A SURGE OF TYPE 1 DIABETES MELLITUS AMONG NIGERIAN CHILDREN DURING THE COVID-19 PANDEMIC

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ABSTRACT

Background: **A substantial increase in Type 1 Diabetes Mellitus (T1DM) has been reported globally among children following the discovery of COVID-19. This study reports a similar trend among Nigerian children.**

Method: **A twelve-year (2010-2021) retrospective review of T1DM cases admitted in the Paediatric wing of a tertiary hospital in South-East Nigeria.**

Result: **During the twelve-year study, 21 T1DM patients were seen: 9 (43%) males and 12 (57%) females. Approximately 60% of these cases presented during the pandemic (2020-2021). The mean age of subjects with T1DM was 10.5 ± 4.1 years, with females being slightly older than the male subjects (11.6 ± 3.7 years vs 9.2 ± 4.3 years respectively; p=0.176). Prior to the pandemic, females were significantly older than males (11.6 ± 3.7 years vs 4.5 ± 2.1 years respectively; p=0.042), but no age difference was observed during the pandemic (11.6 ± 4.1 years vs 10.4 ± 3.9 years respectively; p=0.597). 80% of all males in this study were seen during the pandemic and were older than the males seen before the pandemic (10.4 ± 3.9 years vs 4.5 ± 2.1 years; p=0.078). Following adjustments for age and gender, older children and males had an increased odd of developing T1DM during the pandemic but this was not statistically significant.**

Conclusion: **This study highlights the need for increased awareness and high index of suspicion of T1DM among children during this pandemic. In the interim, more robust multi-centre studies are required to investigate the underlying relationship between COVID-19 and T1DM.**

Keywords: Type 1 Diabetes Mellitus, Covid-19, Pandemic, Coronavirus, Glucose metabolism, Insulin resistance, SARS-CoV-2

INTRODUCTION

In late 2019, a novel virus termed SARS-CoV-2 or simply "COVID-19" emerged in China. Although its origin remains largely unknown, the virus has left in its wake a devastating impact on human life and global economy.[1,2] To date, the ripple effects of this virus are still clearly evident with global recovery progressing slowly due to several factors which include ongoing viral mutation and waning vaccine efficacy; side effects of existing therapies; uncontrolled media misinformation, poor political will; mass resistance to vaccinations and failure to adopt behavioural changes that mitigates viral transmission.[3-8]

As the world struggles to contain the global spread of the virus and its associated co-morbidities, several reports have emerged indicating a rise in pre-existing chronic disease rates, particularly among the immune-compromised and elderly.[9,10] The most recent article supporting this trend was published on January 7th 2022 by the Center for Disease Control and Prevention (CDC). It demonstrated that individuals under the age of 18 with a history of contracting COVID-19 for more than a month were more likely to develop T1DM than those without the viral disease.[13]

Initially, anecdotal evidence attributed this alarming link between T1DM and COVID-19 to a variety of factors, including the effect of pandemic-induced stress on the chronic release of counter-regulatory hormones, late presentation of cases, and delayed diagnosis due to inadequate insurance and out-of-pocket payment. However, the recent discovery of elevated angiotensin-converting enzyme 2 receptors (the primary binding site for COVID-19) in pancreatic tissue substantiated the hypothesis of extensive damage to pancreatic beta cells exacerbating the risk of early-

onset T1DM, particularly in genetically susceptible individuals.[17] Additionally, since children are generally exempt from receiving the COVID-19 vaccine due to the negligible risk of developing severe disease, this may provide another plausible explanation for the increasing prevalence of COVID-19-related late-onset co-morbidities, including T1DM.

Observing a similar trend in the increase of T1DM cases among children at our institution during this ongoing pandemic, we hope to contribute to the growing body of knowledge and, most importantly, raise awareness of a possible COVID-19 diabetogenic effect (both direct and indirect) among children, with particular emphasis on the demographic profile of subjects at risk.

METHODOLOGY

Study Design: A twelve-year retrospective review of all cases of T1DM among children that presented in Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, Anambra State, South-East Nigeria from January 2010 to November 2021.

