



Secondary Failure of Oral Hypoglycaemic Agents Among Type Two Diabetes Mellitus Patients Attending a Tertiary Health Facility in Northern Nigeria

Muazu, Salisu Babura^{1*}, Okpe Innocent Onoja¹, Anumah Felicia² and Bakari Adamu Girei¹

¹Department of Medicine, Ahmadu Bello University/ABUTH, Zaria, Kaduna state, Nigeria

²Department of Medicine, University of Abuja/University of Abuja Teaching Hospital, Abuja, Nigeria

*Corresponding author: Muazu Salisu Babura, Department of Medicine, Endocrine unit, Ahmadu Bello University/ABUTH, Zaria, Kaduna state, Nigeria, Tel: +2348034503116, Email: mbsalisu1@yahoo.com

Abstract

Background: Secondary oral hypoglycaemic agent (OHA) failure is one of the many challenges of diabetes management, the consequence of which is poor diabetes control and early development of chronic complications. Prospective studies on secondary OHA failure have not been done in Nigeria.

The aim of this study was to determine the prevalence and risk factors associated with development of secondary failure of OHA among T2DM subjects.

Methods: A cross sectional study of 200 hundred consecutive T2DM patients was studied over a 12 months period. Parameters studied included age, sex, BMI, WC, c-peptide, glucose and lipids profiles and GADA. The prevalence of OHA failure was determined using simple percentage and risk factors were determined by comparing the clinical and laboratory parameters between subjects with and without OHA failure. The relative risk and predictors of OHA failure were estimated by calculating the odds ratio (O.R) and logistic regression.

Results: The mean (SD) age of the subjects was 52.5(9.7) years. The prevalence rate of secondary OHA failure was 36% (72/200) with a female preponderance 46 (63.9%); males were 26 (36.1%), $P > 0.05$. The means (SD) of BMI 22.9 (5.4) kg/m², WC 87.7 (11.3) cm and c-peptide 0.84 (0.05) were lower in subjects with OHA failure than those without OHA failure. $P < 0.05$. The mean (SD) 2hr PPG [14.5 (3.7) mmol/L] and HbA1c [8.3 (1.42)%] of those with OHA failure were higher than in those without OHA failure. $p < 0.05$. The mean (SD) TC, LDL-C and TG in subjects with OHA failure were lower than in subjects without OHA failure, $p > 0.05$. The prevalence of anti-GAD positivity in those with OHA failure was 30.5%.

Conclusion: It is concluded, in this study, that the prevalence of secondary OHA failure among T2DM patients was found to be 36%. It appeared commoner in females and associated with lean subjects, longer duration of diabetes with β -cell dysfunction and GAD positive.

Keywords

Type two diabetes, Prevalence, Secondary failure, GADA, Nigeria

Introduction

Diabetes Mellitus is a metabolic disease arising from absolute deficiency of insulin secretion or a defect in the biologic secretion/effectiveness of insulin (or both) [1]. It is characterized by chronic hyperglycaemia and manifests with symptoms like polyuria, excessive thirst, weight loss and sometimes blurring of vision. It is associated with acute complications such as ketoacidosis, hyperosmolar state and hypoglycaemia, as well as long-term complications affecting the eyes, kidneys, feet, nerves, brain, heart and blood vessels [1,2].

Although medical nutrition therapy, education and exercise are fundamental to the management of type 2 two diabetes (T2DM) patients, majority of the patients will require pharmacologic agents to achieve acceptable blood glucose control [3]. The major challenges of pharmacologic management of T2DM are gradual and inevitable development of failure to response due to progressive loss of β -cell function, hypoglycaemia and weight gain.

A secondary failure to oral hypoglycaemic agent (OHA) is said to occur when a sulphonylurea (SU) and metformin (MET), in appropriate doses and diet, loses its capacity to produce a desired maximal therapeutic effect (FBG < 8.0 mmol/L or HbA1c $< 7.0\%$) after administration in the absence of other conditions causing hyperglycaemia [4-8].

