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"Predictors of mortality and poor renal outcomes in adults with diabetic ketoacidosis"

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ABSTRACT:

Background: Diabetes mellitus has an overshooting incidence nowadays and diabetic ketoacidosis is one of its common complications. Acute kidney injury is a common complication of diabetic ketoacidosis that adversely affect mortality and morbidity. Early detection with subsequent management of such factors can successfully modify the overall prognosis. The study aims to detect risk factors associated with the development of acute kidney injury in adults with diabetic ketoacidosis and the impact of these factors on mortality and morbidity.

Methods: A prospective study was carried out on ALSALAM General Hospital in the period between August 2021 to April 2022. The study included 60 subjects admitted to ICU with diabetic ketoacidosis (based on Blood Glucose level >250mg/dL, presence of ketonemia or ketonuria, arterial PH <7.3, anion gap > 10, Hco3 < 18 meq/L). Predictors of mortality and renal outcome were studied in this cohort of patients.

Results: Age, comorbidities (e.g., recent stroke), urinary neutrophilic gelatinous lipocalin, glycemic control, the degree of acidosis, estimated glomerular filtration rate, and uric acid were significantly correlated with acute kidney injury, while higher blood glucose was associated with higher mortality.

Conclusion and recommendation: Early detection of multiple risk factors associated with acute kidney injury in patients with diabetic ketoacidosis can improve the prognosis and decrease overall morbidity and mortality.

Introduction:

Acute kidney injury (AKI) is considered one of the most common and serious complications of diabetic ketoacidosis (DKA), representing about 41.2–54.8% of people hospitalized with DKA (Chen et al, 2020).

Multiple risk factors were shown to contribute to AKI in DKA patients such as; dehydration, which is linked to the degree of DKA severity, and the deleterious effect of acidosis itself. Also, hyperuricemia, total leucocytic count (TLC), albumin level, and high blood glucose may carry an additional risk of AKI development and can affect long-term renal outcomes and future development of chronic kidney disease and subsequent mortalities. (Chen, et.al.,2020).

Most cases of AKI in patients with DKA are transient pre-renal azotemia and considered “volume-responsiveness AKI “. However, the renal outcomes differ according to predisposing factors and subsequent management plans. (Orban, et.al., 2014)

Prompt and aggressive treatment of AKI in DKA patients with fluid repletion, acidosis, and hyperglycemia correction carries a good prognosis in most cases and induces reversibility of the renal insult. However, some patients may require more invasive intervention in the form of renal replacement therapy. (Mishra, et.al, 2021)

Although DKA is a serious life-threatening problem, good and early management can improve the prognosis and decrease the mortality rates. Centers for disease control and Prevention (CDC) reported trends for increased hospitalization for DKA cases including all age groups between 2009 to 2014 in the US, while the mortality rates reported a decline between 2000-2014 which was proposed by applying better uniform guidelines for diagnosis and management of DKA. (Benoit, 2018). However, a slight increase in mortality rates due to DKA is documented in 2017 (0.33%, and 0.38% in 2014 and 2017 respectively), which can be explained in some literature by the trends for higher life expectancy with improving healthcare facilities and coverage of medical care that can predispose the elderly to increased mortality rates with DKA especially with associated co-morbid conditions with age advancing (Ramphul, 2020). In developing countries, the mortality rates are still higher ranging from 3.4% to 13.4% in areas such as India, Pakistan, and Bangladesh (Poovazhagi, 2014), while in countries such as Ethiopia, the mortality rates range from 6% to 24% (Kidie, et.al.,2021) The higher rates can be explained by delayed presentation to hospital in developing countries, less patient compliance to therapy and lack of following DKA management protocol.

In this study, we aim to assess the outcomes in patients with DKA with the determination of factors possibly associated with the occurrence of AKI during the in hospital follow up period and detection of possible predictors of mortality.

Methodology:

We carried out a prospective single-center study that included 60 adult patients aged > 18 admitted to the ICU of Al-SALAM general hospital in the period between August 2021 to April 2022. The diagnosis of DKA is based on the American Diabetes Association (ADA) diagnostic criteria (Blood Glucose level >250mg/dL, presence of ketonemia or ketonuria, arterial PH <7.3, anion gap > 10, Hco3 < 18 meq/L). All patients' demographic characteristics were recorded and a thorough medical history was taken regarding the type, and duration of diabetes, compliance, and form of treatment, associated co-morbid conditions and their corresponding medications,

inquiry about the precipitating factors of DKA, the time interval between illness and hospital admission.

