REVIEW ARTICLE

DNA Damage in Type 2 Diabetes: A South Indian Perspective

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ABSTRACT

Type 2 diabetes is highly prevalent in the South Indian population, presenting significant public health challenges. This study emphasizes the critical role of glycated hemoglobin (HbA1c) in the diagnosis and prognosis of Type 2 diabetes, as it reflects long-term glucose regulation and potential complications. The mechanism involves hemoglobin glycation, leading to oxidative stress and red blood cell dysfunction. Recent studies in the Indian population have revealed a correlation between elevated HbA1c levels and increased DNA Damage. This relationship suggests that high HbA1c may contribute to genomic instability, further complicating diabetes management. Understanding the interplay between DNA damage and elevated HbA1c is essential for developing improved diagnostic and therapeutic strategies for Type 2 diabetes. By elucidating this correlation, we aim to enhance patient outcomes and address the pressing public health concerns associated with diabetes in South India. Future research should focus on targeted interventions to mitigate these risks and improve long-term health for affected individuals.

Keywords: DNA damage, glycated haemoglobin (HbA1c), oxidative DNA Damage, South Indian population, type 2 diabetes.
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INTRODUCTION

Hemoglobin A1c (HbA1c) is a biomarker which is critical for diagnosing type 2 diabetes (T2D) and monitoring glycemic control. Its reliability, however, can be influenced by genetic factors, particularly in diverse populations such as those in South India. Studies have shown that HbA1c may reflect different underlying glycemic statuses based on genetic variations prevalent in specific ethnic groups, complicating its role as a universal diagnostic tool[1].

HbA1c formation is a complex biochemical process resulting from non-enzymatic glycation of hemoglobin, primarily due to elevated blood glucose levels. The glycation process begins when glucose reacts with the amino groups of hemoglobin, resulting in the formation of Schiff bases. These then rearrange into more stable Amadori products, which constitute amino acids and hexose sugars, ultimately forming HbA1c over time[2].

In individuals with type 2 diabetes mellitus (T2DM), the persistent state of hyperglycemia initiates and advances non-enzymatic glycation reactions that affect lipids, proteins and nucleic acids. This process contributes to the generation of advanced glycation end products (AGEs), which play a pivotal role in the pathophysiology of diabetic complications by engaging with their principal cellular receptor, RAGE (Receptor for Advanced Glycation End products). The activation of RAGE triggers various signaling pathways, including MAPK/ERK and NF-ºB, which are associated with oxidative stress and inflammation, leading to compromised insulin signaling and metabolic dysregulation[3].

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In South India, the challenges associated with using HbA1c as a diagnostic marker are compounded by the region's unique genetic makeup. South Indians are known to have a higher genetic predisposition to T2D compared to many other ethnic groups. This is also due to their dietary habits and lifestyle changes which may increase the risk of early onset and rapid progression of complications. Studies have shown that South Asians develop diabetes at a younger age and at lower body mass indices (BMI) than Western populations, making the management of complications even more critical[4].

DNA damage is gaining recognition as a significant contributor to the development and progression of type 2 diabetes (T2D). Persistent hyperglycemia in T2D induces the overproduction of reactive oxygen species (ROS), leading to oxidative stress that damages cellular components, including DNA. This damage manifests as strand breaks, base modifications and DNA adduct formation. In individuals with T2D impaired DNA repair mechanisms worsen this damage, contributing to cellular dysfunction and insulin resistance[5,6].

Pancreatic beta cells, which have limited antioxidant defenses, are particularly vulnerable to oxidative stress-induced DNA damage. This damage impairs insulin secretion and promotes beta-cell apoptosis, contributing to disease progression. DNA damage in other tissues, such as endothelial cells, further leads to complications like neuropathy and retinopathy, highlighting a link between genomic instability and metabolic dysfunction in T2D[7].

Furthermore, advanced glycation end products (AGEs) which accumulate in diabetes, contribute to DNA damage by activating the receptor for AGEs (RAGE). This activation promotes inflammation and exacerbates oxidative stress, linking DNA damage to broader metabolic disturbances in T2D[3].

Variants and their effect on HbA1c levels

Variants in hemoglobin A (HbA), particularly structural haemoglobinopathies like HbS, HbC, HbD and HbE, can significantly affect hemoglobin A1c (HbA1c) concentrations, complicating diabetes diagnosis and monitoring. HbA1c reflects the percentage of glycated hemoglobin, typically HbA, and serves as a marker for long-term blood glucose levels. However, individuals with hemoglobin variants or hemoglobinopathies may have altered red blood cell lifespan or glycation rates, which can lead to either falsely elevated or reduced HbA1c values[8].

For example, individuals with the HbS (sickle cell) trait or HbC trait may show lower levels because these variants can reduce the lifespan of red blood cells, decreasing the exposure time for glycation. Similarly, HbE and HbD variants can interfere with the accuracy of HbA1c measurements depending on the assay used[9]. In these cases, alternative measures of glycemic control, such as fructosamine or continuous glucose monitoring, may be more appropriate for assessing blood glucose levels.

