International Journal of Health Sciences and Research
Vol.10; Issue: 9; September 2020
Website: www.ijhsr.org
Original Research Article *ISSN: 2249-9571*

The Incidence of Diabetic Ketoacidosis and Its Relationship with Residential Areas of Adults with Type 1 Diabetes in Nigeria

Collins Amadi[1], Olufisayo G. Ayoade[1], Sarah I. Essien[2], Aniete A. Etuk[3], Chidozie J. Okafor[3], Enobong N. Udoh[4], Ofonmbuk O. Umoh[4]

[1]Consultant Chemical Pathologist, Department of Chemical Pathology, University of Uyo Teaching Hospital, Nigeria
[2]Lecturer 11, Department of Chemical Pathology, University of Uyo, Nigeria
[3]Senior Registrar, Department of Chemical Pathology, University of Uyo Teaching Hospital, Nigeria
[4]Registrar, Department of Chemical Pathology, University of Uyo Teaching Hospital, Nigeria

Corresponding Author: Collins Amadi

ABSTRACT

Objectives: Area of residence impacts diabetic ketoacidosis (DKA) incidence in Sub-Sahara Africa, however, this is yet to be validated. Hence, this study explored the impact of area of residence on DKA incidence among adult Nigerians with type 1 diabetes (TIDM).
Methods: This survey was conducted retrospectively using medical records of adults (≥18 years) presenting with new-onset T1DM complicated with DKA at the Emergency Unit of the University of Uyo Teaching Hospital (UUTH) in Nigeria over 5 years. All relevant socio-demographic, clinical, and biochemical data at the point of TIDM diagnosis complicated with DKA were retrieved and analyzed based on urban-rural differences using standard protocols.
Results: 155 TIDM presented at the Emergency Unit of which 145(93.6%) were complicated with DKA. The mean age at DKA diagnosis was 32.68±5.91 years (range 23-46) with male preponderance (n=74;51%;p=0.049). Of those with DKA, the urban-dwellers predominated (n=82;56.6%) with female preponderance, were relatively younger, and had a higher rate of the most likely DKA trigger - infection. The urban-dwellers also had a higher frequency of polyuria (p<0.001), lower systolic blood pressure, higher plasma glucose, potassium, and creatinine, worse grades/risk of DKA-defined hyperglycemia (HR:1.202;p=0.004), metabolic acidosis (HR:1.242;p=0.0017), ketonuria (HR:1.102; p<0.001) and a greater likelihood of DKA episode (OR:2.288;p=0.007) following adjustment for confounders.
Conclusion: DKA at TIDM diagnosis was highly prevalent in the studied region and was associated with a greater likelihood to occur among adults in urban areas. Hence, health-targeted policies are highly recommended.

Key Words: Diabetes; Adult-onset Type 1 diabetes mellitus; diabetic ketoacidosis

INTRODUCTION

Unlike the type 2 diabetes mellitus (T2DM) and other types of diabetes mellitus (DM), type 1 DM (T1DM) is an endocrine-metabolic disorder associated with absolute endogenous insulin deficiency. [1,2] It arises from autoimmune-mediated destruction of insulin-secreting pancreatic beta cells (1A) or due to idiopathic destruction/failure of the beta cells (1B). [1,2] Though TIDM is mostly reported among children and during adolescence, recent research evidence is indicative of adults constituting a significant proportion (85%) of those with the metabolic disorder. [3,4]

Diabetic ketoacidosis (DKA) is a lethal complication of T1DM which could also occur in T2M in extreme scenarios. [5]

It is a frequent emergency sequela of TIDM with profound morbidity and mortality potentials, usually characterized by a triad of hyperglycemia, metabolic acidosis, and ketosis precipitated by several stressful factors. [5-7] Most cases of T1DM, especially in the developing countries, present at diagnosis with DKA complications, which have been adduced to poor recognition of T1DM symptoms among TIDM subjects and the prevailing weak health care systems in the developing countries. [8]

Epidemiologic data indicate that area of residence (urban-rural) is a significant factor in new-onset DKA at primary TIDM diagnosis which may reflect socio-demographic and socio-economic differences. [9] However, the urban-rural difference of new-onset DKA among adults at primary T1DM diagnosis remains poorly characterized within the developing countries. [10]

Hence, the current study sought to describe the clinical and biochemical characteristics of new-onset DKA at primary TIDM diagnosis, among adults of Nigerian origin, and to compare these characteristics based on their area of residence.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective, cross-sectional, descriptive hospital-based survey of clinical and biochemical features of DKA at diagnosis of adult-onset T1DM over 5 years (1st January 2014 to 31st December 2018) at the University of Uyo Teaching Hospital (UUTH). UUTH is a tertiary-level hospital located in Akwa Ibom State, South-south region of Nigeria.

Ethical Considerations

The study was approved by the Institutional Research Ethics Committee with reference number 2019-287. Informed consent was not deemed necessary from patients due to the retrospective nature of the study using anonymized patients' data and the lack of inclusion of any patient identifiers.

Study Instruments

The study instrument was hospital data, obtained from the Department of Health Information Services, of all the eligible adult-onset TIDM, presenting at diagnosis.

Eligibility Criteria

Criteria for inclusion were medical records, at TIDM diagnosis, of non-pregnant adults (18 years and older) presenting at the Emergency Unit of UUTH during the 5 years. Records with incomplete data, age < 18 years old, pregnant women, and those diagnosed before 2014 and after 2018 were excluded.

