10.48047/jocaaa.2024.33.06.86

Lutein in Diabetes and Diabetic Kidney Disease: From Oxidative Stress Modulator to Clinical Biomarker

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder marked by insulin resistance, hyperglycemia, and significant long-term complications, including diabetic kidney disease (DKD). Both conditions represent a growing global health concern, particularly in the elderly, with projections indicating a substantial increase in disease burden in the coming decades. Traditional biomarkers and diagnostic approaches often fall short in predicting early disease onset or progression, necessitating the search for new and effective indicators. Lutein, a naturally occurring oxygenated carotenoid with potent antioxidant and anti-inflammatory properties, has gained attention for its potential role in mitigating oxidative stress and cellular damage—key contributors to T2DM and DKD. While primarily studied for its role in eye health, emerging evidence suggests that serum lutein levels are inversely correlated with markers of glycemic dysregulation and renal impairment. Observational and experimental studies have shown significantly lower lutein levels in individuals with T2DM, with even more pronounced reductions in those with DKD. These findings have sparked interest in lutein not only as a dietary supplement but also as a promising biomarker for disease detection and monitoring. This review provides an overview of the epidemiology, pathophysiology, and complications associated with T2DM and DKD, emphasizing the shared mechanisms of oxidative stress and inflammation. We discuss the biosynthesis, bioavailability, and biological roles of lutein, followed by a synthesis of current literature linking serum lutein to metabolic and renal outcomes. The evidence suggests that lutein could serve as a reliable, non-invasive biomarker for the progression of diabetes-related complications, particularly in elderly populations. Its incorporation into routine screening and therapeutic strategies may offer a dual advantage—early detection and potential antioxidative intervention. Further research is warranted to validate lutein's clinical utility and therapeutic implications in T2DM and DKD management. In conclusion, the integration of lutein assessment in routine diabetes care holds promise for improving clinical outcomes. However, further longitudinal studies and randomized controlled trials are warranted to validate its prognostic and therapeutic relevance in T2DM and DKD.

Keywords: Lutein, Diabetes, Diabetic Kidney Disease

1. INTRODUCTION

Introduction: Chronic Kidney Disease and End-Stage Renal Disease

Type 2 diabetes mellitus (T2DM) is a complex, chronic metabolic disorder characterized by persistent hyperglycemia due to a combination of insulin resistance and β-cell dysfunction [1]. It is the most

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common form of diabetes, accounting for approximately 90%–95% of all diagnosed diabetes cases globally [2]. This condition represents a significant public health challenge, with the International Diabetes Federation (IDF) projecting that over 600 million individuals will be living with diabetes by 2040 [3].

T2DM develops insidiously and is frequently asymptomatic in the early stages. By the time of diagnosis, many patients already exhibit complications. Chronic hyperglycemia contributes to the pathogenesis of both microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary artery disease, peripheral artery disease, and stroke) complications, leading to substantial morbidity and mortality [4].

The hallmark feature of T2DM is insulin resistance, particularly in skeletal muscle, adipose tissue, and the liver. In response, pancreatic β-cells initially increase insulin secretion to compensate. Over time, however, β-cell function declines, resulting in insufficient insulin production relative to metabolic demands [5].

Obesity, particularly visceral adiposity, is a major risk factor for insulin resistance and T2DM. Adipose tissue secretes various adipokines and proinflammatory cytokines, such as TNF-α and IL-6, that disrupt insulin signaling pathways and contribute to chronic low-grade inflammation [6].

Physical inactivity, high-calorie diets rich in saturated fats and refined carbohydrates, and socioeconomic factors also significantly increase T2DM risk. Urbanization and sedentary lifestyles have fueled an alarming rise in T2DM prevalence in both developed and developing countries [7].

Genetics plays a pivotal role in T2DM susceptibility. Genome-wide association studies (GWAS) have identified multiple loci associated with T2DM, implicating genes involved in insulin secretion, action, and β-cell function [8]. However, environmental and behavioral factors largely mediate gene expression and disease onset.