The background insulin resistance coupled with the progressive loss of β -cell function, in T2DM patients, will lead to eventual failure of OHA to induce insulin secretion. In UKPDS-16&24 reports [9,10], it was shown that T2DM is a progressive disease involving gradual and continuous beta-cell destruction leading to insulin deficiency over six years from the time of diagnosis and failure of sulphonylurea therapy.

Mathews *et al.* [11] in another UKPDS-26 report, found that sulphonylurea failure is common among those patients with lower beta-cell functional reserve and the failure depends on the phenotype and type of therapeutic agent used. Festa *et al.* [12] in, Insulin Resistance Atherosclerosis Study, among African-Americans, Hispanics and Whites subjects reported similar decline of beta-cell function over 5.2 years after diagnosis. This shows that the natural

history of T2DM is that of gradual loss of beta-cell, irrespective of the ethnic background, and eminent failure of OHA therapy that will require insulin supplementation or replacement.

Host factors including genetics, chronic hyperglycaemia, lipotoxicity, amyloid deposition in the β -cells, GAD positive, low body mass index (BMI), duration of diabetes and type of OHA used are associated with secondary failure [8,13,14]. Davies *et al.* [15] in UKPDS-70 and Fukai *et al.* [16] in Japan, found positive association between the failure of sulphonylurea therapy with GAD positivity, leaner subjects and younger age group. These factors tend to worsen or accelerate the process of the background β -cell damage and hence the failure of OHA. At the time of diagnosis of T2DM more than 50% of β -cell function has been lost and it is a better predictor of secondary failure to OHA than any other factor [15,17].

The therapeutic efficacy of OHA varies between individuals and pharmacogenetics factors contribute to this variability. The polymorphism in the genes of IRS-1, CAP-10, E23K variants and PPAR γ -2 are involved in pancreatic β -cell dysfunction and a poor response to the action of SU [7,18,19]. In contrast to above, the disturbance of SU metabolism by a variant cytochrome enzyme, CYP2C, is associated with a better response to SU and decrease failure to therapy [20].

The type of oral hypoglycaemic agents used at the initial stage of management may also predict the development of secondary failure [21,22]. Harrower *et al.* [14] found in a study comparing the efficacy, secondary failure rate and complications of sulphonylureas that gliclazide is a potent agent with a low rate of secondary failure and a low incidence of side effects.

The difference in efficacy and secondary failure rate between sulphonylureas may be related to the mechanism of insulin release from the β -cell as exhibited by gliclazide.

The prevalence of Secondary failure to OHA among T2DM patients taking oral agents particularly late into the disease, in different populations, ranges from 30% to 60% over 5 years after initiation of therapy [6,9,17,18]. The consequences of poorly managed T2DM is early development of chronic complications and this poses a lot of management challenges especially in a poor resource setting countries. It is therefore pertinent, in the management of these patients, to identify those at risk of developing secondary failure to OHA, as early as possible, so as to institute a rational approach in their management to prevent these devastating chronic complications.

There is scanty data in Nigeria on OHA failure in T2DM patients. There has not been any study in Northern Nigeria. The aim of this study is to determine the prevalence, characteristics and risk factors for the development of secondary failure to OHA among T2DM patients in Northern Nigeria.

Methods

Study design

The study was a cross sectional, conducted among 200 T2DM patients attending the diabetes clinic of Ahmadu Bello University Teaching Hospital (ABUTH), Zaria Northern Nigeria. The study was approved by the ethics committee of the hospital and patient consent sought. The study lasted one year between December 2007 and January 2008.

Inclusion criteria were T2DM patient with initial response to OHA, age at onset of diabetes at 30 or more years, at least one year on daily 20 mg glibenclamide and 2 gm metformin. Patients on insulin, pregnant women, presence of systemic diseases or organ failure and use of drugs, especially steroids, were excluded.