Data Acquisition

Following the review of all medical cases attended to during 2014-2018, sorting out the total DM cases, and identifying all the TIDM cases diagnosed during 2014-2018, the following data at the point of T1DM diagnosis were retrieved from each of the T1DM medical files: mode of presentation, age, gender, area of residence determined using the urban percentage, marital, educational, and occupational status, family history of DM, cigarette consumption, and alcohol intake history, presenting features, comorbidities (likely precipitant), weight, height, calculated body mass index (BMI), plasma glucose in mmol/l, sodium (Na^+) in mmol/l (Normal 135-145), potassium (K^+) in mmol/l (Normal 3.5-5.5), chloride (Cl^-) in mmol/l (Normal 96-106), bicarbonate (HCO_3) in mmol/l (Normal 22-28), urea in mmol/l (Normal 3.3-6.6), creatinine (Cr) in µmol/l (Normal 60-110 male; 45-90 female), and urinalysis findings (glucose, ketones, proteins, nitrite, blood, PH, specific gravidity). Data template with columns under the mentioned key variable headings was designed and utilized for data acquisition from each cohort.

Laboratory Protocols

During the study period, all laboratory protocols had been undertaken using standard guidelines. Plasma glucose was determined using the glucose oxidase method with standard reagents (Randox

Laboratories, London, United Kingdom. Plasma sodium, potassium, chloride, and bicarbonate were determined using Ion-Selective Electrode (ISE) method. Plasma urea was determined using Diacetyl Monoxime colorimetric method while plasma creatinine was determined using Jaffe Kinetic Method. Precision during laboratory analysis was monitored using at least 2 levels of commercial quality control samples (Randox Laboratories, London, United Kingdom). Ketones in urine (ketonuria) were determined qualitatively using standard dipstick (Medi-Test, Macherey Nagel, Germany).

Laboratory Diagnosis

A. TIDM diagnosis using the World Health Organization guidelines. [11]

B. DKA was diagnosed using the American Diabetes Association (ADA) criteria (plasma glucose ≥ 13.9 mmol/l, significant ketonuria ≥ 1+, metabolic acidosis with bicarbonate ≤ 18 mmol/l) in the presence of the classic DKA features. [12]

Operational Definitions and Stratifications

A. T1DM cases were defined based on meeting the following characteristics:

1. Diagnosed in UUTH during the 2014-2018 period by the specialist endocrinologist.
2. Persistent usage of insulin therapy for at least a year following T1DM diagnosis.
3. Responsive to insulin therapy for TIDM for at least a year following T1DM diagnosis.
4. Nil history of being on oral hypoglycemic agents.

B. An adult was defined as any subject ≥18 years of age.

C. Heart rate in beats/minute (bpm) was stratified as normal (60-100 bpm), tachycardia (>100 bpm), and bradycardia (<60 bpm if not a trained athlete or <40 bpm if a trained athlete).

D. Respiratory rate in cycles/minute (cpm) was stratified as normal (12-20 cpm), tachypnoea (>20 cpm), and bradypnoea (<12 cpm).

E. Blood pressure in mmHg was stratified based on the Joint Nation Committee on the prevention, detection, evaluation, and treatment of high blood pressure in adults (JNC) 7th edition. [13]

Hypotension was defined as blood pressure <90/60 mmHg or calculated mean arterial blood pressure <65 mmHg. [14]

D. Plasma Na^+ was corrected for hyperglycemia using the formula: [15]

$$\text{Corrected } Na^+ = \text{Measured } Na^+ \text{ (mmol/l)} + \frac{1.6 \times \text{plasma glucose (mmol/l)} - 5.6}{5.6}$$

E. Plasma Cl^- was corrected for changes in extracellular fluid content by using the formula:

Corrected chloride = Measured Cl^- x 140/plasma Na^+.

F. Effective plasma osmolality (EPO) in mOsmol/kg was calculated using the formula:

Calculated EPO = 2 (Na^+) + Glucose (concentrations in mmol/l). [12]

G. Anion Gap (AG) was calculated using the following formula:

$AG = Na^+ - HCO_3 + Cl^-$ (concentrations in mmol/l). [12]

H. Normonatrenia was defined, based on institutional reference interval. as corrected plasma Na^+ level of 135-145,then hypernatremia defined as correctedNa+ level >145 while hyponatremia was defined as corrected Na^+ level <135.

I. Normochloremia was defined, based on institutional reference interval, as corrected Cl^- level 96-106, then hyperchloremia was defined as plasma Cl^- <96 mmol/l while hypochloremia was defined as plasma Cl^- >106 mmol/l.

I. Chloride/Sodium ratio was calculated from the value of corrected plasma chloride divided by the value of the corrected plasma sodium.

I. Normokalemia was defined, based on institutional reference interval, as K^+ level 3.5-5.5, then hyperkalemia defined as plasma K^+ level > 5.5, while hypokalemia was defined plasma K^+ level < 3.5 mmol/l.

J. HCO_3 deficit, used as an index/surrogate marker of metabolic acidosis in the present

study, was defined as mild (15-18), moderate (10 – 15 mmol/l) or severe (< 10 mmol/l). [12]

K. Ketonuria was graded as mild (1+), moderate (2+), or severe (3+).

Data Management and Statistical analysis

Retrieved data were managed and analyzed using Statistical Package for Social Sciences software version 21 (IBM Corp., Armonk, NY, United States of America). The subjects were categorized based on urban and rural areas of residence before analysis.

