measures, including a balanced diet and appropriate glycemic management, may also support metabolic control and indirectly improve diabetes-associated skin changes [10]. Overall, optimization of glycemic control remains an important component of managing diabetes-associated dermatological manifestations [9]. Drug Repurposing Strategies for Hyperpigmentation (**Figure 3**). Controlling blood sugar with the right medications, such as insulin or oral hypoglycemic agents, can help lower the metabolic stress that causes many skin changes [30]. Eating a balanced diet that includes foods with a low glycemic index, fiber, lean protein, and only a small amount of saturated fats can help keep blood sugar levels stable and lower the need for insulin [10]. These treatments make the body more sensitive to insulin, lower oxidative stress, and improve

blood vessel health. These effects may help with skin problems in a roundabout way [9]. The most effective strategy is to enhance underlying glycemic control [9]. As insulin resistance goes down and stress on the blood vessels and metabolism goes down over time, many skin changes may either go away or look better.

CONCLUSION

Diabetes mellitus is increasingly recognized as a systemic metabolic disorder with significant effects on melanogenesis and cutaneous pigmentation. This review highlights the intricate relationship between metabolic dysregulation, oxidative stress, chronic inflammation, and melanocyte function, demonstrating how hyperglycemia and insulin resistance influence key melanogenic signaling pathways, including AGEs, AMPK, IGF-1R, MAPK, and PKA. These molecular interactions contribute to characteristic pigmentary disorders such as acanthosis nigricans, diabetic dermopathy, and hypopigmentation, which may provide clinical indicators of underlying metabolic dysfunction. The growing understanding of the crosstalk between metabolic and pigmentary pathways also identifies potential therapeutic opportunities, including repurposing antidiabetic agents with anti-melanogenic properties and developing targeted interventions addressing both metabolic abnormalities and cutaneous manifestations. Future studies integrating molecular, clinical, and translational approaches are needed to validate emerging biomarkers, clarify mechanisms linking diabetes to melanogenesis, and develop personalized strategies for prevention and management of diabetes-associated pigmentary disorders. A deeper understanding of these interconnected pathways may improve dermatological care and support earlier recognition and comprehensive management of metabolic disease.

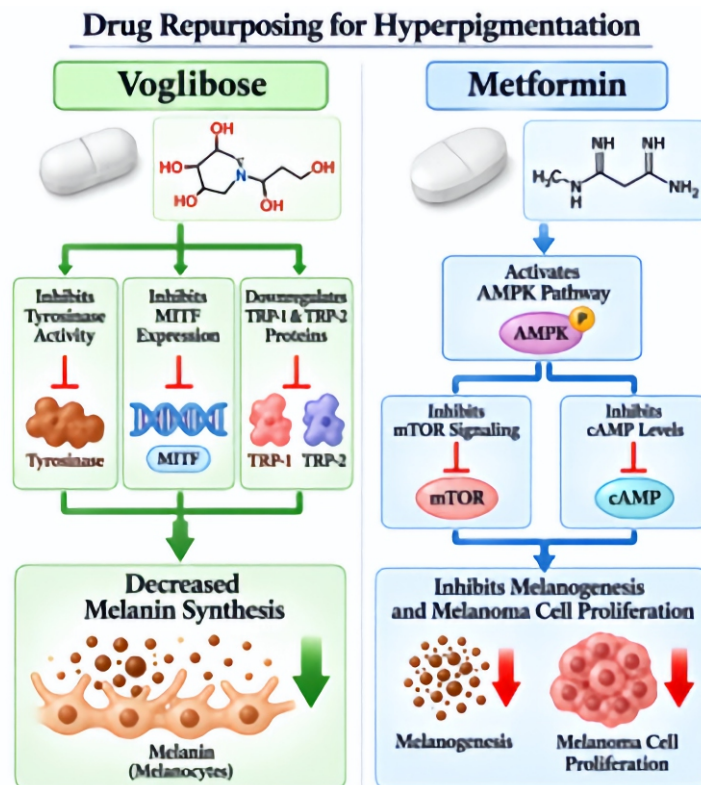


Figure 3. Drug Repurposing for Hyperpigmentation

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

HbA1c: Glycated Hemoglobin

FBG: Fasting Blood Glucose

T1DM: Type 1 Diabetes Mellitus

AUTHOR INFORMATION

Dr. Vaishali Thakur: Research Scholar

Dr. Durgesh Agase: Assistant Professor, <https://orcid.org/0000-0002-5874-3232>

Dr. Harsh Tiwari:

Dr. Karan Singh Saini: Assistant Professor

Dr. Jyoti Thakre: Research Scholar

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.

ACKNOWLEDGEMENT

The authors sincerely acknowledge the seniors of the PMCOE Government Post Graduate College, Sheopur and JataShankar Trivedi Post Graduate College, Balaghat, Madhya Pradesh, India. We are grateful to our college for providing the necessary resources to carry out this work. We also extend our heartfelt thanks to our colleagues and technical staff for their valuable assistance during the study.

CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

FUNDING

None

ETHICAL APPROVAL & CONSENT TO PARTICIPATE

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.