On admission, a complete medical examination was performed including an assessment of central venous pressure for the degree of dehydration and level of consciousness. All laboratory findings were recorded on admission including the level of blood glucose, PH, HCO3, anion gap, ketone bodies in urine, serum albumin, leucocytic count, uric acid level, serum creatinine, blood urea nitrogen to creatinine ratio, and estimated GFR was calculated for all cases using a modification of diet in renal disease (MDRD) formula. Urine output was recorded over 24 hours. Assessment of urinary neutrophilic gelatinous lipocalin (uNGAL) was performed on admission as a possible predictor of AKI. Urine was collected following the standard precautions for preventing infection. Urine was cleaned by centrifuging it (1500xg at 4 °C for 15 minutes) to get rid of any sediment. The samples were frozen at -20 degrees Celsius. The samples were mixed gently and warmed to room temperature (18-25°C) before the test was run. Elisa kit applies to the in vitro quantitative determination of human NGAL concentrations in urine.

We follow those 60 patients in ICU for 7 days for the development of AKI, 34 patients out of 60 developed AKI according to Kidney Disease Improving Global Outcome (KDIGO) criteria. Analysis of different variables & risk factors were done to detect factors that correlate with mortality and act as predictors of AKI.

Statistical analysis:

Qualitative variables were coded to facilitate the transfer of data. all of the members were calculated on a computer running SPSS 20 (statistical program for the social science). the process of data analysis which consists of: 1.the mean (standard deviation) and number (percentage) were calculated using descriptive statistics to provide quantitative descriptions of the data. 2. The significance of correlations between outcome measures and program elements were examined using the Chi-square test for categorical variables, the paired student t-test for continuous variables with normally distributed data, the Mann-Whitney Rank test for non-parametric data, or other appropriate tests. At a95 percentage level of confidence, statistical significance was predetermined (differences are significant of P less than 0.005)

Results:

Regarding demographic data, the mean age of the group is 52.7 ± 19.31 years, with 40% female and 60% male. Hypertension and ischemic heart disease were the commonest comorbidities representing 37% & 10% respectively. Other comorbidities were studied, such as recent stroke, bronchial asthma, COPD exacerbation, diabetic foot, and heart failure. The mean duration of diabetes of the included subjects was (21 ± 11.23), with 48.33 % with type 2 diabetes and 51.67% with type 1. 70% of the patients using insulin in their regimen, and 48.33% using different forms of oral antidiabetic drugs. 63.33% of patients were on poor glycemic control. The most common precipitating factor of DKA was variable forms of chest infections such as; pneumonia, bronchopneumonia, and acute bronchitis (represents 45%), followed by uncontrolled diabetes (represents 40%), other causes such as diabetic foot infections, urinary tract infections, and one case precipitated by burn. (Table 1) GCS on admission was 13.85 ± 1.66. The mean & SD of the examined clinical parameters; Systolic Blood Pressure, diastolic Blood Pressure, height, weight, Body Mass Index & Central Venous Pressure was 162 ± 192.33, 88.5 ± 20.57, 163.88 ± 8.12, 73.88 ± 14.75, 27.29 ± 5.04, 14.87 ± 7.13 respectively. (Table 1).

Table 1

Demographics &clinical characteristics of the studied population

Parameters	Value (N = 60)	Mortality cases (N = 4)
Age (years)	52.7 ± 19.31	64.75 ± 4.79
Sex		
Female	24 (40%)	2 (50%)
Male	36 (60%)	2 (50%)
Smoking	5 (8.33%)	0 (0%)
Co-Morbidity		
HTN	37 (61.67%)	4 (100%)
IHD	10 (16.67%)	0 (0%)
recent stroke	5 (8.33%)	0 (0%)
Hypothyroidism	1 (1.67%)	0 (0%)
AF	5 (8.33%)	2 (50%)
asthma	3 (5%)	1 (25%)
Covid fever	1 (1.67%)	0 (0%)
HF	2 (3.33%)	1 (25%)
DVT	1 (1.67%)	0 (0%)
COPD exacerbation	4 (6.67%)	2 (50%)
Dilated Cardiomyopathy	1 (1.67%)	0 (0%)
Precipitating factors		
Pneumonia, bronchopneumonia, acute bronchitis	27(45%)	2 (50%)
Uncontrolled diabetes	24(40%)	0 (0%)
Diabetic foot infection	5 (8.33%)	3 (75%)
UTI	3 (5%)	0 (0%)
Burn	1 (1.67%)	0 (0%)
Type of DM		
Type 2 diabetes	29 (48.33%)	4 (100%)
Type 1 diabetes	31 (51.67%)	0 (0%)