The non-categorical variables were summarized using means and standard deviations; comparisons between two groups conducted using Student's t-tests.

The categorical variables are summarized using frequencies (count) and relative frequencies (percentage); between-group comparisons were performed using chi-squared tests with Yate's continuity correction applied when the expected frequency is between 5 and 10 or using Fisher's exact test when the expected frequency is less than 5.

Binary logistic and Cox proportional hazards regression models were employed to explore the association (strength of association ascertained using odd and hazard ratios) between outcome and explanatory variables at 95% confidence intervals. Two-tailed $p<0.05$ were considered statistically significant.

RESULTS

Between 2014 and 2018, 362 cases of T1DM were diagnosed in the study center of which 155 (42.8%) presented in the emergency unit while 207 (57.2%) presented through the clinics. Of the 155 new adult-onset TIDM cases who presented in the emergency unit, 145 (93.6%) presented with DKA. Among the total 145 cases who presented with DKA complications, 82 (56.6%) were from the urban center while 63 (43.4%) were from the rural center without a statistically significant difference ($p = 0.115$).

In table 1, the mean age of the overall cohort was 32.68 ± 5.91, range 23-46 years. No age difference was deduced based on the area of residence ($p = 0.173$). However, the urban-dwellers (mean: 32.10 ± 6.12; range: 23-41) were relatively younger than the rural-dwellers (mean: 33.46 ± 5.68; range: 24-46). The cohorts within the age group 30-39 years dominated among the overall (n=66; 45.5%), the urban (n=41; 50%) and rural-dwellers (n=25; 39.7%) with significant difference based on the area of residence (p=0.002) (Table 1). The majority (n=74; 51.0%) of the overall study cohorts were males (Table 1). Females predominated among the urban-dwellers (n=46; 64.8%) while the males predominated among the rural-dwellers (n=38; 51.4%) with significant difference (Table 1).

Depicted in Table 1, most (n=78; 53.8%) of the overall cohorts had attained tertiary educational status at the time of presentation with urban-dwellers predominating (p=0.001). While the urban-dwellers were mostly of tertiary educational class (n=61; 74.4%), the rural-dwellers were mostly of secondary educational class (n=40; 63.5%), with a significant difference based on the area of residence (p=0.035). The majority of the cohorts (overall, urban, and rural-dwellers) were traders with rural-dwellers predominating (0.035) and they were mostly in a marital union at presentation with a non-significant difference based on the area of residence (Table 1).

Family history of DM was documented among 24.1% (n=35), 22.0% (n=18), and 27.0% (n=17) of the overall, urban, and rural dwellers respectively, with a non-significant difference based on the area of residence (Table 1).Most of the urban-dwellers (n=14; 17.1%) were present alcohol consumers while most of the rural-dwellers (n=3; 4.8%) attested to be present-smokers at DKA diagnosis, without significant difference (Table 1).

Table 1: Socio-demographics of DKA subjects and subgroups at DKA diagnosis

Variables	Overall cohorts, n=145	Urban, n=82	Rural, n=63	p-value Urban vs Rural
1. Age at onset, years				
M ± SD	32.68 ± 5.91	32.10 ± 6.12	33.46 ± 5.68	0.173
Range	23 – 46	23 - 41	24 – 46	
2. Age-groups, n%				0.002*
18-29	50 (34.5)	33 (40.2)	17 (27.0)	
30-39	**66 (45.5)**	**41 (50.0)**	**25 (39.7)**	
40-49	29 (20.0)	8 (9.8)	21 (33.3)	
>50	0(0)	0(0)	0(0)	
3. Gender				0.049*
Male	**74 (51.0)**	36 (48.6)	**38 (51.4)**	
Female	71 (49.0)	**46 (64.8)**	25 (35.2)	
4. Level of Education				0.001*
Primary	6 (4.1)	1 (1.2)	4 (7.9)	
Secondary	59 (40.7)	19 (23.2)	40 (63.5)	
Tertiary	**78 (53.8)**	**61 (74.4)**	**17 (27.0)**	
No formal education	3 (1.4)	1 (1.2)	1 (1.6)	
5. Cadre of Occupation				0.035*
Civil servant	28 (19.3)	11 (13.4)	17 (27.0)	
Public servant	14 (9.7)	9 (11.0)	5 (7.9)	
Business	10 (6.9)	10 (12.2)	0 (0)	
Traders	**62 (42.8)**	**32 (39.0)**	**30 (47.6)**	
Retired	5 (3.4)	4 (4.9)	1 (1.6)	
Student	24 (16.6)	15 (18.3)	9 (14.3)	
Others‡	2 (1.4)	1 (1.2)	1 (1.6)	
6. Marital union				0.813
Married	**85 (58.6)**	**47 (57.3)**	**38 (60.3)**	
Never married	55 (37.8)	32 (39.0)	23 (36.5)	
Bereaved	4 (2.8)	2 (2.4)	2 (3.2)	
Separated	1 (0.7)	1 (1.2)	0 (0)	
7. Family history of DM				0.108
Yes	**35 (24.1)**	**18 (22.0)**	**17 (27.0)**	
No	76 (52.4)	49 (59.8)	27 (42.9)	
MD	34 (23.4)	15 (18.2)	19 (30.2)	
8. Alcohol intake history				0.099
Never	101 (69.7)	52 (63.4)	49 (77.8)	
Past	26 (17.9)	16 (19.5)	10 (15.9)	
Present (Active)	18 (12.4)	**14 (17.1)**	4 (6.9)	
9. Cigarette consumption				0.395
Never	133 (91.7)	77 (93.9)	56 (88.9)	
Past	8 (5.5)	4 (4.9)	4 (6.3)	
Present (Active)	4 (2.8)	1 (1.2)	**3 (4.8)**	

*Statistically significant; DM: Diabetes mellitus; N/A: Missing data; ‡Daily laborer, mechanic.