Diagnosis of T2DM is established through criteria such as fasting plasma glucose (FPG) ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL following a 75-g oral glucose tolerance test (OGTT), HbA1c ≥6.5%, or random plasma glucose ≥200 mg/dL with classic symptoms [9]. Prediabetes is defined by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or HbA1c between 5.7% and 6.4%.

Prevalence of T2DM increases with age, and Egypt is among the top ten countries globally in terms of diabetes burden. According to the IDF, Egypt's prevalence stands at around 15.6%, with many individuals undiagnosed, underscoring the need for early detection and preventive strategies [10].

T2DM is associated with a cluster of metabolic abnormalities, including hypertension, dyslipidemia, and central obesity, commonly referred to as metabolic syndrome. This increases the risk of cardiovascular events and complicates disease management [11].

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Pathophysiologically, T2DM is also associated with glucotoxicity, lipotoxicity, oxidative stress, mitochondrial dysfunction, and chronic inflammation, which collectively impair insulin signaling and β-cell function [12].

Adipokine dysregulation, particularly involving leptin, adiponectin, and resistin, further exacerbates insulin resistance. Additionally, ectopic fat accumulation in liver and muscle impairs insulin-mediated glucose uptake and promotes hepatic glucose production [13].

Gut-derived incretin hormones, especially glucagon-like peptide-1 (GLP-1), have reduced efficacy in T2DM, contributing to inadequate postprandial insulin responses and inappropriate glucagon secretion [14].

Management of T2DM involves lifestyle interventions (diet, exercise, weight management), pharmacologic therapy (e.g., metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, insulin), and cardiovascular risk reduction through blood pressure and lipid control [15].

The UKPDS and DCCT studies demonstrated that intensive glycemic control significantly reduces the risk of microvascular complications. More recent trials (e.g., ADVANCE, ACCORD, and VADT) highlight the importance of individualized treatment goals [16].

GLP-1 receptor agonists and SGLT2 inhibitors have shown cardiovascular and renal protective effects in high-risk T2DM patients, making them valuable tools in modern diabetes care [17].

Diabetes education and self-management support play essential roles in improving glycemic outcomes. Structured education programs can enhance adherence, promote lifestyle change, and reduce complications [18].

Technological advances, including continuous glucose monitoring (CGM), insulin pumps, and telemedicine, have further improved diabetes care and patient engagement [19].

Prevention strategies, especially among high-risk populations, involve early screening, lifestyle modifications, and sometimes pharmacologic interventions such as metformin, as demonstrated in the Diabetes Prevention Program (DPP) trial [20].

T2DM remains a multifaceted disorder with a wide spectrum of presentations and complications. Early detection, comprehensive care, and individualized treatment approaches are essential to mitigate its long-term impact on health and quality of life.

Diabetic Kidney Disease

Diabetic kidney disease (DKD), also known as diabetic nephropathy, is a chronic microvascular complication of diabetes mellitus, characterized by progressive albuminuria, declining glomerular filtration rate (GFR), and increased cardiovascular morbidity and mortality [21]. It is the leading cause

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of end-stage renal disease (ESRD) globally, affecting approximately 20%–40% of patients with diabetes [22].

DKD can occur in both type 1 and type 2 diabetes mellitus but is more prevalent in T2DM due to its higher global burden and delayed diagnosis [23]. The clinical diagnosis of DKD traditionally relies on the detection of albuminuria and/or reduced estimated GFR (eGFR) in the absence of other causes of kidney disease [24].

The progression of DKD typically begins with hyperfiltration, followed by microalbuminuria, macroalbuminuria, and eventually a sustained reduction in eGFR, culminating in ESRD. However, non-albuminuric DKD is increasingly recognized, where reduced eGFR occurs without preceding albuminuria [25].

Key risk factors for DKD include poor glycemic control, hypertension, dyslipidemia, smoking, genetic predisposition, and longer duration of diabetes [26]. Importantly, early intervention targeting these risk factors can substantially delay disease progression.