Duration of DM	21.15 ± 11.23	25 ± 9.13
current therapy		
Insulin	42 (70%)	2 (50%)
Oral hypoglycemic therapy	29 (48.33%)	0 (0%)
Combined treatment	15 (25%)	0 (0%)
Glycemic control		
Uncontrolled (HbA1C > 7%)	38 (63.33%)	4 (100%)
Controlled (HbA1C < 7%)	22 (36.67%)	0 (0%)
The time interval between the beginning of illness and hospital admission (in Hours)	9.31 ± 13.7	2.88 ± 2.32
Clinical parameter on admission	value	
GCS	13.85 ± 1.66	13.75 ± 2.5
SBP	162 ± 192.33	145 ± 41.23
DBP	88.5 ± 20.57	95 ± 26.46
height	163.88 ± 8.12	164 ± 6.68
weight	73.88 ± 14.75	81.5 ± 14.08
BMI	27.29 ± 5.04	30.4 ± 7.12
CVP as a sign of dehydration (mmHg)	14.87 ± 7.13	15.25 ± 3.86

Urinary NGAL was assessed on admission for all cases with mean ± SD (230.25 ± 147.83). Blood glucose was 615.25 ± 123.84, blood PH was 7.12 ± 0.29, ketone bodies was 2.3 ± 0.59, HCO3 level was 14.19 ± 5.96, and anion gap was 20.69 ± 12.19, serum albumin was 3.65 ± 4.18, sodium was 132.27 ± 10.74, uric acid was 4.5 ± 0.99, potassium was 4.5 ± 0.99, urine output 1533.24 ± 825.84, and leucocytic counts was 11.94 ± 6.16 (as shown in Table 2).

Table 2

Laboratory investigation of the studied population on admission and on follow-up on the 7th day

Laboratory investigations	On admission	On 7th day	Mortality cases (N = 4)
Urinary NGAL (ng/ml)	230.25 ± 147.83		317.33 ± 56.96
Blood Glucose(mg/dL)	615.25 ± 123.84	298.95 ± 72.01	438.33 ± 135.12
blood PH	7.12 ± 0.29	7.35 ± 0.05	7.12 ± 0.28
HCO3 (meq/L)	14.19 ± 5.96	24.86 ± 3.54	10.48 ± 4.39
Ketone bodies in urine (mmol/L)	2.3 ± 0.59	0.3 ± 0.57	
Anion gap	20.69 ± 12.19	15.85 ± 7.09	25 ± 7.39
Serum creatinine (mg/dL)	1.42 ± 0.51	2.29 ± 1.1	1.58 ± 0.31
eGFR (ml/min/1.73m²)	67.13 ± 28.6	48.35 ± 29.03	50.33 ± 11.5
BUN/creatinine ratio	46.36 ± 25.56	44.24 ± 22.38	33.58 ± 6.68
Serum uric acid (mg/dL)	6.34 ± 2.24	5.94 ± 2.03	8.25 ± 0.96
Leucocytic count (cell/ mm³)	11.94 ± 6.16	11.66 ± 4.83	16.43 ± 6.74
Urine output (mL/24 hours)	1533.24 ± 825.84	1338.75 ± 569.74	1925 ± 531.51
Serum Na+ (mmol/L)	132.27 ± 10.74	138.43 ± 5.38	131.75 ± 12.58
Serum K+ (mmol/L)	4.5 ± 0.99	4.9 ± 0.74	3.93 ± 1.09
Serum albumin (gm/dl)	3.65 ± 4.18	4.21 ± 4.25	3.38 ± 0.25

In the current study, age (p=0.03634, r = 0.271), presence of recent stroke (P=0.0418, r = 0.264), and COPD (P= 0.01756, r = 0.306) (as comorbidities), uNGAL (P=0.00109, r = 0.412), serum creatinine (P=0.03258, r = 0.276), BUN to creatinine ratio (p=0.04252, r = 0.263), and serum uric acid (P=0.00136, r = 0.404) showed a positive correlation with AKI, while Good glycemic control (P=0.01532, r = -0.312), HCO3 level (P=0.01254, r = - 0.321), and eGFR (using MDRD formula) (P= 0.00766, r = -0.341) showed a -ve correlation. No significant correlation was found regarding serum Na, K, albumin, leucocytic count, ketone bodies in urine, and blood PH.