Shown in Table 2, polyuria was significantly reported mostly by the urban residents ($p<0.001$). Infection (n=117; 80.7%) was the most likely trigger of DKA among the overall study cohorts with the urban-dwellers predominating (n=70; 85.4%) though without statistical significance ($p=0.104$). The urban-dwellers had lower SBP, higher plasma glucose, plasma potassium, and plasma creatinine ($p<0.05$) (Table 2).

In Table 3, no difference was deduced in all the stratified clinical and biochemical disorders among the urban and rural-dwellers ($p>0.05$). However, all the study cohorts presented with tachycardia (n=145; 100%) and tachypnea (n=145; 100%) at diagnosis (Table 3). The urban-dwellers had higher frequencies of fever, hypertension, hypotension, hyponatremia, hypochloremia, hyperkalemia, severe metabolic acidosis, and severe (3+) ketonuria while the rural-dwellers had higher frequencies of hypothermia, pre-hypertension, hypernatremia, hypokalemia, mild-moderate metabolic acidosis and moderate (2+) ketonuria (Table 3).

In Table 4, the urban-dwellers were also at increased risk of developing all the DKA-defined biochemical features (hyperglycemia, metabolic acidosis, ketonuria) compared with the rural dwellers following Cox proportional regression analyses with non-significant significance.

Though statistically non-significant, the urban-dwellers were more likely to

develop DKA at TIDM diagnosis (OR: 1.057; 95% CI: 0.694 – 1.609; p=0.796) compared to rural-dwellers on non-adjusted binary logistic regression analyses (Table 5; Model 1).

However, while adjusting for various confounders, the likelihood of DKA episode at TIDM diagnosis occurring among the urban-dwellers was amplified (OR: 2.288; 95% CI: 1.283 – 4.824; p=0.007) with statistical significance (Table 5; Model 2).

Table 2: Descriptive analysis of the clinical/laboratory variables among DKA subjects and subgroups at DKA diagnosis

Variables	Overall cohorts, n=145	Urban, n=83	Rural, n=63	p-value Urban vs Rural
A. Presenting features, n (%)				
Polyuria	**124 (85.5)**	**78 (94.0)**	**46 (73.0)**	**<0.001***
Polydipsia	104 (71.7)	59 (72.0)	45 (71.4)	0.945
Polyphagia	**95 (65.5)**	**48 (58.5)**	**47 (74.6)**	**0.060**
Weight loss	94 (64.8)	54 (65.9)	40 (63.5)	0.768
Generalized weakness	**115 (79.3)**	**70 (85.4)**	**45 (71.4)**	**0.054**
Fever	88 (60.7)	53 (64.6)	35 (55.6)	0.267
Nausea/vomiting	**137 (94.5)**	**77 (92.7)**	**58 (92.1)**	**0.263**
Abdominal pain	80 (55.2)	50 (61.0)	30 (47.6)	0.109
Altered sensorium	106 (73.1)	61 (74.4)	45 (71.4)	0.690
B. Likely Triggers, n (%)				
Acute Infection‡	**117 (80.7)**	**70 (85.4)**	**47 (74.7)**	**0.104**
Malaria	11 (7.6)	6 (7.3)	5 (7.9)	0.889
Alcohol excess	29 (20.0)	16 (19.5)	13 (20.6)	0.867
Trauma	7 (4.8)	6 (6.1)	2 (3.2)	0.699
Indeterminate	22 (15.2)	11 (13.4)	11 (17.5)	0.414
C. Vital signs, M ± SD				
SBP (mmHg)	**118.86 ± 8.64**	**116.84 ± 4.46**	**120.43 ± 7.25**	**0.028***
DBP (mmHg)	77.50 ± 7.58	78.63 ± 3.45	76.03 ± 7.29	0.141
Temperature (^{o}C)	37.45 ± 1.11	37.55 ± 1.10	37.32 ± 1.21	0.800
Heart rate/minute	113.26 ± 5.23	113.35 ± 5.12	113.14 ± 5.40	0.850
Respiratory rate/minute	27.12 ± 3.10	27.10 ± 3.14	27.16 ± 3.02	0.565
D. Laboratory variables, M ± SD				
Plasma glucose (mmol/l)	**21.80 ± 4.93**	**23.06 ± 5.26**	**21.45 ± 4.45**	**0.034***
Corrected plasma sodium (mmol/l)	136.33 ± 5.74	136.14 ± 5.13	136.23 ± 6.48	0.145
Plasma potassium (mmol/l)	**5.10 ± 1.02**	**5.25 ± 0.75**	**4.98 ± 0.99**	**0.017***
Plasma bicarbonate (mmol/l)	11.60 ± 1.80	11.70 ± 1.70	11.46 ± 1.80	0.698
Corrected plasma chloride (mmol/l)	91.11 ± 3.42	91.45 ± 3.13	91.41 ± 3.80	0.168
Plasma urea (mmol/)	19.52 ± 1.24	19.45 ± 1.20	18.87 ± 1.13	0.406
Plasma creatinine (µmol/l)	**86.40 ± 7.90**	**90.33 ± 0.87**	**81.28 ± 6.80**	**0.035***
Chloride/Sodium ratio	0.67 ± 1.58	0.67 ± 2.11	0.67 ± 1.89	0.417
Plasma osmolality (mOsm/kg)	292.82 ± 5.56	292.97 ± 5.26	291.11 ± 5.95	0.164
Anion gap	20.22 ± 1.85	20.41 ± 1.90	20.43 ± 1.81	0.715
E. Anthropometry				
Weight, kg	66.49 ± 6.41	66.41 ± 7.01	66.60 ± 8.60	0.914
Height, m	1.66 ± 0.06	1.66 ± 0.04	1.65 ± 0.02	0.180
BMI, kg/m^2	24.14 ± 3.97	23.75 ± 2.73	24.66 ± 4.24	0.672