PUBLISHER'S NOTE

All statements made in this article are the sole responsibility of the authors and do not necessarily reflect the views of the publisher, editors, or reviewers. The journal maintains a neutral stance regarding jurisdictional claims in institutional affiliations presented in published work.

ARCHIVING INFORMATION

-  zenodo
- Self-archiving on Google and Amazon Web Services (AWS) cloud servers, as well as on three dedicated in-house servers.
- PKP Preservation Network

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

REFERENCE

1. Ben Sahra I, Le Marchand-Brustel Y, Tanti JF, et al. Metformin in cancer therapy: a new perspective for an old antidiabetic drug? Mol Cancer Ther. 2010;9:1092-1099. <https://doi.org/10.1158/1535-7163.mct-09-1186>

2. Binkley GW. Dermopathy in the diabetic syndrome. Arch Dermatol. 1965;92(6):625-634. <https://doi.org/10.1001/archderm.1965.01600180017003>
3. Brady MF, et al. Acanthosis nigricans. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. <https://www.ncbi.nlm.nih.gov/books/NBK431057>
4. Danowski TS, Sabeh G, Sarver ME, et al. Shin spots and diabetes mellitus. Am J Med Sci. 1966;251(5):570-575. <https://doi.org/10.1097/00000441-196605000-00011>
5. Diabetic Medicine. Diabet Med. 2016;34(7):925-933. <https://doi.org/10.1111/dme.13297>.
6. Edwards E, Yosipovitch G. Skin manifestations of diabetes mellitus. In: Endotext. South Dartmouth (MA): MDText.com, Inc.; 2025:1-80. <https://www.ncbi.nlm.nih.gov/books/NBK481900/>
7. Fatoki TH, Ibraheem O, Adeseko CJ, Afolabi BL, Momodu DU, Sanni DM, et al. Melanogenesis, its regulatory process, and insights on biomedical, biotechnological, and pharmacological potentials of melanin as antiviral biochemical. Biointerface Res Appl Chem. 2021;11(4):11969-11984. <https://doi.org/10.33263/briac114.1196911984>
8. Fu C, Chen J, Lu J, Yi L, Tong X, Kang L, et al. Roles of inflammation factors in melanogenesis (Review). Mol Med Rep. 2020;21(3):1421-1430.
9. Harris R, Reddy BY. Acanthosis nigricans. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. <https://www.ncbi.nlm.nih.gov/books/NBK431057>
10. Healthline. Skin conditions and type 2 diabetes. 2023. <https://www.healthline.com/health/type-2-diabetes/skin-problems>
11. Hu D, Wu Y, He D, Rong J, Sun M, Yu Z, et al. Salivary biomarkers in diabetes mellitus diagnostics: a bibliometric analysis. Medicine (Baltimore). 2025;104(32):e43760. <https://doi.org/10.1097/md.00000000000043760>
12. Kim HM, Hyun CG. Drug repurposing of voglibose, a diabetes medication for skin health. Pharmaceuticals (Basel). 2025;18(2):1-18. <https://doi.org/10.3390/ph18020224>
13. Kim HR, Lee SH, Noh EM, Oh BJ, Kim SY, Park MH. Anti-melanogenic effect of Moju through inhibition of tyrosinase activity. Mol Cell Toxicol. 2023;20(2):243-250. <https://doi.org/10.1007/s13273-022-00329-8>
14. Edwards E, Yosipovitch G. Skin manifestations of diabetes mellitus. In: Feingold KR, Adler RA, Ahmed SF, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc.; 2025. <https://www.ncbi.nlm.nih.gov/books/NBK481900/>
15. Lause M, Kamboj A, Kumar P. Ophthalmic manifestations of endocrine disorders—endocrinology and the eye. Adv Ophthalmol Vis Syst. 2017;6(4):286–299. <https://doi.org/10.21037/tp.2017.09.13>
16. Legiawati L. The role of oxidative stress, inflammation, and advanced glycation end product in skin manifestations of diabetes mellitus. Curr Drug Targets. 2022;18(3):87–92. <https://doi.org/10.2174/1573399817666210920102318>
17. Lehraiki A, Abbe P, Cerezo M, Rouaud F, Regazzetti C, Chignon-Sicard B, et al. Inhibition of melanogenesis by the antidiabetic metformin. J Invest Dermatol. 2014;2589–2597. <https://doi.org/10.1038/jid.2014.202>
18. Ly L, Vo KL, Cruel AC, Shubrook JH. Dermatological manifestations of diabetes mellitus and its complications. Diabetology. 2025;6(3):1-18. <https://doi.org/10.3390/diabetology6030018>
19. Lorente Prieto E. Cosmetic topical use of vitamin C. In: Ascorbic acid: biochemistry and functions. London: Intech Open; 2023:1–21. <https://doi.org/10.5772/intechopen.109644>
20. Mackiewicz-Wysocka M, Araszkiewicz A, Schlaffke J, Kuczynski S, Micek I, Zozulinska-Ziolkiewicz D. Lower melanin content in the skin of type 1 diabetic patients and the risk of microangiopathy. Exp Clin Endocrinol Diabetes. 2014;122(4):231-235. <https://doi.org/10.1055/s-0034-1367003>
21. Melin H. An atrophic circumscribed skin lesion in the lower extremities of diabetics. Acta Med Scand. 1964;176(Suppl 423):9-75.
22. Montero I, Requena C, Traves V, Garcia-Casado Z, Kumar R, Nagore E. Age-related characteristics of cutaneous melanoma in a Spanish Mediterranean population. Int J Dermatol. 2015;54:778-784. <https://doi.org/10.1111/ijd.12496>
23. Moraes VR, Melo MO, Maia Campos PMBG. Evaluation of morphological and structural skin alterations in diabetic subjects. Life (Basel). 2023;13(2):1-13.
24. Morgan AJ, Schwartz RA. Diabetic dermopathy: a subtle sign with grave implications. J Am Acad Dermatol. 2008;58(3):447-451. <https://doi.org/10.1016/j.jaad.2007.11.013>
25. Naik PP, Farrukh SN. Clinical significance of diabetic dermopathy. Diabetes Metab Syndr Obes. 2020;13:4823-4827. <https://doi.org/10.2147/dms.s286887>
26. Ngo BT, Hayes KD, DiMiao DJ, et al. Manifestations of cutaneous diabetic microangiopathy. Am J Clin Dermatol. 2005;6(4):225-237.
27. Orlow I, Satagopan JM, Berwick M, et al. Genetic factors associated with naevus count and dermoscopic patterns. Br J Dermatol. 2014;172:1081-1089.
28. Pollak M. Metformin and other biguanides in oncology: advancing the research agenda. Cancer Prev Res (Phila). 2010;3:1060-1065. <https://doi.org/10.1158/1940-6207.capr-10-0175>
29. Poonja PP, Kiss F. Pathophysiology of the skin in type 1 and type 2 diabetes and emerging therapeutic opportunities. Int J Diabetes Clin Res. 2024;11:1-9. <https://doi.org/10.23937/2377-3634/1410182>
30. Rudnicka L, Schwartz RA, Borkowski A. Dermatological manifestations of diabetes mellitus. Int J Mol Sci. 2022;23(19):6-11.
31. Shemer A, Begman R, Linn S, Kantor Y, Friedman-Birnbaum R. Diabetic dermopathy and internal complications in diabetes mellitus. Int J Dermatol. 1998;37(2):113-115. <https://doi.org/10.1046/j.1365-4362.1998.00273.x>

