

Infiltration of Macrophages and Oxidative stress in IgA Nephropathy

Abstract

Diabetic nephropathy (DN) is the second most frequent and prevalent consequence of diabetes mellitus (DM). A chronic hyperglycemic state that can cause oxidative damage to macromolecules (lipids, carbohydrates, proteins, and nucleic acids) is what causes an increase in the generation of oxidative stress (OS). The expression of the DNA repairer enzyme is influenced by OS, which promotes the creation of oxidative damage to the histones of the double-chain DNA, which results in apoptosis, the cell death process. The presence of inflammation, growth, and an increase in the synthesis of the extracellular matrix (ECM) in DN are all caused by the chronic hyperglycemic state's release of an increase in advanced glycation end-products (AGE), which interact through cellular receptors to favour activation of the transcription factor NF- κ B and the protein kinase C (PKC) system. Due to the fact that prolonged hyperglycemia enhances ROS generation, ROS play a significant role in the pathophysiology of diabetes complications. The mitochondria, which have the ability to produce more endogenous antioxidants than necessary, are the main cause of the excessive generation of ROS. There are several approaches to particular treatment targets or adjuvant management options in the control of glycaemia in DN since the mechanisms involved in the development of DN have not been fully elucidated.

Keywords: Nephropathy • Pathophysiology • Diabetic nephropathy • Cardiovascular disease • Diabetes mellitus

Introduction

The frequency of persons with diabetes mellitus (DM) has significantly increased over the world in recent decades. According to the 7th edition of the diabetes mellitus (DM) Atlas, which was published in 2015, there are currently 415 million adults worldwide who have the disease, and by the year 2045, it's predicted that there will be 693 million. When glucose levels are not adequately controlled, significant micro- and macrovascular problems start to manifest. Cardiovascular disease (CVD), which increases the risk of having a heart attack or a stroke, is one of the typical macrovascular consequences. Neuropathy, retinopathy, and diabetic nephropathy (DN) stand out among the microvascular consequences [1].

Albumin excretion rate (AER) > 300 mg/24 h and a decline in glomerular filtration rate (GFR) > 5 years in the absence of urinary tract infections, other renal disorders, or heart insufficiency are the two main symptoms of DN. between 5 and 20% of people with type

2 DM and between 15 and 40% of type 1 DM patients experience proteinuria. On the morbidity and mortality of DM patients, DN has considerable long-term impact. Mitochondrial function and cell death due to apoptosis in DN, since the mechanisms in the appearance of DN have not yet been fully described. Some management options that can be used in conjunction with standard DN risk factors and glycaemia control are also discussed. We stress that maintaining sufficient glycemia control is the best course of treatment for patients with DM in order to prevent and manage the development of renal impairment [2].

In the world, diabetes mellitus is the leading cause of chronic kidney disease (CKD), with 1 in 4 adults with DM having the condition and 1 in 10 to 20% of DM patients dying from it. In more than 50% of patients treated in Singapore, Malaysia, Jalisco (Mexico), and Chile, DM was shown to be the main cause of end-stage renal disease (ESRD), About three to five times

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as many African-Americans as Caucasians are affected by diabetic nephropathy. In type 1 DM, CKD develops slowly for the first five to ten years before rapidly increasing during the next ten years, peaking at roughly three percent per year after 15 years of DM. The percentage of CKD declines from 15% after 15 years of type 1 DM to 1% after 40 years of the condition. Patients who have had type 1 DM for more than 35 years but have not yet shown DN have a low likelihood of doing so [3].

In type 2 DM, systemic arterial hypertension patients and people who have had renal disease in the past are more likely to acquire DN. DN can accompany diabetic retinopathy and can occur in young people on occasion. Retinopathy and proteinuria can be absent or limited in older people with type 2 diabetes, but other renal disorders should be looked at and ruled out. Proteinuria and diabetic retinopathy may potentially be connected to arterial hypertension [4].

Discussion

Warfarin-related nephropathy (WRN) is another name for anticoagulant-related nephropathy (ARN), which is a type of acute kidney injury brought on by excessive anticoagulation. When a patient has unexplained acute renal injury, which is defined as a rise in serum creatinine of more than 0.3 mg/dL within one week of an INR reading of more than 3, in a patient on warfarin, and after ruling out other causes of AKI and bleeding, the diagnosis should be suspected. Recent research reveals that WRN-like symptoms can develop with other anticoagulants, including acenocoumarol and dabigatran, and are not just related to warfarin anticoagulation [5].