Study Centre: The study was carried out in Nnamdi Azikiwe University Teaching Hospital, Nnewi. This tertiary hospital has a 450 bed capacity with one paediatric and four adult endocrinologists. As the only tertiary health institution in Anambra state, it serves as a referral centre for various institutions in Anambra and neighbouring States such as Delta, Imo, Abia and Enugu States. The hospital has a very robust and well-equipped paediatric clinics and emergency centre with highly trained specialists who cater to the health care needs of children.

For the purpose of this study, health care records of patients managed for T1DM from January 2010 to November 2021 were retrieved from the nurses' and unit registers to collate data on variables of interest such as year of presentation, age, gender and diagnosis. Hospital folders of patients who were admitted between 2017 and 2021 were retrieved to obtain the pattern of clinical presentation, incidence of diabetic ketoacidosis and blood glucose concentration on admission. For each patient, clinical diagnosis was made following careful clinical assessment and appropriate laboratory investigations.

Statistical Analysis: Statistical analysis was done using the Statistical Package for the Social Sciences version 22 (IBM Corp., Armonk, NY, USA) and R statistical programming for graphical representation of data.[11] Categorical data were expressed as frequencies and percentages, while continuous data were presented as mean and standard deviations. Student's t-test was applied to compare means between continuous variables with normally distributed data. Box plots and bar charts were used for the graphical representation of quantitative and factorised categorical variables. Logistic regression analysis was employed to determine the odds and confidence intervals of associated factors before and during the pandemic. The significance level was determined as $p < 0.05$.

RESULT

A total of 21 T1DM cases were seen between January 2010 and November 2021, comprising of 9 (43%) males and 12 (57%) females with a male to female ratio of 0.8:1. Over half (55%) of these cases were seen during the pandemic (2020-2021) (Figure 1). The mean age of all subjects with T1DM was 10.5 ± 4.1 years with a range of 3 to 17 years. Female subjects were slightly older than the males (11.58 ± 3.7 years vs 9.2 ± 4.3 years respectively; p=0.176).

During the 12-year study period, a total of 11,680 paediatric cases were seen with a T1DM prevalence rate of 1.8/1000 persons. Prior to the pandemic (2010-2019), the calculated prevalence rate of T1DM was 0.9/1000 persons. This increased approximately eight-fold to 6.96/1000 persons following the emergence of COVID-19 in Nigeria.

No differences were observed in the pattern of presentation, diabetic ketoacidosis or glucose

Table 1: Demographic distribution of all subjects

		Total	Male	Female	*p*
Overall Subjects	n (%)	21	9 (43)	12 (57)	0.176
	Age in years (SD)		9.2 ± 4.3	11.6 ± 3.7	
Pre-Pandemic	n (%)	9	2 (22)	7 (78)	0.042
	Age in years (SD)		4.5 ±2.1	11.6 ± 3.7	
Post-Pandemic	n (%)	12	7 (58)	5 (42)	0.597
	Age in years (SD)		10.4 ± 3.9	11.6 ± 4.1	