The influence of these variants on HbA1c readings underscores the importance of selecting appropriate diagnostic assays and interpreting results carefully, especially in populations with a higher prevalence of hemoglobinopathies[10].

Relationships between HbA1c and DNA damage

Hemoglobin A1c (HbA1c), a key biomarker for long-term glycemic control, is not only influenced by blood glucose levels but also associated with DNA damage, especially in the context of type 2 diabetes (T2D). Chronic hyperglycemia leads to the overproduction of reactive oxygen species (ROS), which induces oxidative stress and contributes to both protein glycation and DNA damage. Elevated HbA1c levels are linked to the generation of advanced glycation end products (AGEs) that exacerbate oxidative stress, further damaging cellular structures, including DNA[11].

This oxidative stress - induced DNA damage manifests as strand breaks, base modifications, and the formation of DNA adducts, which impair cellular function. In diabetic patients, the accumulation of AGEs and their interaction with the receptor for advanced glycation end products (RAGE) promotes inflammatory responses, amplifying the production of ROS. This creates a feedback loop where DNA damage and HbA1c levels are interconnected, contributing to the pathophysiology of diabetes - related complications such as neuropathy and cardiovascular disease[12].

Therefore, elevated HbA1c not only indicates poor glycemic control but also correlates with increased oxidative DNA damage, which may play a role in development of diabetic complications. Addressing both glycemic control and oxidative stress is essential to mitigate

these damaging effects.

Pancreatic beta cells are particularly sensitive to oxidative stress due to their low antioxidant capacity. Chronic hyperglycemia, reflected by elevated HbA1c, increases the oxidative burden on these cells leading to DNA damage, impaired insulin secretion and eventual apoptosis. This contributes to the progression of T2D and its complications T2D[6,7].

Type 2 Diabetes and DNA damage

Type 2 Diabetes (T2D) is associated with a range of complications that rise due to chronic hyperglycemia and the resultant oxidative stress. Long-term elevated blood glucose levels lead to the formation of advanced glycation end products (AGEs) and increased production of reactive oxygen species (ROS), which are central contributors to oxidative stress. The oxidative environment can cause significant damage to cellular components, including lipids, proteins and DNA. The most well-documented form of DNA damage in T2D is the oxidative modification of guanine bases, particularly the formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a biomarker for oxidative stress and DNA damage[13].

Studies have shown that T2D patients exhibit higher levels of 8-OHdG in their tissues and circulating blood, indicating widespread DNA damage. This is particularly concerning in tissues prone to diabetes related complications, such as the kidneys, eyes, nerves and cardiovascular system. The accumulation of DNA damage impairs cellular function, promotes apoptosis and amplifies the progression of diabetic complications like nephropathy, retinopathy, neuropathy and cardiovascular diseases[14]. Additionally, impaired DNA repair mechanisms in T2D further exacerbate the damage, leading to sustained genomic instability[15].

South Indian populations face unique lifestyle challenges, including a rapid shift towards urbanization, sedentary lifestyles and dietary changes that favor high-calorie, processed foods. These factors further contribute to poor glycemic and increased oxidative stress. Moreover, the limited healthcare access in some regions makes early detection and management of T2D and its complications more difficult, increasing the likelihood of complications associated with high HbA1c and DNA damage[16].

Gut Dysbiosis and DNA Damage

Gut dysbiosis, defined as an imbalance in the gut microbiota composition, has been implicated in the pathogenesis of various diseases, including Type 2 Diabetes (T2D), through its role in promoting systemic inflammation and oxidative stress. Dysbiosis can lead to an overgrowth of pathogenic bacteria and a reduction in beneficial microbes, resulting in increased production of reactive oxygen species (ROS) and inflammatory mediators such as cytokines, which are known to induce DNA damage[17,18]. The oxidative stress generated by dysbiotic microbiota contributes to DNA damage through mechanisms such as base oxidation, strand breaks, and telomere shortening[19]. Additionally, dysbiosis can compromise the intestinal barrier, allowing the translocation of endotoxins like lipopolysaccharides (LPS) into the bloodstream, which further exacerbates systemic inflammation and promotes DNA damage[20]. The gut-liver-brain axis, influenced by the microbiome, has been shown to affect DNA repair processes, with dysbiosis impairing the efficacy of DNA repair mechanisms and enhancing genomic instability[21]. Furthermore, emerging evidence suggests that modulating the gut microbiota with prebiotics or probiotics might mitigate oxidative stress and improve DNA repair, offering potential therapeutic strategies for managing T2D-related complications[22]. Thus, understanding the complex interplay between gut dysbiosis and DNA damage may open new avenues for therapeutic interventions aimed at improving metabolic health and reducing genomic instability in individuals with T2D.