In WRN, glomerular hematuria leads to extensive tubular blockage and AKI. RBCs were found in tubules and occlusive RBC casts were mostly found in the distal nephron segments, according to biopsy studies. There were several suggested pathogenic processes. The crucial factor appears to be the interaction of even mild glomerular disease with warfarin-induced coagulopathy. Particularly when urine flow is reduced, this results in glomerular hematuria and a large accumulation of RBCs that form occlusive casts within nephrons. Although interstitial haemorrhage appears to be crucial, glomerular hematuria is still necessary. Therefore, tubular blockage by

RBC casts, in conjunction with interstitial haemorrhage, is likely the main cause of AKI in WRN. This enhanced oxidative stress in the kidney is brought on by the interstitial haemorrhage [6].

Age, CKD, due to a higher risk of supratherapeutic INR, diabetes and diabetic nephropathy, hypertension, heart failure, and diabetic nephropathy are just a few of the underlying risk factors for WRN. An anticoagulant called Dabigatran is used to prevent strokes in people with atrial fibrillation. According to recent research, Dabigatran produces a lot of hemorrhagic side effects. However, there is little information available regarding renal involvement. In order to avoid hemorrhagic consequences, Dabigatran requires a dose adjustment in individuals with creatinine clearance between 15 and 30 mL/min. Dabigatran has an 80% renal elimination rate and is not advised for patients on dialysis or with a creatinine clearance less than 15 mL/min [7].

Dabigatran may cause AKI through two major pathogenic processes, according to evidence from animal studies: first, tubular obstruction by RBCs, and second, a potential mechanism involving protease-activated receptor 1 (PAR-1). The primary effector of thrombin signalling is the G protein-coupled receptor PAR-1, which controls endothelial functions, vascular permeability, leukocyte migration, and adhesion. Direct thrombin inhibitors or vitamin K antagonists both reduce thrombin activity. Thrombin activates protein C and modifies the anticoagulation cascade by acting on thrombomodulin.

The similar thing occurs with PAR-1. The authors of the aforementioned study hypothesised that thrombin is crucial to the operation of the glomerular filtration barrier and that, as a result of anticoagulation, thrombin activity is lowered, leading to anomalies in the glomerular filtration barrier. In fact, specific PAR-1 inhibition causes elevated creatinine, hematuria, and tubular RBC casts, effects that are comparable to those seen in animals with WRN or those receiving dabigatran. These outcomes are comparable to WRN. But unlike WRN, where kidney damage was solely evident in animals with CKD, dabigatran's effects were also clearly noticeable in control rats. These results imply that dabigatran may carry a higher renal risk than warfarin [8].

The primary clinical symptom of IgA nephropathy is hematuria, which can be microscopic or macroscopically and is usually not observed by the patient. It is conceivable that something that by its very nature predisposes to hematuria may be associated to or a risk factor for ARN. Fundamental WRN pathological abnormalities similar to those mentioned previously were also present in our case, indicating that tubular blockage and interstitial haemorrhage may be common physiopathological causes of AKI. In the instance of our patient, we suggest that the confluence of IgA nephropathy, which is linked to age, CKD, and a history of hypertension, may lead to the ideal background [9].

Hemodialysis appears to be helpful in the treatment of dabigatran-related AKI, with the primary goal of treatment being to return the aPTT to a therapeutic range while doing supportive renal care. There appear to be differences in the prognosis between WRN and dabigatran-related AKI. In a WRN research, the clinical outcome was not favourable: 66% of patients did not regain baseline performance. Regarding the two occurrences of dabigatran-induced AKI that were reported, both patients' renal function got well. In our case, renal function appears to be improving, and we believe that the absence of histological indicators of IgA nephropathy's poor prognosis, such as the absence of interstitial fibrosis, tubular atrophy, glomerular sclerosis, or endocapillary hyper cellularity, may have played a role in this positive outcome. Dabigatran's lower dose and brief delivery interval may have had an impact. However, it is impossible to compare the results of these two entities because there are so few reported cases of dabigatran-related nephropathy.

This highlights the need for caution while using oral anticoagulation in kidney disease patients. They are more likely to develop gross hematuria, excessive anticoagulation, and AKI. So, whether using warfarin or another anticoagulant like dabigatran, physicians involved in the clinical management of anticoagulated patients should be aware of the ARN. Correct monitoring of coagulation and renal function is necessary, and anticoagulants should be reduced or discontinued as appropriate [10].

Conclusion

KLHDC8A was shown to be elevated in gliomas

in our study and to be related with a bad prognosis. We emphasised the connection between KLHDC8A expression and tumor-associated macrophages. We proposed the possibility that the glioma therapeutic target KLHDC8A would be promising.

Acknowledgment

None

Conflict of Interest

None

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