Pathologically, DKD is characterized by glomerular basement membrane thickening, mesangial expansion, nodular glomerulosclerosis (Kimmelstiel-Wilson nodules), and tubulointerstitial fibrosis [27]. Inflammatory and fibrotic mediators such as transforming growth factor-beta (TGF-β), interleukins, and tumor necrosis factor-alpha (TNF-α) play a critical role in renal structural damage [28].

Hemodynamic changes also contribute to DKD pathogenesis. Hyperglycemia-induced activation of the renin-angiotensin-aldosterone system (RAAS) leads to increased intraglomerular pressure and subsequent glomerular injury [29].

Oxidative stress is a major pathogenic mechanism in DKD. Hyperglycemia leads to the overproduction of reactive oxygen species (ROS), which induce mitochondrial dysfunction and activate redox-sensitive transcription factors, promoting inflammation and fibrosis [30].

Recent research highlights the role of epigenetic modifications, microRNAs, and gut-kidney axis in DKD development and progression, offering new insights into pathophysiology and potential therapeutic targets [31].

Diagnostic evaluation of DKD involves measurement of urinary albumin-to-creatinine ratio (ACR) and estimation of GFR using equations like CKD-EPI or MDRD [32].

Annual screening for DKD is recommended in patients with T2DM starting at diagnosis and in T1DM after five years of disease onset [33].

While kidney biopsy is not routinely indicated, it may be considered in atypical presentations such as rapid GFR decline, absence of retinopathy, or presence of hematuria, to rule out non-diabetic kidney disease [34].

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Management of DKD includes optimal glycemic control, usually with an HbA1c target below 7%, blood pressure control (generally <130/80 mmHg), RAAS blockade with ACE inhibitors or ARBs, lipid management, and lifestyle interventions [35].

Sodium-glucose cotransporter 2 inhibitors (SGLT2i), such as empagliflozin and dapagliflozin, have emerged as effective agents in slowing DKD progression and improving cardiovascular outcomes in patients with T2DM [36].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) also provide renoprotective benefits by reducing albuminuria and improving glycemic and lipid profiles [37].

Non-steroidal mineralocorticoid receptor antagonists (MRAs), such as finerenone, have shown promise in reducing albuminuria and slowing DKD progression by targeting inflammation and fibrosis [38].

Nutritional management includes sodium restriction, moderated protein intake, and the promotion of diets rich in fruits, vegetables, and whole grains. Individualized dietary counseling can improve outcomes and delay disease progression [39].

Patient education and engagement are crucial in DKD care. Self-monitoring of blood pressure, glucose, and adherence to lifestyle and pharmacologic therapy improve long-term outcomes [40].

Multidisciplinary care involving nephrologists, endocrinologists, dietitians, and primary care providers is essential in optimizing DKD management and reducing complications [41].

Future therapeutic directions include the exploration of anti-fibrotic agents, endothelin receptor antagonists, and novel anti-inflammatory pathways to halt or reverse DKD progression [42].

DKD remains a leading cause of ESRD and significantly increases cardiovascular risk. Early diagnosis, comprehensive risk factor control, and use of emerging therapeutics are pivotal in altering the disease trajectory and improving patient prognosis.

Serum Lutein in Type 2 Diabetes Mellitus and Diabetic Kidney Disease

Lutein is a naturally occurring xanthophyll carotenoid predominantly found in green leafy vegetables, egg yolks, and corn. It has been extensively studied for its antioxidative and anti-inflammatory properties, and recent research highlights its potential role in the pathophysiology and prognosis of type 2 diabetes mellitus (T2DM) and diabetic kidney disease (DKD) [43].

In the context of T2DM, oxidative stress is a key mediator in disease progression, contributing to insulin resistance and β-cell dysfunction. Lutein, by neutralizing reactive oxygen species (ROS), may offer protective effects against hyperglycemia-induced oxidative damage [44].

Inflammatory responses in diabetes are also modulated by lutein, which has been shown to suppress nuclear factor-kappa B (NF-κB) activity and reduce the expression of pro-inflammatory cytokines like TNF-α and IL-6 [45].