*Statistically significant; DM: Diabetes mellitus; NA: Not applicable; SBP: systolic blood pressure; DBP: Diastolic blood pressure; mmHg; millimeter mercury; mmol/l; millimol per liter; µmol/l; micromol per liter; M: Mean; SD: Standard deviation; kg: Kilogram; m: Meters; BMI: Body mass index; ‡Pneumonia, gastroenteritis, urinary tract infection, sepsis, cellulitis, pharyngitis, acute otitis media.

Table 3: Clinical/biochemical stratifications of study variables among DKA subjects and subgroups at DKA diagnosis

Variables	Overall cohorts, n=145	Urban, n=83	Rural, n=63	p-value Urban vs Rural
Body temperature, n (%)				0.304
Normothermia	59 (40.7)	29 (35.4)	30 (47.6)	
Fever	82 (56.6)	**51 (62.2)**	31 (49.2)	
Hypothermia	4 (2.8)	2 (2.4)	**2 (3.2)**	
Heart rate, n (%)				NA
Normocardia	0 (0)	0 (0)	0 (0)	
Tachycardia	**145 (100)**	**82 (100)**	**63 (100)**	
Bradycardia	0 (0)	0 (0)	0 (0)	
Respiratory rate, n (%)				NA
Normopnoea	0 (0)	0 (0)	0 (0)	
Tachypnoea	**145 (100)**	**82 (100)**	**63 (100)**	
Bradypnoea	0 (0)	0 (0)	0 (0)	

Blood pressure, n (%)				0.509
Normotensive	99 (68.3)	53 (64.6)	46 (73.0)	
Pre-hypertensive	2 (2.1)	1 (1.2)	**2 (3.2)**	
Hypertensive	40 (27.6)	**26 (31.7)**	14 (22.2)	
Hypotensive	3 (2.1)	**2 (2.4)**	1 (1.6)	
Dysnatremia, n (%)				0.163
Normonatremia	72 (49.7)	37 (45.1)	35 (55.6)	
Hypernatremia	9 (6.2)	4 (4.9)	**5 (7.9)**	
Hyponatremia	64 (44.1)	**41 (50.0)**	23 (36.5)	
Dyschloremia, n (%)				0.925
Normochloremia	35 (24.1)	20 (24.4)	15 (23.8)	
Hyperchloremia	0 (0)	0 (0)	0 (0)	
Hypochloremia	110 (75.9)	**62 (75.6)**	48 (76.2)	
Dyskalemia, n (%)				0.118
Normokalemia	77 (53.1)	45 (54.9)	32 (50.8)	
Hyperkalemia	59 (40.7)	**35 (42.7)**	24 (38.1)	
Hypokalemia	9 (6.2)	2 (2.4)	**7 (11.1)**	
HCO_3^-deficit (MA), n (%)				<0.001*
Mild MA	0 (0)	0 (0)	0 (0)	
Moderate MA	67 (46.2)	23 (28.0)	**44 (69.8)**	
Severe MA	78 (53.8)	**59 (72.0)**	19 (30.2)	
Ketonuria grades, n (%)				<0.001*
1+ (Mild)	0 (0)	0 (0)	0 (0)	
2+ (moderate)	61 (42.1)	6 (7.3)	**55 (87.3)**	
3+ (Severe)	84 (57.9)	**76 (92.7)**	8 (12.7)	

*Statistically significant; NA: Not applicable;HCO_3^-: Bicarbonate; MA: Metabolic acidosis

Table 4: Hazard ratios of DKA-defined biochemical triads based on the area of residence

Biochemical Features	HR	95% CI	p-value
1.Hyperglycemia ≥13.9 mmol/l			
Rural	Reference		
Urban	**1.302**	**0.361 – 2.692**	**0.004***
2. Ketonuria ≥ 2+			
Rural	Reference		
Urban	**1.242**	**0.719 – 2.146**	**0.016***
3. MA (HCO_3^- ≤ 18 mmol/l)			
Rural	Reference		
Urban	**1.103**	**0.775 – 1.571**	**<0.001***

