The influence of toxic advanced glycation end-products (TAGEs) on the development of diabetic nephropathy

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Abstract
Acquired blindness, end-stage renal failure, accelerated atherosclerosis, and other neuropathies are all primarily caused by diabetic complications. Through a variety of metabolic disturbances, chronic hyperglycaemia plays a primary role in the etiology of diabetic micro- and macrovascular problems. The synthesis of several kinds of advanced glycation end products (AGEs) was enhanced by high glucose. It was recently shown that AGEs (AGE-2) produced from glycerolaldehyde are crucial to the pathophysiology of angiopathy in diabetic individuals. The receptor for AGEs (RAGE), which is present on a variety of cell types in diabetes-affected cells, is of great interest. According to recent research, the interaction between RAGE and AGE-2, which is primarily the structure of toxic AGEs or TAGE, can change gene expression, intracellular signalling, the release of pro-inflammatory molecules, and the generation of reactive oxygen species (ROS), all of which are factors in the pathophysiology of diabetic complications. The pathophysiology of diabetic complications involves factors such as gene expression, intracellular signalling, the release of pro-inflammatory molecules, and the generation of reactive oxygen species (ROS). Recent research indicates that the interaction between RAGE and AGE-2, which is primarily the structure of toxic AGEs or TAGE, can affect these processes.

1. Introduction
Globally, diabetes mellitus-induced diabetic nephropathy (DN) is a leading cause of end-stage renal failure (Qi et al., 2017). It has been suggested that both hereditary and environmental variables influence the likelihood of hyperglycaemia-related late-life renal damage, with just one in three diabetic individuals ever developing nephropathy. The primary risk factors for the development of nephropathy have been identified as hyperglycaemia, hypertension, proteinuria, high body mass index, smoking, and genetic susceptibility (Satirapoj, 2013). Hyperglycaemia is a hallmark of the complicated metabolic disease known as diabetes mellitus. With a global death rate of 1% to 2%, the disease is affecting an increasing number of individuals and is mostly caused by diabetes complications such as retinopathy, nephropathy, and neuropathy. Nevertheless, there is still much to learn about the processes behind the pathophysiology of diabetes problems. The glycation process, commonly known as the "Maillard reaction," is one of the processes that lead to persistent hyperglycaemia and increases the formation of protein adducts with various glucose derivatives. Through non-enzymatic processes, glucose and protein, lipid, or nucleic acid are converted into advanced glycation end-products (AGEs). Patients with diabetes were shown to have a buildup of AGEs in a variety of tissues. It is still unclear, therefore, if and how AGEs contribute to the pathophysiology of diabetes problems. Though the term "AGEs" was originally used to describe a wide range of advanced products of the Maillard reaction, such as N-carboxymethyllysine (CML) and pyrraline, which do not show colour or fluorescence and do not cross-link proteins, it is currently used to describe a variety of products that were originally defined by their ability to form crosslinks with and between amino groups and by their fluorescent yellow-brown colour. Glyoxal and glycolaldehyde can be converted into CML by an intramolecular Cannizzaro reaction, which is mainly unaffected by glucose autoxidation. There has been fresh evidence to support the theory that CML is a measure of oxidation rather than glycation. It was highlighted that both forms of AGEs have considerable toxicity. Studies recently shown that in diabetes patients, glycerolaldehyde-derived AGEs (AGE-2) and glycolaldehyde-derived AGEs (AGE-3), but not glucose-derived AGEs (AGE-1) and CML, contribute to neuronal cell toxicity. Toxic AGEs (TAGEs) and their non-toxic counterparts, CML, pentosidine, pyrraline, and crossline, are the two families of AGEs that are linked to cell toxicity (Sato et al., 2006).

2. Diabetes mellitus and environmental pollution
Almost half million individuals worldwide had diabetes in 2019, and 700 million adults globally are expected to have diabetes by 2045, with type 2 diabetes accounting for the bulk of cases. Chronic kidney disease is mostly caused by diabetes; around 40% of people with type 2 diabetes develop diabetic kidney disease known as diabetes mellitus and environmental pollution.
disease, which is now the primary cause of end-stage renal disease (ESRD), accounting for half of all new occurrences of ESRD annually. Moreover, the risk of dying from cardiovascular disease and other causes is two to four times higher in those with T2D. The defining characteristic of diabetes is hyperglycaemia, which has been used as a screening and diagnostic biomarker for the disease. Nevertheless, metabolic changes that contribute to diabetes can occur decades before hyperglycaemia manifests. Complex interplay between genetic information, developmental exposures, and environmental variables such pollution, physical activity, and food are thought to be the cause of type 2 diabetes (Jin et al., 2021).