Clinical procedure

The consecutive patients attending the diabetes clinic that satisfied the inclusion criteria and consented were administered questionnaires on first contact. The demographic data including age,

sex, age at onset, duration of diabetes, type of OHA and its dose used, history of hypertension or diabetes, family history of diabetes were recorded. Other information sought includes insulin usage, use of steroid drugs, alcohol and symptoms of systemic diseases that may cause hyperglycaemia.

All subjects had clinical examination including blood pressure which was taken in the sitting position in the dominant arm. The weight was measured to the nearest 0.5 kg and height in metres using stadiometer. BMI was calculated from weight and height [23]. Waist circumference (WC) was measured to the nearest centimeter at the midpoint between the lower most rib and the anterior superior iliac spine while hip circumference was measured at the level of greater trochanter. The patients were then asked to come for a next visit (2 weeks) after fasting for 8 hours.

Sample collection

On the second visit, a 10 mls of fasting venous blood was taken from all the subjects. The samples were immediately separated and the plasma samples analyzed for glucose, total cholesterol (TC), low density cholesterol (LDL), high density cholesterol (HDL), triglyceride (TG), HbA1c, c-peptide and anti-GAD antibody.

Glutamic acid decarboxylase antibody: The GAD-Ab estimation was done using kronus anti GAD ELISA kit (Boise, USA). It depends on the ability of GAD autoantibodies to act divalently and form a bridge between GAD coated on ELISA plate wells and liquid phase GAD biotin. The GAD-biotin bound is then quantitated by addition of streptavidin peroxidase and a colorogenic substrate Tetramethylbenzidine (TMB) with reading of final absorbance at wavelengths (450 nm and 405 nm) to obtain maximum measuring range (4-200 units per ml of WHO reference preparation). ≥ 5 units per ml is considered positive [24].

Fasting plasma glucose: Plasma glucose was estimated using glucose oxidase method.

Glycated Haemoglobin (HbA1c): The principle involved is micro-column method as a direct way of estimating HbA1c. After preparing the haemolysate where the labile fraction is eliminated, HbA1c is specifically eluted after washing away; the HbA1a+b fraction is quantified by direct photometric reading at 415 nm. HbA1c Quantitative kit (Agappe diagnostic India) was used [25].

Lipids: Total cholesterol was estimated through enzymatic method using the generated colour to show the amount of cholesterol in the sample. HDL was estimated after the precipitation of LDL and VLDL by polyanions in the presence of magnesium ion. Triglycerides in the sample was measured by the same spectrophotometry, while LDL-C was estimated using Friedwald's formula $LDL-C = TC - HDL + triglycerides/2.2$.

C-Peptide: C-peptide estimation was done using kronus ELISA kit (Boise, USA) reading was done at 450 nm with value $< 1.0 \mu/ml$ as considered low.

Statistical analysis: The data was analyzed using SPSS version 20 and it was presented as mean \pm standard deviation, student T-test was used to compare means while chi-square was used to compare nominal data. An odds ratio was used to determine the relative risk while logistic regression analysis was used to predict risk. $P < 0.05$ is significant.

Results

Characteristics of the study population

The study population comprised of 200 T2DM subjects. The mean (SD) age of the subjects was 53(9.2) years, range (34-75) and comprising 80(40%) males and 120(60%) females (Table 1).

Prevalence of secondary failure to OHA

Out of the 200 patients studied 72(36%) were found to have failure to OHA therapy (FBG > 8.0 mmol/L), figure 1, comprising 26(36.1%) males and 46(63.9%) females. Chi-square = 0.67 $p > 0.05$.