*Statistically significant; HR: Hazard ratio; CI: Confidence interval; MA: Metabolic acidosis; HCO_3^-: Bicarbonate; mmol/l: millimole per liter;

Table 5: Likelihood of DKA episode at TIDM diagnosis based on the area of residence

Model 1	OR	95% CI	p value
Rural	Reference		
Urban	1.057	0.694 – 1.609	0.096
2. Model 2**			
Rural	Reference		
Urban	**2.488**	**1.283 – 4.824**	**0.007***

*Statistically significant; OR: Odd ratio; CI: Confidence interval; Model 1: Crude; Model 2: Adjusted for age, gender, BMI, educational status, cadre of occupation, marital union, family history of DM, active smoking and alcohol consumption.
**Thirty-four participants with missing data for DM family history were excluded from the analysis in model 1

DISCUSSION

We had retrospectively evaluated the impact of an area of residence (urban-rural difference) on the incidence of DKA at diagnosis of adult-onset (≥18 years) TIDM among residents of Uyo in Nigeria presenting at the Emergency Unit of the University of Uyo Teaching Hospital over five years (2014-2018).

In the present series, 93.6% of the TIDM subjects visiting the emergency unit had a DKA diagnosis. Our rate is higher than the frequencies documented in Ethiopia (28.8%), South Africa (60.95%), United Arab Emirates (58%), Mexico (21.1%), and previously in Nigeria (41.6%). [7,16-19] Similarly, two recent studies from the United States reported 38% and 70.6% frequencies respectively. [20,21] Additionally, our rate remained higher than the 12.8-80% documented among children presenting with DKA at TIDM diagnosis. [22] However, in a similar previous Nigerianstudy limited by its small sample size, Edo and colleagues reported 90% (9 incident DKA of 10 adult-onset TIDM; 9/10) frequency among their studied subjects which compares, but still lower, to our reported rate. [23] Hence, our findings indicate a high frequency of DKA among the studied population.

The urban residents predominated among those presenting with DKA, though without difference compared to rural residents; however, they had a greater likelihood of DKA incidence following the adjusted regression model. Our finding conforms to a report documented by Bedazo and colleagues who also observed increased

odd of DKA incidence among urban residents compared with the rural residents, though without statistical significance. [7] Similar preponderance of urban residents has also been reported in Iranian. [24] However, this contrasts with similar studies from South Africa, Australia/New Zealand, and Iraq. [9,16,25,26] These observed variations may be adduced to racial, geographic, and socio-demographic differences.

The predominance of urban-dwellers may be indicative of the enhanced exposition to various sociocultural (higher current alcohol consumption rate observed) and environmental factors linked to TIDM incidence with subsequent DKA evolution. [27]

The urban residents were mostly females, presented at a younger age, and were mostly tertiary-level educated at the time of TIDM with concurrent DKA diagnosis. These three demographic characteristics have been reported in association with DKA and could probably explain the preponderance of the urban residents in the current study. [10,18,28] First, besides their greater predisposition to autoimmune disorders, the female preponderance may also reflect the global gender-based pattern of TIDM wherein regions of low incidence (Africa) exhibit female predominance while regions of high incidence (Europe) exhibit male predominance. [28-30] Secondly, the diagnosis of DKA at a younger age may indicate poor recognition of symptoms and poor health-seeking behaviors which could trigger DKA episodes. [18,28] Thirdly, tertiary-level educated individuals are likely to increase once awareness of health status and enhance recognition of clinical features of TIDM and possibly DKA, thereby prompting early presentation for emergency medical care. [18]

Infection was the most likely DKA trigger among our study cohorts which conforms with global findings and its presence in DKA has been linked to the worst clinical outcome. [31] Consistent with our findings, Nazneen and colleagues had previously documented similar findings in Bangladesh. [32] The urban residents had the highest frequency of infection rate in the present series. The reason for this high infection rate is very unclear. However, this could be related to the higher glycemic status observed among the urban residents compared to the rural residents. Studies have shown that higher glycemic status depresses immune responses with attendant higher infection rates among diabetics. [33] The higher frequency of infection could also explain the high fever rate documented among the urban residents.

Polyuria was common among the urban residents while all study cohorts presented with tachycardia and tachypnea, which are all common clinical features previously, reported in association with DKA episodes. [7,34] Polyuria, attributed to osmotic diuresis induced by glycosuria, is usually attributed to hyperglycemia and has been linked with very poor glycemic status. [34] Though we did not describe the organ-specific infections which were likely triggers of DKA in the current study due to limited data, polyuria could also indicate concomitant urinary tract infection which is common among adult subjects, especially females, presenting with DKA at TIDM diagnosis. [33] Tachycardia and tachypnea, unsurprisingly observed among all of our study cohorts, are both usual cardio-respiratory clinical signs that characterize DKA severity. [35]

The urban-dwellers also had lower SBP, higher glycemic status, plasma potassium, and creatinine levels including severe grades and increased risk of the biochemical triads of DKA. These findings are reported to the define worst prognostic features of DKA. [36-40] High glycemic status at DKA diagnosis has been linked to further exacerbation of beta-cell loss in TIDM. [36,37] Indian DKA subjects with lower SBP were reported to exhibit poorer outcomes compared to those with higher SBP. [38] Studies have shown that lower admission PH and hyperkalemia are both associated with longer hospital stay and mortality among TIDM subjects presenting in DKA.