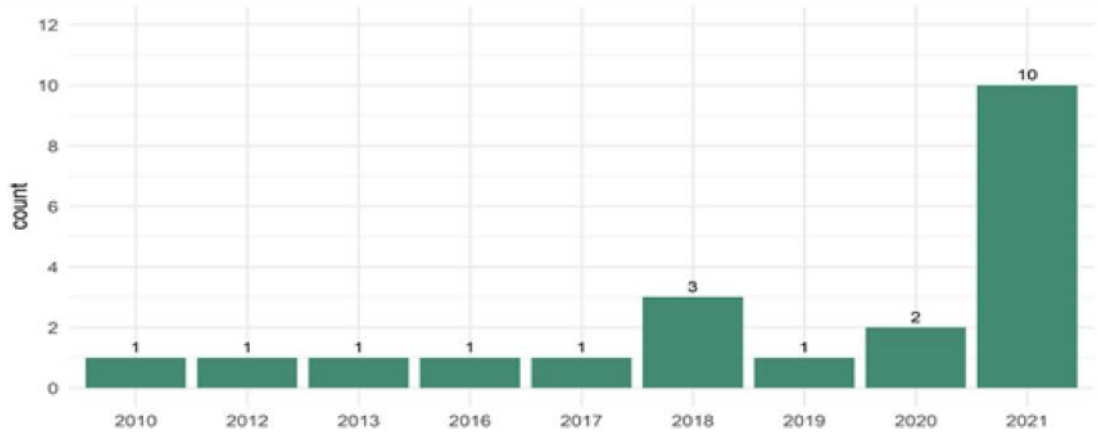

Figure 1: Distribution of TIDM cases from January 2010 to November 2021

concentration among patients who presented before and during the pandemic.

Gender

In the pre-COVID era, approximately 80% of subjects with T1DM were females. This distribution pattern changed during the pandemic as almost two-thirds of subjects who presented with T1DMwere observed to be males (Figure 2). In all, 80% of male subjects seen within the study period presented during the pandemic. Following adjustments for age and gender, males had an increased odds of developing T1DM during the pandemic compared to the pre-pandemic era (9.657 CI: 0.960-97.143; p-value = 0.054) (Table 2).

Table 2: Logistic regression analysis on factors associated with T1DM comparing events before and during the pandemic

	Univariate Logistic Regression Analysis			
		95 CI for β		
	B	**Lower**	**Upper**	**p-Value**
Age	1.056	0.850	1.311	0.624
Gender	5.600	0.814	38.512	0.080
	Multivariate Logistic Regression Analysis			
		95 CI for β		
	B	**Lower**	**Upper**	**p-Value**
Age	1.178	0.894	1.551	0.245
Gender	9.657	0.960	97.143	0.054

CI: Confidence Interval

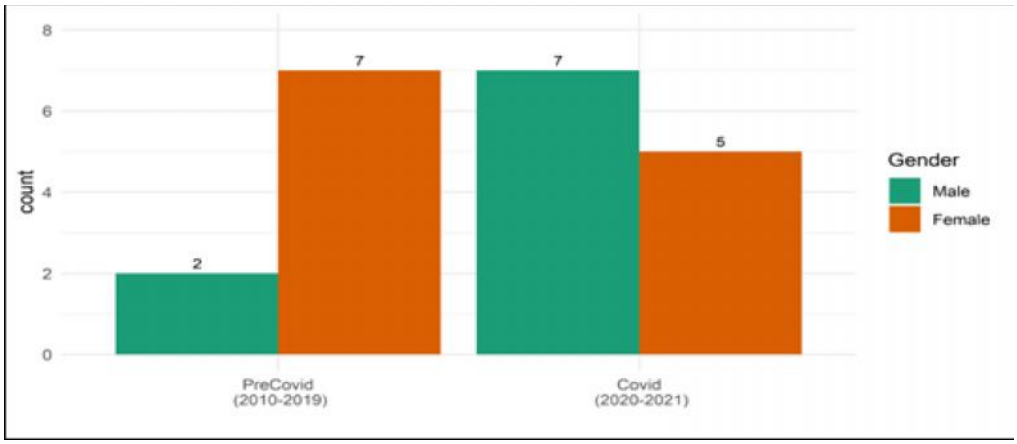

Figure 2: Gender Distribution of T1DM before and during the COVID-19 Pandemic

Age

Prior to the pandemic, female subjects were significantly older than males (11.6 ± 3.7 years vs 4.5 ± 2.1 years respectively; p=0.042) (Table 1 and Figure 2). This age distribution changed during the pandemic as no differences in age was observed across both gender (Table 1). Male subjects seen during the pandemic were observed to be considerably older than males seen before the pandemic (10.4 ± 3.9 years vs 4.5 ± 2.1 years; p=0.078). However, in females, the ages remained essentially the same between both time frames (11.6 ± 3.7 years vs 11.6 ± 4.1 years; p = 0.990). Following adjustments for both age and gender, increasing age was associated with an increased odds of developing T1DM during the pandemic, but this was not statistically significant (1.178 CI: 0.894-1.551 p-value = 0.245) (Table 2).