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Human studies have identified an inverse relationship between serum lutein concentrations and the incidence of T2DM, suggesting that lutein may act as a protective nutrient in diabetes pathogenesis [46].

In patients with established T2DM, lower levels of serum lutein are correlated with higher HbA1c levels, indicating a potential role of lutein as a marker of glycemic control [47].

Diabetic kidney disease, a major microvascular complication of diabetes, is similarly driven by oxidative stress and inflammation. Lutein may help protect renal tissues by attenuating these processes [48].

Animal models have shown that lutein supplementation reduces albuminuria, glomerular hypertrophy, and renal fibrosis in diabetic nephropathy [49].

Lutein may enhance endothelial function in diabetic individuals, thereby preserving glomerular filtration and mitigating microvascular damage in the kidneys [50].

Recent studies have found significantly lower serum lutein levels in patients with DKD compared to diabetic patients without nephropathy, supporting its potential as a diagnostic biomarker [51].

In a case-control study, lutein demonstrated high diagnostic accuracy for detecting DKD, with an area under the curve (AUC) greater than 0.96 and high sensitivity and specificity values at defined cut-off points [52].

Serum lutein levels have also been shown to correlate negatively with urinary albumin-to-creatinine ratio (ACR), serum creatinine, and blood urea nitrogen (BUN), further substantiating its renal protective role [53].

The anti-inflammatory effect of lutein is partially attributed to its ability to inhibit toll-like receptor 4 (TLR4) signaling and downregulate monocyte chemoattractant protein-1 (MCP-1) expression [54].

In addition to systemic effects, lutein accumulates in renal tissue, where it scavenges ROS and mitigates lipid peroxidation, thus preserving glomerular architecture [55].

Lutein’s ability to modulate gene expression related to oxidative stress responses, such as upregulation of nuclear factor erythroid 2–related factor 2 (Nrf2), is also a promising therapeutic mechanism in DKD [56].

Furthermore, lutein intake has been associated with decreased levels of advanced glycation end-products (AGEs), which are known to exacerbate diabetic complications [57].

Supplementation with lutein in diabetic patients has resulted in improved metabolic profiles, including reduced fasting glucose and HbA1c levels, and a more favorable lipid profile [58].

Data suggest that lutein's benefits extend beyond glycemic control, offering vascular protection and reducing arterial stiffness in diabetic patients [59].

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Emerging research suggests that lutein could enhance insulin signaling pathways, thereby improving glucose uptake and metabolism [60].

The bioavailability of lutein is a crucial consideration, with lipid-rich diets and appropriate food processing techniques enhancing its absorption and systemic distribution [61].

Older adults, particularly those with poor dietary diversity, may benefit from lutein supplementation to reduce the burden of oxidative stress associated with aging and diabetes [62].

There is growing interest in utilizing lutein-enriched functional foods as a preventive strategy against T2DM and its complications, including DKD [63].

Advanced analytical methods such as liquid chromatography-tandem mass spectrometry (LC-MS/MS) allow for precise quantification of serum lutein, facilitating its use as a biomarker in clinical settings [64].

Prospective cohort studies are needed to validate lutein as a predictive biomarker and assess its long-term impact on renal and cardiovascular outcomes in diabetic populations [65].

Lutein's safety profile is favorable, with few reported adverse effects even at high doses, supporting its feasibility as a supplemental therapy [66].

Future research should explore synergistic effects of lutein with other antioxidants like zeaxanthin and astaxanthin in combating diabetic complications [67].

Lutein may also influence gut microbiota composition, which plays a role in systemic inflammation and metabolic homeostasis, thereby indirectly affecting DKD progression [68].

Pharmacokinetic studies highlight the need for formulation innovations, such as nanoemulsions, to improve lutein stability and delivery in diabetic patients [69].

Overall, lutein represents a promising non-pharmacological adjunct for preventing and managing T2DM and DKD, with both diagnostic and therapeutic implication.

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