32. Sil A, Poddar S, Das A, Ray D. Metabolic syndrome and pigmentation: a review of the connecting link. *Clin Exp Dermatol*. 2025;50(10):1953-1962. <https://doi.org/10.1093/ced/llaf218>
33. Singh NK, Verma AK, Gupta JK. Understanding mechanisms and key factors influencing melanogenesis for the management of melasma: an updated review. *Curr Pharm Biotechnol*. 2025;26(10):1564-1581. <https://doi.org/10.2174/0113892010301957240424110023>
34. Sultan F, Basu R, Murthy D, Kochar M, Attri KS, Aggarwal A, et al. Temporal analysis of melanogenesis identifies fatty acid metabolism as key skin pigment regulator. *PLoS Biol*. 2022;20(5):1-32. <https://doi.org/10.1101/2021.04.06.438588>
35. Svoboda SA, Shields BE. Cutaneous manifestations of nutritional excess: pathophysiologic effects of hyperglycemia and hyperinsulinemia on the skin. *Cutis*. 2021;107(2):74–78. <https://doi.org/10.12788/cutis.0173>
36. Tomic T, Botton T, Cerezo M, et al. Metformin inhibits melanoma development through autophagy and apoptosis mechanisms. *Cell Death Dis*. 2011;2:1-10. <https://doi.org/10.1038/cddis.2011.86>
37. Videira IFS, Moura DFL, Magina S. Mechanisms regulating melanogenesis. *An Bras Dermatol*. 2013;88(1):76-83. <https://doi.org/10.1590/s0365-05962013000100009>
38. Watts CG, Dieng M, Morton RL, Mann GJ, Menzies SW, Cust AE. Clinical practice guidelines for melanoma risk. *Br J Dermatol*. 2015;172:33-47.
39. Woodard J, Plataniias LC. AMP-activated kinase signals in melanoma cell growth. *Biochem Biophys Res Commun*. 2010;398:135-139. <https://doi.org/10.1111/bjd.13403>
40. Yoon JH, Jang WY, Park SH, Kim HG, Shim YY, Reaney MJT, et al. Anti-melanogenesis effects of a cyclic peptide derived from flaxseed. *Int J Mol Sci*. 2023;24(1):1-18. <https://doi.org/10.3390/ijms24010536>

Cite this article: Vaishali Thakur, Durgesh Agase, Harsh Tiwari, Karan Singh Saini & Jyoti Thakre. A Review on Metabolic Dysregulation & Cutaneous Pigmentation: Elucidating the Role of Diabetes Mellitus in Melanogenic Pathways *JBMB: Journal of Biology, Medicine & Biomedicine*. 2026;1(1):1-8.