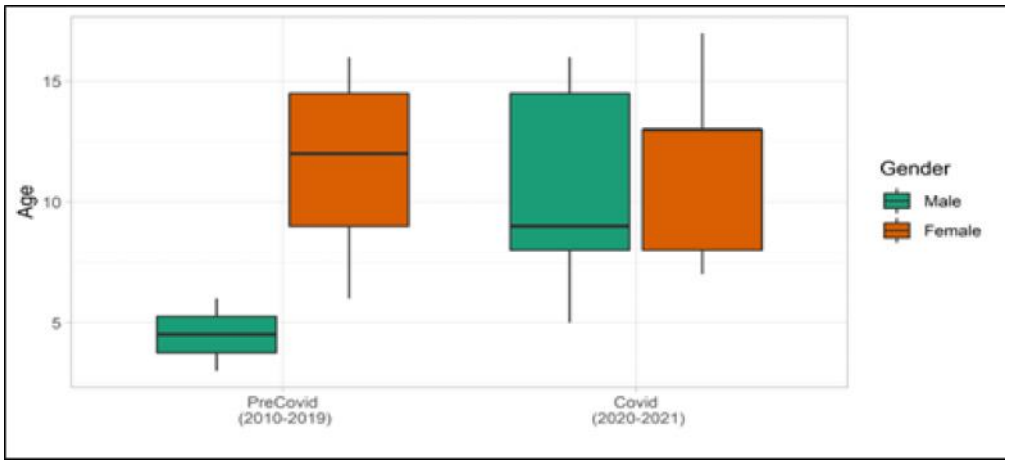

Figure 3: Age Distribution of T1DM cases across gender before and during the COVID-19 pandemic

DISCUSSION

The association between viruses and T1DM is not new. Prior to the emergence of COVID-19, T1DM had been linked to several viral infections, particularly respiratory viruses and enteroviruses.[18,19] During this pandemic, several centres across the world have reported a remarkable increase in the incidence of T1DM among children, which quite recently was affirmed by CDC.[11-16] In Africa, this is the first report to indicate a similar phenomenon in children. In our institution, before the emergence of COVID-19, T1DM cases were relatively rare, as shown in Figure 1. Following the outbreak of the virus in Nigeria, we observed an 80% increase in new cases of T1DM compared to the preceding two years and an approximately 60% increase (1.3-fold) compared to the past decade. These values far exceed the estimated global annual incidence rate of T1DM and past reports of hospital prevalence rates across several centres in Nigeria.[20-25] Although there were few cases of T1DM reported in the year 2020, this may be attributed to the national lockdown of major activities, hospitals and school visits, with better adherence to strict hygiene and social distancing. We believe that these measures presumably minimized to a large extent the spread of the virus thus protecting against the early evolution of T1DM in susceptible individuals. Regrettably, these precautionary measures were not sustained in the year 2021.

Several theories exist on the possible underlying mechanism between T1DM and COVID-19. The most consistent entails the discovery of a marked tissue concentration of COVID-19 sensitive receptors in the pancreas, which potentially leads to extensive damage of the organ, thus accelerating the natural evolution of T1DM, particularly among vulnerable children with pre-diabetes and a family history of diabetes mellitus.[17] Other existing theories allude to COVID-19 being a potential stressor that fosters a diabetogenic state characterised by insulin resistance and hyperglycaemia in susceptible subjects. We believe that since children are generally exempted from being vaccinated against COVID-19 due to the associated mild morbidity, it may increase the risk of this sub-population in developing certain co-morbidities that may be associated with the virus, inclusive of T1DM. This hypothesis is also consistent with the fact that there are very few reports of a similar marked trend among the adult population who may be protected against the long-term effects of the virus because of their immunisation status.[26]