[31] Rising creatinine levels have been linked to poor renal perfusion with increased risk of renal injury among T1DM subjects presenting in DKA. [39] The severity of ketonuria indicates the degree of disturbances in ketone metabolism, occasioned by low insulin levels and concomitant increased levels of the counter-regulatory hormones, inherent in DKA cascade. [40]

The study was limited by some factors that must be interpreted in the context of these factors. First, as a cross-sectional study, its findings do not allow for conclusions of causal relationships but associations. Secondly, it is a single-center hospital-based study, whose findings may not reflect the general population in the studied region.

Thirdly, none of the autoimmune biomarkers, which are characteristic of TIDM, were taking into account to define the TIDM subjects in the current study owing to lack of data. Lastly, due to limited resources, the study was not designed to ascertain, through follow-up, the clinical outcome of the studied subjects.

CONCLUSION

This study demonstrated that a significant number of adult-onset T1DM subjects presenting for management in the study center were complicated with DKA. The majority of those diagnosed with DKA at presentation were mostly urban residents. Compared to the rural residents, the urban residents had higher frequencies of the severe metabolic features of DKA, were more at increased risk of all the DKA-defined biochemical triads, and were more likely to present with DKA. Hence, the findings obtained from the current study should inform health-targeted intervention and public health policies towards the management of DKA and its associated complications.

Funding:
The study was self-funded by all the authors.

Acknowledgment:
The authors extend special gratitude to all staff of the Department of Chemical Pathology, UUTH who assisted in form or the other during the conduct of this study.

Conflict of Interest:
Authors had no conflicts of interest to warrant declaration.

REFERENCES

1. Puchulu FM. Definition, Diagnosis and Classification of Diabetes Mellitus. In: Cohen Sabban EN, Puchulu FM., Cusi K, Eds. Dermatology and Diabetes: Cham, Switzerland: Springer International Publishing; 2018. pp. 7–18.
2. Petersmann A, Nauck M, Müller-Wieland D, Kerner W, Müller UA, Landgraf R, et al. Definition, classification and diagnosis of diabetes mellitus. Exp Clin Endocrinol Diabetes 2018; 126: 406-10.
3. Diaz-Valencia PA, Bougnères P, Valleron AJ. Global epidemiology of type 1 diabetes in young adults and adults: a systematic review. BMC Public Health 2015; 15:255. DOI: 10.1186/s12889-015-1591-y
4. Rogers MA, Kim C, Banerjee T, Lee JM. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. BMC Medicine 2017;15:199. DOI: 10.1186/s12916-017-0958-6.
5. Hadgu, FB, Sibhat, GG, Gebretsadik LG. Diabetic ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes in Tigray, Ethiopia: a retrospective observational study. Ped Health Med Therapy. 2019;10; 49–55.
6. Nasir MB, Mushtaq J, Abass A, Nabitayyab GU, Haq I. A Retrospective Study to Evaluate Precipitating Factors, Outcome and Importance of Health Education in Diabetic Ketoacidosis. Pak J Med Health Sci 2017;11: 1426-9.
7. Bedaso A, Oltaye Z, Geja E, Ayalew M. Diabetic ketoacidosis among adult patients with diabetes mellitus admitted to emergency unit of Hawassa university comprehensive specialized hospital. BMC Research Notes 2019;12:137. DOI: 10.1186/s13104-019-4186-3.
8. Jawaid A, Sohaila A, Mohammad N, Rabbani U. Frequency, clinical characteristics, biochemical findings and outcomes of DKA at the onset of type-1 DM