It has been shown that air pollution affects endothelial function, causes inflammation and insulin resistance, modifies the gut microbiota, and raises the risk of hypertension. Recent research has demonstrated a clear link between increasing exposure to air pollution and a higher risk of type 2 diabetes. Very large research conducted in Japanese care settings suggested that exposure to light at night may be linked to type 2 diabetes despite the fact that only a small number of studies examined the impact of light exposure on metabolic illnesses. The ensuing impacts on lifestyle especially sleep disturbance, which may lead to higher glucose levels, may account for this connection (Beulens et al., 2022).

Higher levels of noise exposure at home, but not at work, have been linked to an increased risk of type 2 diabetes, according to two meta-analyses (Fig. 1). Peripheral insulin sensitivity and insulin secretion can be impacted by noise as an environmental stressor, although sleep and other lifestyle variables may also play a role. Lastly, additional urbanization-related issues, including air pollution, may complicate the relationships between noise and light and type 2 diabetes (Beulens et al., 2022).

Elevated body temperature may have an adverse effect on glucose metabolism by reducing the amount and activity of brown adipose tissue. High effectiveness of cold exposure as a possible treatment for type 2 diabetes has been shown in experimental trials. However, there is no evidence linking ambient temperature to type 2 diabetes with the exception of one research that found a greater prevalence of diabetes with rising yearly outdoor temperature (Beulens et al., 2022). Eventually, a number of studies found links between chemical pollutants and a higher incidence of type 2 diabetes, including pesticides, heavy metals, and persistent organic pollutants. The complex chemical environment, which includes food contamination, air and water pollution, and occupational dangers, may be the source of these pollutants. Numerous findings point to a higher correlation between chemical pollutants and type 2 diabetes in females and those who are overweight or obese (Beulens et al., 2022).

Figure 1 The influence of environmental pollution on the development of diabetes mellitus (Beulens et al., 2022)
3. Diabetic nephropathy

One of the most common and serious side effects of diabetes mellitus (DM) is diabetic nephropathy (DN), which is linked to higher rates of morbidity and death in diabetic patients. Globally, the prevalence of diabetes is rising quickly, particularly in emerging nations. If the therapeutic approach for DN prevention does not improve immediately, it is anticipated that the prevalence of DN will rise along with the prevalence of diabetes. In around 1/3 of people with diabetes, DN develops following latency periods that might vary by several years. Poor therapy results are caused by the complexity and incomplete understanding of the etiology of diabetic nephropathy. It has been demonstrated that standard treatment, which involves stringent blood pressure and blood sugar management, is unable to halt DN (Liu et al., 2023). Standard care for individuals with classic DN focuses on controlling blood pressure and blood sugar concentrations; however, these measures are ineffective at halting or reversing the disease’s development (Samsu, 2021). Numerous routes and mediators, including as oxidative stress, angiotensin II (Ang-II), and inflammatory processes—which are now thought to be crucial—are implicated in the onset and development of DN (Liu et al., 2023).

The glomerular lesions, particularly the widespread and nodular mesangial enlargement and the thickening of the Glomerular Basement Membrane, are the most notable and persistent pathological abnormalities found in renal biopsies of clinical DN patients. Light microscopy reveals diffuse mesangial growth as the first discernible alteration as early as the fifth year after the beginning of diabetes. In both type 1 and type 2 diabetes, there is a correlation between the mesangial fractional volume and the albumin excretion rate and glomerular filtration rate. Diffuse mesangial expansion gradually transforms into nodular accumulations of mesangial matrix in the late stage of the illness, known as diffuse DN. About 25% of individuals with advanced DN have these nodular lesions, also known as Kimmelstiel-Wilson nodules. Patients with nodular diabetic glomerulosclerosis has worse renal prognosis, longer diabetes durations, and more severe renal damage than individuals with diffuse mesangial expansion (Qi et al., 2017).

An overview and clinical connection of results from renal biopsies from individuals with DN were initially published in 1959 by Gellman et al. Prior to their research, autopsies were the only times the renal pathology of diabetes mellitus patients was discussed. Gellman put out a complex, methodical analysis that looked at the interstitium, glomeruli, tubules, and arterioles but was not appropriate for real-world application (Tervaert et al., 2010).

4. AGEs and diabetic nephropathy

The nonenzymatic condensation of sugar and the creation of a free amino group via the labile Schiff base are the first stages in the production of AGEs. The intramolecular Amadori rearrangement of the Schiff base is followed by a sequence of events, dehydration, and polymerization, resulting in the macromolecular forms of AGEs. Under normal physiological circumstances, such as aging, AGEs are formed in modest amounts. However, in a chronic hyperglycaemic milieu, their levels significantly increase in both the cellular and extracellular compartments in many tissues, especially in organs that are vascularized (Kanwar et al., 2011).