Although no gender predilection exists in T1DM, a significant proportion of the subjects who presented with T1DM before the pandemic were females which corresponds to the general belief that females suffer

more from auto-immune related diseases. This gender-based distribution dramatically changed during the pandemic, with approximately 80% of all male subjects in the twelve-year study period presenting within this time frame. Although the reason for this change is not readily apparent, we believe that it may be consistent with existing reports among adults which demonstrated an increased prevalence of COVID-19related morbidities in males compared to females, a phenomenon which is also obtainable in children.[27-29] More so, a study recently demonstrated that COVID-19 may decrease blood adiponectin concentrations in affected patients.[30] Adiponectin is a novel hormone consistently proven to be an excellent insulin sensitizer. In children, this hormone is naturally lower in males compared to females due to the inhibitory effect of testosterone on adiponectin.[31-33] An earlier exposure to COVID-19 might have decreased the baseline adiponectin concentration of the males in this study, thus promoting an insulin-resistant state that predisposes this gender to develop diabetes. This hypothesis needs to be further explored in future works.

Age appeared to be a relatively crucial factor in the evolution of T1DM during the pandemic, especially among males. Male subjects that presented with T1DM during the pandemic were considerably older than the males seen before the pandemic (Figure 2). During peri-pubertal and pubertal stages of development, physiological changes such as the rise in gonadal steroid mediated growth hormone-insulin growth factor 1(GH-IGF-1) and an increase in adipose tissue trigger insulin resistance. Additionally, the physiological drop in adiponectin which occurs as the male child ages may have been worsened by an earlier exposure to COVID-19.[33] These factors in consonance with the presumed direct hit effect of the virus on insulin secretion may explain to a reasonable degree why older males appear to be more affected with T1DM during the pandemic. Although a majority of the subjects who presented with T1DM in our institution had diabetic ketoacidosis, there were no differences observed in the clinical presentation or glycaemic status of patients that presented prior to and during the pandemic. This is inconsistent with a number of published works that demonstrated a poorer clinical course among children with T1DM seen during the pandemic.[34-36]

This study has several limitations especially the relatively small number of affected subjects. Notwithstanding that there was no formal testing for the antigenic response to COVID-19 nor of its antibodies which is indicative of an earlier exposure, it does not preclude the possibility of a plausible link between the virus and this metabolic disease. None of our subjects had presented with symptoms suggestive of COVID-19, thus did not meet the national practise guideline for free viral testing. In addition, no available infrastructure exists for the assay for COVID-19 antibody titres. Despite these limitations, we feel strongly that the sudden increase in T1DM cases, particularly in the year 2021, is clearly suggestive of a probable link between T1DM and SARS-Cov-2, especially given the relative rarity of the disease in our centre prior to the pandemic. Our observations are also consistent with similar reports across the globe, which substantiates a possible diabetogenic effect of COVID-19 among children.

Addressing these growing concerns globally and particularly in resource-constrained regions such as Nigeria begins with the periodic screening of children at risk of T1DM, such as children with a positive family history of T1DM and a prior history of pre-diabetes. These vulnerable children should be followed up and efforts made to maintain a normal body mass index through enhanced physical activity and adoption of healthy dietary choices. In resource-rich nations, periodic screening of all children aged ten years and above should be adopted with special attention to male adolescents for timely detection of new cases.

CONCLUSION

This study adds to the growing body of evidence indicative of a possible link between COVID-19 and T1DM among adolescents. There is an imperative need for multi-centre studies to further establish the evolution of this disease and its probable link with COVID-19. In the interim, we advocate for a revision of the existing national COVID-19 clinical practising guidelines to incorporate cases of pre-existing diseases suspected to be linked to the virus for free viral testing, which can only improve the veracity of published works emanating from the resource-constrained region.

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Authors' Contributions

This work was carried out in collaboration among all authors. Authors CAN and TOU conceptualized and designed the research, Authors CAN, KNO, EIN, STE, NVA and ITO collected the data. Author CAN analysed the data, Authors CAN and KNO interpreted the data. Author CAN drafted the initial manuscript. All authors read and approved the final manuscript.

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The authors declare no financial support for this study and no conflicts of interest.

Data Availability
The dataset generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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