(Table 3). Blood glucose level only showed a +ve significant correlation with mortality in the pass-away group (P=0.01, r = 0.333). (Table 3)

Table 3

Correlation of the studied parameters with AKI and mortality

Variable	AKI		Mortality	
	Pearson correlation	P value	Pearson correlation	P value
age	.271*	0.03634		
Sex				
Female	0.027462	0.83501		
Male	-0.02746	0.83501		
smoking	-0.10141	0.44072		
Comorbidities				
HTN	0.140659	0.28374		
IHD	0.21058	0.10631		
Recent stroke	.264*	0.0418		
Hypothyroidism	0.113847	0.38642		
AF	0.020282	0.87776		
asthma	0.046297	0.7254		
Covid fever	0.113847	0.38642		
Diabetic foot	-0.2231	0.08663		
HF	-0.02498	0.84972		
DVT	0.113847	0.38642		
COPD exacerbation	0.306*	0.01756		
Dilated Cardiomyopathy	-0.14888	0.25626		
Type of diabetes				
Type 2 DM	0.038139	0.77234		
Type 1 DM	-0.03814	0.77234		
duration of DM	0.232167	0.08808		
Form of medication				
Insulin	0.161468	0.21775		
Oral medication	0.240053	0.06468		
Glycemic control				
Uncontrolled HbA1c > 7%	.312*	0.01532		

Controlled HbA1c < 7%	-.312*	0.01532		
The time interval between the beginning of illness and hospital admission (in Hours)	0.194563	0.13977		
GCS	-0.05942	0.65198	-0.016	0.902
SBP	-0.13015	0.32161	-0.024	0.857
DBP	0.084092	0.52295	0.085	0.518
Height	-0.00849	0.94866	0.004	0.977
Weight	0.07353	0.57661	0.139	0.289
BMI	0.102506	0.43577	0.166	0.205
sign of dehydration CVP	0.002536	0.98465	0.014	0.913
Laboratory values				
Urinary NGAL (ng/ml) on admission	.412**	0.00109	0.159	0.226
Blood Glucose (mg/dL)	0.113789	0.39082	0.333**	0.01
blood PH	0.00552	0.96661	-0.008	0.953
HCO3(meq/L)	-.321*	0.01254	-0.168	0.199
anion gap	-0.22803	0.07972	0.095	0.469
Serum creatinine (mg/dL)	.276*	0.03258	0.081	0.538
eGFR (ml/min/1.73m^2)	-.341**	0.00766	-0.158	0.227
BUN to creatinine ratio	.263*	0.04252	-0.135	0.305
urine output (mL/24 hours)	0.266415	0.0515	0.135	0.329
ketone bodies in urine (mmol/L)	0.103321	0.43211	-0.023	0.863
Serum Na (mmol/L)	-0.0539	0.68254	-0.013	0.922
Serum K (mmol/L)	0.132859	0.31155	-0.155	0.235
uric acid (mg/dL)	.404**	0.00136	0.23	0.077
Albumin (gm/dL)	0.097685	0.45777	-0.018	0.894
Leucocytic count (cell/ mm^3)	0.110005	0.40275	0.196	0.133

Table 4
Regression analysis of the associations of the studied parameters with AKI on the follow-up period

Laboratory investigations	p	OR (LL – UL 95%C.I)
Urinary NGAL (ng/ml)	0.028*	1.112(1.011 – 1.222)
Blood Glucose(mg/dL)	0.368	0.995(0.985 – 1.005)
blood PH	0.894	0.342(0.0 – 2549294)
HCO3 (meq/L)	0.026*	1.157(1.017 – 1.317)
Anion gap	0.676	1.024(0.915 – 1.146)
Serum creatinine (mg/dL)	0.006*	30.241(2.685 – 340.640)
eGFR (ml/min/1.73m^2)	0.013*	0.778(0.639 – 0.949)
BUN/creatinine ratio	0.520	0.991(0.965 – 1.018)
Serum uric acid (mg/dL)	0.022*	1.750(1.085 – 2.820)
Leucocytic count (cell/ mm^3)	0.445	0.936(0.788 – 1.110)
Urine output (mL/24 hours)	0.071	1.001(1.0 – 1.002)
Serum Na+ (mmol/L)	0.136	3.612(0.668 – 19.522)
Serum K+ (mmol/L)	0.054	2.555(0.983 – 6.643)
Serum albumin (gm/dl)	1.435	0.524(0.472 – 4.359)

Discussion:

The pathogenic mechanism of DKA can induce multiple metabolic disruptions which have an impact on AKI either separately or combined, of which the effect of hyperglycemia, acidosis, ketosis effect, sodium, and other electrolyte disturbances, and volume depletion. (Chen, et al, 2020).