Studies on type 1 and type 2 diabetes, both clinical and experimental, clearly point to the role of AGE in the etiology of diabetic sequelae, including DN. DN, the most prevalent chronic microvascular consequence, affects 20% to 40% of individuals with type 1 and type 2 diabetes. Roughly one-third of newly diagnosed instances of end-stage renal disease are caused by DN.

When glomerular capillaries are compromised in diabetic kidney disease, the glomerular filtration rate gradually decreases. This is followed by several stages of proteinuria, including microalbuminuria, macroalbuminuria, and overt proteinuria, which ultimately lead to end-stage renal disease that requires renal replacement therapy (Pasupati et al., 2016). Other characteristics of type 2 diabetes include hyperglycaemia and hypertension, which accelerate the progression to end-stage renal disease. Patients with diabetes who have renal illness have both hemodynamic (hyperfiltration) and structural problems. A research in which AGEs were administered to non-diabetic rats revealed proteinuria and degenerative changes in DN, demonstrating the crucial role that AGEs play in the pathophysiology of renal damage (Vlassara et al., 1994).

The blood levels of fluorescent non-CML AGEs are markedly elevated in patients with type 1 diabetes who progress from normal renal function to end-stage renal disease (Miura et al., 2003). On the other hand, a different study found a correlation between the severity of nephropathy and CML in individuals with type 1 diabetes (Turralde et al., 1987). CML- and hydroimidazolone-AGEs are significantly elevated in individuals with type 2 diabetes (Kilhovd et al., 2003). The degree of AGE production and RAGE expression in the glomerular and tubulointerstitial compartments is correlated with the severity of diabetic neuropathic pain. An additional characteristic of DN is a reduction in glomerular filtration rate (GFR) (Prabhakar et al., 2004).

5. TAGE and diabetic nephropathy

The findings of the studies suggest that, among the several kinds of AGE structures that might develop in vivo, the TAGE structures (AGE-2 and AGE-3) are most likely to be crucial in the pathophysiological mechanisms by which AGEs are formed. Particularly in the first stages of development, TAGE play a role in the pathophysiology of diabetic retinopathy and nephropathy. Additionally, TAGE causes Schwann cells to undergo apoptosis and might be a key factor in the development of diabetic neuropathy. Although non-toxic AGE structures could be physiologically relevant defenses against the advanced glycation process’s potentially harmful effects (Sato et al., 2006).

Although the exact structure of TAGE is still unknown, the rearrangement of glyceraldehyde addition products is the greatest evidence we currently have for its formation (Takeuchi, 2000). The pyridinium moiety of AGEs produced from glycolaldehyde and glyceraldehyde has been shown in recent research, indicating that a particular structure may be in charge of TAGE’s cytotoxicity. Studies on the pathophysiology and structural makeup of TAGE provide valuable insights into the emergence of diabetes complications and their prevention. The Epidemiology of Diabetes Interventions and Complications in the Diabetes Control and Complications Trial (DCCT) According to research, even with rising hyperglycaemia, individuals with type 1 diabetes who received comprehensive therapy had a decreased chance of developing progressive retinopathy and nephropathy for at least four years. These clinical findings clearly imply that persistent anomalies in diabetic arteries caused by so-called "hyperglycaemic memory" are difficult to cure, even with subsequent reasonably successful blood glucose management. The AGEs hypothesis—more specifically, the TAGE theory—seems to be the most consistent with hyperglycaemic memory among the different theories linked to the pathophysiology of diabetes problems (Sato et al., 2006).
6. Conclusion

In summary, a significant amount of the disease burden associated with type 2 diabetes can be attributed to environmental factors. It is believed that the environment primarily influences the risk of type 2 diabetes by influencing lifestyle variables including food and physical exercise, the microbiota, inflammation, and long-term stress. Hyperglycaemia, the essential component of diabetes mellitus, is the first step toward diabetic kidney damage. Hyperglycaemia causes a complex disruption of hemodynamic effects, extracellular events, and cellular functioning that together change the biology of almost all kidney cell types, whether they are in the nephron proper, the vasculature, or the surrounding interstitial parenchyma. The modest glucose molecule produces hexosamines, polyols, a changed redox environment, Amadori adducts, AGEs, and ROS when it is digested more quickly through its many metabolic pathways. These chemicals then set off a series of signalling processes that ultimately result in the many metabolic pathways. These changes set off a series of signalling processes that ultimately result in maladaptive behavior. The diabetic nephropathic symptoms of podocytopenia, remnogaly, mesangial matrix enlargement, Kimmelstiel-Wilson lesions, GBM thickening, interstitial fibrosis, and arteriolar hyalinization are caused by these processes. These ailments, however, just scratch the surface of the renal cellular machinery's complexity. This is not the end of the pathophysiology of diabetic nephropathy described. Further studies about AGE, TAGE and diabetic nephropathy are necessary.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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