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Risk factors and salient features of Acute Kidney Injury in Diabetic Ketoacidosis

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Abstract

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus (DM). The morbidity, mortality and long-term renal outcomes in DKA are influenced by the occurence of acute kidney injury (AKI). However, AKI in DKA remains undiagnosed and the incidence and severity of AKI in DKA is still unknown. This review article focusses on the risk factors and salient features of acute kidney injury in diabetic ketoacidosis. Peer reviewed articles from 1995 to 2021 were accessed from PubMed and reviewed.

Introduction

Diabetic ketoacidosis (DKA) is one of the leading causes of hospitalization, morbidity and mortality in diabetic patients [1-4]. DKA manifests with hyperglycaemia, metabolic acidosis, ketosis, volume loss, and electrolyte abnormalities along with AKI. AKI in DKA is known to lead to worsening of short- and long-term outcomes but has not been systematically studied. Brenden E et al. found that 44 of 106 (41.5%) DKA patients with AKI did not have documentation of AKI resolution prior to discharge [5]. AKI remained undiagnosed in the absence of universal diagnostic criterion but using the RIFLE classification [6], the incidence and severity of AKI among different populations and settings can now be compared [7]. We conducted a PubMed search including articles published from 1995 to 2021 with the MeSH terms "acute kidney injury", "acute renal failure" and "diabetic ketoacidosis"

Risk Factors for Developing Acute Kidney Injury in Diabetic Ketoacidosis

AKI was more common in elderly patients. Tachycardia, coma, severity of acidosis and proteinuria were independently associated with increased incidence of AKI in DKA patients. Movement of fluid from the intracellular to extracellular compartment due to insulin deficiency and renal hypoperfusion leads to development of AKI in DKA. AKI in DKA is often volume responsive. Almost 50% of AKI patients had recovery of renal function in less than 24 hours [8,9].

Junzhe Chen et al. found that the AKI group was older and had a higher incidence of cardiovascular disease (CVD) and chronic kidney disease (CKD) than the non-AKI group (P<0.05). Tachycardia, coma on admission and proteinuria were documented more in the AKI group compared to the non-AKI group (P< 0.05). AKI patients had higher blood glucose, serum uric acid and total leukocyte count (TLC) and lower pH and serum albumin levels compared to the non-AKI patients (P<0.05) [1].

Using multivariate logistic regression, Junzhe Chen et al identified older age [odds ratio-OR (95% confidence interval-CI) 1.033 (1.009–1.058), P=0.008]; increased glucose [OR (95%CI) 1.087 (1.034–1.142), P=0.001], serum uric acid [OR (95%CI) 1.006 (1.002–1.009), P = 0.001], and TLC [OR (95%CI) 1.089 (1.026–1.157), P=0.005]; and decreased pH [OR (95%CI) 0.001 (0.000–0.080), P=0.002], and serum albumin [OR (95%CI) 0.937(0.881–0.996), P=0.038]; along with coma at the time of admission [OR (95%CI) 12.389 (1.823–84.185), P=0.010] and pre-existing CKD [OR (95%CI) 6.250 (1.461–26.732), P=0.013] as risk factors for development of AKI in DKA patients [1]. Jean-Christophe Orban et al. found age, blood glucose and serum protein level as risk factors for developing AKI in DKA [2].

Risk Factors for Long-Term Mortality in Dka Patients

The AKI group had significantly lower survival rate than the non-AKI group. Severity of AKI was associated with increased long-term mortality in DKA patients. Incidence of AKI, severity of AKI, need for renal replacement therapy and pre-existing chronic kidney disease were associated with progression of renal disease in DKA patients.

Junzhe Chen et al used Cox proportional hazards model to identify risk factors associated with long-term renal outcomes and mortality. In the study by Junzhe Chen et al, Kaplan-Meier analysis and the log-rank test were used to compare long-term renal outcomes and mortality between different AKI stages according to the KDIGO criteria. Cox proportional hazards modelling demonstrated that age (P=0.001) and AKI (P=0.036) were significantly associated with long-term mortality in DKA patients. The AKI group had lower survival rate than the non-AKI group [1]. The study by Giacomo Zoppini et al. [10] showed that eGFR decline in the DKA patients in the AKI group was 6.4 ± 5.0ml/min/1.73m2 per year, while that in the DKA patients in the non-AKI group was 1.9 ± 3.8ml/min/1.73m2 per year during the average follow-up period of 22 months (P< 0.01). The decrease in eGFR in AKI group was 10.5 ml/min/1.73m2 in the first 6 months to 1 year, whereas the decrease in the eGFR in the non-AKI group was 4.11 ml/min/1.73m2 (P=0.001). The deterioration of renal function slowed after 1 year but was significantly different between the AKI and non-AKI groups.

AKI is a key risk factor for progressive CKD and advanced stages of AKI are associated with higher risk of progressive CKD. Possible mechanisms involved in AKI transition to CKD include mitochondrial dysfunction, persistent chronic inflammation, oxidative stress endothelial dysfunction and microvascular rarefaction, inadequate regeneration of tubular cells, cell cycle arrest, response to DNA damage [11,12]. Many studies have demonstrated that diabetes is an independent risk factor for AKI and diabetic patients with AKI have significantly higher risk of progressing to CKD [13,14]. Diabetes is associated with reactive oxygen species (ROS) overproduction, mitochondrial dysfunction, inflammation and hypoxia [13]. Endothelial cell injury including abnormal function and apoptosis and a decrease in peritubular capillaries is associated with the reduced expression of VEGF-A which can be induced by hyperglycaemia [15,16]. Mitochondrial damage has been noted in podocytes treated with high glucose and experimental or clinical diabetic kidney disease [17,18]. In a pathological state, the tubular system can set up and maintain the cycle for inflammation, hypoxia and apoptosis [19]. *In vivo* and *in vitro* studies have demonstrated that hyperglycaemia can induce proximal tubular cells to secrete extracellular matrix through the TGF-β-dependent pathway which is the main mechanism of AKI to CKD progression [20,21]. The increase in proinflammatory cytokines, oxidative stress and raised levels of ketones can increase the expression of adhesion molecules in endothelial cells and cause monocytes to adhere, resulting in tissue damage [22-23]. The above-mentioned mechanisms may explain how AKI affects the long-term renal outcome of DKA.

Conclusion

Diabetic ketoacidosis with AKI is not uncommon. Tachycardia, coma, severity of acidosis and proteinuria were associated with increased incidence of AKI in DKA patients. AKI patients had higher blood glucose, serum uric acid and TLCs and lower pH and serum albumin levels than non-AKI patients. Severity of AKI was associated with increased long-term mortality in DKA patients. Incidence of AKI, severity of AKI, need for renal replacement therapy and pre-existing chronic kidney disease are associated with progression of renal disease in DKA patients. Recognising and prevention of AKI in DKA patients is crucial in determining both short term and long-term renal outcomes.

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