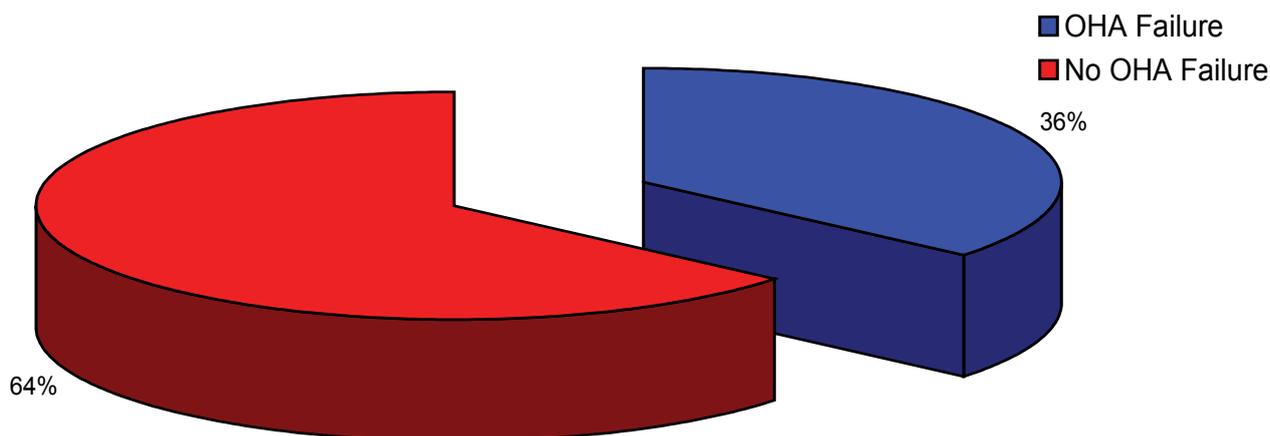


Figure 1: prevalence of OHA failure among the study population.

Table 1: Clinical characteristics of study subjects (T2DM).

Variable	Mean (SD)
Age (years)	53.23 (8.91)
AAD (years)	46.20 (9.03)
DOD (years)	6.95 (5.50)
BMI (kg/m ²)	26.7 (5.20)
WC (cm)	90.8 (10.31)
WHR-	0.92 (0.05)
DBP (mmHg)	89.4 (11.43)
SBP (mmHg)	143 (24.21)
HbA1c (%)	7.45(1.85)
TC (mmol/L)	5.9 (0.95)
LDL-c (mmol/L)	3.9 (1.02)
HDL-c (mmol/L)	0.72 (0.24)
TG (mmol/L)	1.05 (0.33)

M = Male, F = Female, SD= Standard deviation, DOD = Duration of diabetes, AAD= Age at diagnosis, BMI = Body mass/index (kg/m²), WC = Waist circumference (cm), WHR = Waist-hip-ratio, DBP = Diastolic blood pressure, SBP = Systolic blood pressure, TC = Total Cholesterol, LDL = Low density lipoprotein cholesterol, HDL-C = High density lipoprotein cholesterol, Tg = Triglycerides, HbA1c = Glycated haemoglobin A1c

Table 2: Educational level of the subjects with OHA failure and those without OHA failure.

Educational level	OHA failure	No OHA failure	χ^2 (p value)
None	40	70	0.015 (0.902)
Primary	14	22	1.22 (0.268)
Secondary	12	24	1.65 (0.193)
Post-secondary	6	12	7.28 (0.063)

OHA = Oral hypoglycaemic agent

In table 2, it was observed that 57.1% (40/72) subjects with OHA failure and 54.7% (70/128) subjects without OHA failure had no formal education. $\chi^2 = 0.015$ ($p > 0.05$).

Clinical characteristics of subjects with and without secondary OHA failure compared

Table 3, showed the mean ages and sex distribution were similar in the two groups. The patients with OHA failure were younger and had longer duration of diabetes, $p > 0.05$.

The study subjects with OHA failure had significant lower mean BMI and WC [22.9(5.4) kg/m², 87.7(11.3) cm], than those without OHA failure [27.2(4.8) kg/m², 93.5(10.0) cm], ($p < 0.05$).

The systolic and diastolic blood pressure is lower in those with secondary OHA failure than those without. ($p > 0.05$).

Laboratory parameters of subjects with and without secondary OHA failure compared

In table 4, showed FPG and 2 hours PPG of subjects with OHA

Table 3: Comparison of the Clinical characteristics of the subjects with OHA failure and those without OHA failure.