Prevalence of Type 2 Diabetes in South India

Type 2 diabetes (T2D) has emerged as a significant public health challenge in South India, where its prevalence has been rising rapidly over the past few decades. The region, home to over 250 million people, is experiencing an epidemic of T2D, driven by both genetic and lifestyle factors. Epidemiological studies have shown that the prevalence of T2D in South India is notably high compared to other parts of the country, with some states, such as Tamil Nadu, Kerala, and Andhra Pradesh, reporting adult prevalence rates ranging from 10-15%[23,24]. This trend is fueled by a complex interplay of factors, including genetic susceptibility, urbanization, and shifts in diet and physical activity. Traditional South Indian diets, once centred on rice and vegetables, have increasingly been replaced by diets rich in refined carbohydrates, fats, and sugar, a change that has contributed significantly to the rising burden of obesity

and insulin resistance[25]. Additionally, the rapid urbanization of the region has led to more sedentary lifestyles, further exacerbating the risk of developing T2D[26].

Genetic predisposition plays a critical role in the high rates of T2D observed in South Indian populations. Studies have identified several genetic factors that contribute to the increased susceptibility to diabetes in this region, including variations in the TCF7L2 gene, which is known to influence insulin secretion and glucose metabolism[26]. Other research has highlighted the role of gene-environment interactions in the development of T2D, particularly in relation to dietary habits, physical activity levels, and obesity. Furthermore, South Indians have been shown to have a unique metabolic phenotype characterized by lower muscle mass and higher visceral fat, which increases the risk of insulin resistance and T2D compared to other populations[28].

Environmental factors also play a significant role in the growing diabetes burden in South India. The rapid industrialization of the region has resulted in increased exposure to environmental pollutants, which may exacerbate oxidative stress and inflammation, both of which are implicated in the pathogenesis of T2D. Moreover, changes in food processing and agricultural practices have led to an increased availability of highly processed foods, which are low in fiber and micronutrients but high in unhealthy fats and sugars. These dietary patterns, coupled with limited access to physical activity opportunities in urban areas, have further contributed to the rising incidence of T2D.

Compounding these issues, South Indians are at a heightened risk for early onset of T2D and are more prone to developing diabetes-related complications, such as diabetic retinopathy, nephropathy, and cardiovascular disease, compared to other populations (unnikirishnan,2007). For instance, studies have demonstrated that the incidence of diabetic retinopathy in South Indian patients is significantly higher than in Western populations, and the onset of nephropathy occurs at a younger age (Pradeepa R, 2021). This makes early detection, prevention, and management of T2D particularly crucial in this region.

Given these complexities, addressing the diabetes epidemic in South India requires a multifaceted approach that takes into account the genetic, environmental, and lifestyle factors unique to the region. Public health initiatives focusing on lifestyle modification, improved access to diabetes care, and targeted genetic screening could play key roles in reducing the burden of T2D in this population.

Conclusion

The growing burden of type 2 diabetes (T2D) in South India is significantly influenced by a combination of environmental, genetic, and lifestyle factors. Rapid industrialization has led to increased exposure to environmental pollutants, exacerbating oxidative stress and inflammation—key contributors to the pathogenesis of T2D. Concurrently, changes in food processing and agricultural practices have resulted in a higher availability of highly processed foods that are low in fiber and micronutrients but high in unhealthy fats and sugars. This shift in dietary patterns, coupled with limited access to physical activity opportunities in urban areas, has further propelled the rising incidence of T2D.

South Indians face a heightened risk for early onset of T2D and are more susceptible to diabetes-related complications, such as diabetic retinopathy, nephropathy, and cardiovascular disease, compared to other populations. Research indicates that the incidence of diabetic retinopathy among South Indian patients is significantly higher than in Western populations, and nephropathy occurs at a younger age. This underscores the urgent need for early detection, prevention, and management of T2D in this region.

Addressing the diabetes epidemic in South India requires a multifaceted approach that considers the unique genetic, environmental, and lifestyle factors at play. Public health initiatives that focus on lifestyle modifications, improved access to diabetes care, and targeted genetic screening could play crucial roles in alleviating the burden of T2D. Elevated hemoglobin A1c (HbA1c) levels among South Indians reflect poor glycemic control, closely linked to increased oxidative stress and resultant DNA damage. Notably, oxidative damage, marked by elevated biomarkers like 8-hydroxy-2'-deoxyguanosine (8-OHdG), accelerates the development of diabetes-related complications.

To effectively mitigate the impact of T2D and reduce oxidative stress and DNA damage, culturally tailored interventions are essential. These should focus on early diagnosis, effective glycemic management, and lifestyle modifications. By addressing the complex interplay of factors contributing to T2D, we can improve health

outcomes for affected individuals in South India and curb the diabetes epidemic in this vulnerable population.

Declarations

Ethical Approval

This work is a review of the current literature and does not present any new studies involving human or animal participants.

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Conflict of Interest

All Authors declare that they have no conflict of interest.

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