Age in the current study is a predictor of AKI, owing to the effect of comorbidities which have a higher incidence in old age, especially in the need for additional procedures, drugs, and interventions, in addition to the normal physiological drop in the anatomical and functional capacity of both kidneys. (Coca, 2010)

Co-morbidities such as recent stroke and COPD were positively correlated with AKI in our results. stroke can affect renal function through brain-kidney interaction mechanisms including the effect of disrupted central autonomic neurons, noxious activation of hypothalamic neurons

with the production of injurious renal neurotransmitters and hormones, activation of Renin angiotensin aldosterone system following stroke, the interaction between ADH and their receptors, impairment of autoregulation of renal blood flow, and the role of inflammatory and immune responses with the production of inflammatory mediators such as IL-6, IL-1β, and TNF-α, and CRP (Zhao, et.al., 2020). This result goes with a Meta-analysis study conducted to analyze the association between stroke and the risk of AKI and the influence of AKI on the prognosis of stroke. (Huang, et al 2020)

The correlation of COPD with AKI is demonstrated by the state of CO2 retention which deteriorates acidosis through disabling the respiratory buffers. Also, the effect of hypoxia and hypercapnia in decreasing renal blood flow. A similar result was declared by Wan et. al. study that demonstrated also poor short-term outcomes in such patients (Wan, et. al.,2020)

Glycemic control in our study shows a correlation with the development of AKI. Many previous studies support this point suggesting that improving glycemic control may reduce the risk of AKI. (Xu, et.al., 2020).

In the current study, Urinary NGAL on admission was shown to be associated with the development of AKI during the in-hospital follow-up period (p-value 0.00109). The validity of uNGAL was discussed as a predictor in several studied issues such as during sepsis (wang, et.al., 2014), in DKA children as a predictor of diabetic kidney disease (Elsharkawy, et. al,2019) (Hebbar et.al, 2016) (Yürük Yıldırım, et.al, 2015). However, only one previous study as far as we know discusses the predictive role of uNGAL for AKI in children with DKA (Williams et.al, 2021).

The estimated GFR in the current study showed a significant negative correlation with AKI (using the MDRD formula) which supports the result by Lippi & Guidi which suggests using the MDRD-estimated GFR as a criterion for diagnosing and staging AKI. (Lippi & Guidi, 2008). Another study by Candela-Toha et.al. concurs with this point and demonstrated the predictive ability of estimated GFR using the MDRD formula in the detection of AKI following cardiac surgery (Candela-Toha et.al., 2018)

A negative correlation was found between serum HCO3 on admission and the development of AKI, which reflects the effect of the degree of acidosis and severity of DKA and the development of AKI. A similar result was published by George, et. al. during the Correlation between the outcomes and severity of DKA. (George, et. al., 2018)

Serum Uric acid analysis revealed a highly significant positive association with AKI (p-value 0.00136). Several mechanisms may be interplayed to demonstrate the role of hyperuricemia on AKI. Hyperuricemia exerts proinflammatory & antiangiogenic effects with decreasing in nitric oxide levels and impairment of renal microvasculature and autoregulatory mechanisms. In addition, crystal-induced tubulopathy is another mechanism contributing to AKI in the setting of hyperuricemia. **(Hahn et.al.,2017)**

A similar study **by Park, et.al**, found that hyperuricemia is independently associated with an increased risk of in-hospital mortality and AKI in patients treated with PCI. The study investigated 1247 patients who had percutaneous coronary intervention (PCI), the study found the association of AKI with clinical, biochemical, and procedural variables within 7 days of PCI. **(Park, et.al., 2011)**

Analysis of factors associated with mortality, only blood glucose level was correlated. A study by Sato et al used a Japanese national inpatient database to study risk factors associated with inpatient mortality in DKA patients. The study identified 25,627 DKA patients and 839 (3.3%) in-hospital deaths. Obesity, sepsis, type 2 diabetes, and higher Charlson comorbidity index (≥4) are associated with a highly significant correlation with AKI, plus other factors such as; age, male sex, conscious activity, and sedentary life (Sato, et. al., 2021). Another study by George et.al. found that the ADA classification of the severity of DKA correlates well with the duration of in-hospital stay, costs of care, requirement of ICU care, and mortality. (George et.al. 2018)

Conclusion and recommendation

Age, comorbidities (e.g., recent stroke), urinary neutrophilic gelatinous lipocalin, glycemic control, the degree of acidosis, estimated glomerular filtration rate, and uric acid were significantly correlated with acute kidney injury, while higher blood glucose was associated with higher mortality. Close observation of risk factors associated with AKI in DKA permits early intervention and prevents progression to poor outcome

Limitations

Our study had several limitations. First, the sample size was small and was from a single medical unit. Second, the severity of co-morbidities in the studied group wasn't evaluated for their association with AKI. Finally, a longer period of follow-up was difficult to be applied. Also, Urinary NGAL was assessed at a single point in time due to financial obstacles.

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