in young children and adolescents living in a developing country–an experience from a pediatric emergency department. J Ped Endocrinol Metab 2019;32:115-9.
9. Al-Obaidi AH, Alidrisi HA, Mansour AA. Precipitating Factors for Diabetic Ketoacidosis among Patients with Type 1 Diabetes Mellitus: The Effect of Socioeconomic Status. Int J Diabetes Metab 2019;25:52-60.
10. Farsani SF, Brodovicz K, Soleymanlou N, Marquard J, Wissinger E, Maiese BA. Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review. BMJ Open 2017;7: e016587.
11. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic Medicine. 1998; 15:539-53.
12. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes care 2006;29:2739-48.
13. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 2003; 289: 2560-71.
14. Kennelly S, Collins O. Walking the cognitive "minefield" between high and low blood pressure. J Alzheimers Dis. 2012; 32:609–21.
15. Katz MA. Hyperglycemia-induced hyponatremia: calculation of the expected serum sodium depression. N Engl J Med. 1973;289:843–44.
16. Ndebele NF, Naidoo M. The management of diabetic ketoacidosis at a rural regional hospital in KwaZulu-Natal. Afri J Prim Health Care Fam Med. 2018;10:1-6.
17. Abbas S, Nazir Z, Azhar T, Alhaj A, Hafidh K. Clinical profiles and precipitating factors for diabetic ketoacidosis at a tertiary center in Dubai, United Arab Emirates. J Diabetes Endocrinol Pract 2019;2:1-3.
18. Doubova SV, Ferreira-Hermosillo A, Pérez-Cuevas R, Barsoe C, Gryzbowski-Gainza E, Valencia JE. Socio-demographic and clinical characteristics of type 1 diabetes patients associated with emergency room visits and hospitalizations in Mexico. BMC Health Ser Res 2018;18:602.DOI: 10.1186/s12913-018-3412-3.
19. Iloh GU, Amadi AN. Epidemiology of Diabetic Emergencies in the Adult Emergency Department of a Tertiary Hospital in South-Eastern Nigeria. Int J Trop DiseaseHealth2018; 30: 1-10.
20. Pasquel FJ, Tsegka K, Wang H, Cardona S, Galindo RJ, Fayfman M, et al. Clinical outcomes in patients with isolated or combined diabetic ketoacidosis and hyperosmolar hyperglycemic state: a retrospective, hospital-based cohort study. Diabetes Care 2020;43:349-57.
21. Benoit SR, Hora I, Pasquel FJ, Gregg EW, Albright AL, Imperatore G. Trends in Emergency Department Visits and Inpatient Admissions for Hyperglycemic Crises in Adults With Diabetes, United States 2006-2015. Diabetes Care 2020; dc192449. doi.org/10.2337/dc19-2449.
22. Usher-Smith JA, Thompson M, Ercole A, Walter FM. Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review. Diabetologia 2012;55:2878-94.
23. Edo AE. Clinical profile and outcomes of adult patients with hyperglycemic emergencies managed at a tertiary care hospital in Nigeria. Niger Med J 2012;53: 121-5.
24. Razavi Z, Hamidi F. Diabetic Ketoacidosis: Demographic Data, Clinical Profile and Outcome in a Tertiary Care Hospital. Iran J Pediatr 2017;27:e7649. DOI: 10.5812/ijp.7649.
25. Venkatesh B, Pilcher D, Prins J, Bellomo R, Morgan TJ, Bailey M. Incidence and outcome of adults with diabetic ketoacidosis admitted to ICUs in Australia and New Zealand. Crit Care 2015;19:451. doi.org/10.1186/s13054-015-1171-7
26. Mansour AA, Abdu-Alla MA. Predictors of Diabetic Ketoacidosis among Patients with Type 1 Diabetes Mellitus Seen in the Emergency Unit. J Adv Med Med Res 2016;10:1-12.

27. Cheema A, Adeloye D, Sidhu S, Sridhar D, Chan KY. Urbanization and prevalence of type 2 diabetes in Southern Asia: A systematic analysis. J Global Health 2014;4: doi: 10.7189/jogh.04.010404.
28. Everett E, Mathioudakis NN. Association of socioeconomic status and DKA readmission in adults with type 1 diabetes: analysis of the US National Readmission Database. BMJ Open Diabetes Res Care 2019;7: doi: 10.1136/bmjdrc-2018-000621.
29. Maahs DM, West NA, Lawrence JM, Mayer-Dams EJ. Epidemiology of Type 1 diabetes. Endocrinol Metab Clin North Am 2010;39:481 – 97.
30. Desai MK, Brinton RD. Autoimmune disease in women: endocrine transition and risk across the lifespan. Front Endocrinol 2019;10:doi: 10.3389/fendo.2019.00265.
31. Lee MH, Calder GL, Santamaria JD, MacIsaac RJ. Diabetic ketoacidosis in adult patients: an audit of factors influencing time to normalization of metabolic parameters. Int Med J 2018;48:529-34.
32. Nazneen S, Ahmed F, Ashrafuzzaman SM, Uddin KN, Ahsan AA, Faruq MO, et al. Clinical Presentation and Biochemical Abnormalities in Patients Presented with Diabetic Ketoacidosis in BIRDEM Hospital. Bangladesh Crit Care J 2017;5:7-10.
33. Abegaz TM, Mekonnen GA, Gebreyohannes EA, Gelaye KA. Treatment Outcome of Diabetic Ketoacidosis Among Patients Attending General Hospital in North-West Ethiopia: Hospital-Based Study. BioRxiv 2018:441964.
34. Pawar SD, Thakur P, Radhe BK, Jadhav H, Behere V, Pagar V. The accuracy of polyuria, polydipsia, polyphagia, and Indian Diabetes Risk Score in adults screened for diabetes mellitus type-II. Med J DY Patil Univ 2017;10:263-7.
35. Fayfman M, Pasquel FJ, Umpierrez GE. Management of hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. Med Clin North Am 2017;101:587-60.
36. Duca LM, Wang B, Rewers M, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes predicts poor long-term glycemic control. Diabetes Care. 2017;40:1249-55.
37. Atkinson MA, Bluestone JA, Eisenbarth GS, Hebrok M, Herold KC, Accili D, et al. How does type 1 diabetes develop?: the notion of homicide or β-cell suicide revisited. Diabetes 2011;60:1370-9.
38. Agarwal A, Yadav A, Gutch M, Consul S, Kumar S, Prakash V, et al. Prognostic factors in patients hospitalized with Diabetic Ketoacidosis. Endocrinol Metab 2016; 31:424-32.
39. Westerberg DP. Diabetic ketoacidosis: evaluation and treatment. Am Fam Physician 2013;87:337-46.
40. Nyenwe EA, Kitabchi AE. The evolution of diabetic ketoacidosis: an update of its etiology, pathogenesis and management. Metabolism 2016;65:507-21.

How to cite this article: Amadi C, Ayoade OG, Essien SI et.al. The incidence of diabetic ketoacidosis and its relationship with residential areas of adults with type 1 diabetes in Nigeria. Int J Health Sci Res. 2020; 10(9):15-25.

******