Variable	OHA failure	No OHA failure	(p value)
	Mean(SD)	Mean(SD)	
Age	52.5 (9.7)	53.8 (9.2)	-0.572
Sex- M	26 (36.1%)	54 (42.2%)	-0.225
- F	46 (63.9%)	74 (57.8%)	
AAD (yrs)	44.5 (9.8)	46.6(9.4)	-0.369
DOD (yrs)	8.0 (6.1)	7.2(5.5)	-0.595
BMI (kg/m ²)	22.9 (5.4)	27.2(4.8)	(0.039)*
WC (cm)	87.7 (11.26)	93.5 (10)	(0.037)*
WHR	0.90 (0.05)	0.94 (0.06)	-0.652
DBP (mmHg)	87.8 (11.7)	90.2 (8.8)	-0.324
SBP (mmHg)	138.2 (23.9)	148.8 (22.7)	-0.062

OHA = Oral hypoglycaemic agent, M = Male, F= Female, AAD= Age at diagnosis, DOD = Duration of diabetes WT = weights, BMI = Body mass index, WC = Waist Circumference, WHR = Waist hip ratio, DBP = Diastolic blood pressure, SBP = Systolic blood pressure,* = Significant p value

Table 4: Comparison of the laboratory characteristics of the subjects with OHA failure and those without OHA failure.

Variable	OHA failure	No OHA failure	(p-value)
	Mean(SD)	Mean(SD)	
FPG (mmol/L)	11.7 (2.6)	5.7 (1.5)	(0.000)*
2hrPPG (mmol/L)	14.5 (3.7)	11.1 (2.8)	(0.000)*
Tc (mmol/L)	4.98 (0.9)	5.12 (0.9)	-0.572
LDL-c (mmol/L)	3.8 (0.9)	4.1 (1.0)	-0.254
HDL-c (mmol/L)	0.74 (0.3)	0.69 (0.2)	-0.381
Tg (mmol/L)	0.95 (0.3)	1.1 (0.3)	-0.7
HbA1c (%)	8.3 (1.4)	7.0 (2.1)	(0.003)*
C-peptide	0.84 (0.05)	1.72 (0.43)	(0.002)*

OHA = Oral hypoglycaemic agent, FPG = Fasting plasma glucose, 2hrPPG = Two hours post prandial glucose, Tc = Total cholesterol, LDL-c = Low density lipoprotein cholesterol, HDL-c= High density lipoprotein cholesterol, Tg = Triglycerides, HbA1c = Glycated haemoglobin A1c, * = Significant p value

failure [11.7(2.6), 14.5(3.7) mmol/L] compared to subjects without OHA failure [5.7(1.5) and 11.1(2.8) mmol/L] respectively, $p < 0.05$.

The glycated haemoglobin level in those with OHA failure [8.3(1.4)] compared to those without OHA failure [7.0(2.0) $p < 0.05$]. The c-peptide is lower in those with OHA failure 0.84(0.05) vs. 1.72(0.93), $p < 0.05$.

The mean values of TC, LDL-c and TG in subjects with OHA failure were lower than in subjects without OHA failure. $p > 0.05$.

GAD autoantibody positivity among subjects with and without secondary OHA failure compared

The prevalence of glutamic acid decarboxylase autoantibody among the subjects with OHA failure and those without OHA failure were 22/72(30.5%) and 7/128(5.5%) respectively. $\chi^2 = 0.85$ ($p < 0.05$).

Table 5: Odds ratio estimates for risk factors of OHA failure among the study population.

Variable	Odd ratio (O.R)	Confidence Interval	(p-value)
Age	1.9	0.1-4.0	0.057
AAD	4.3	1.5-9.0	0.369
DOD	2.7	0.33-8.7	0.024*
BMI	1.7	0.35-5.3	0.039*
WC	3.9	1.45-4.90	0.037*
WHR	0.35	0.59-0.4	0.652
FPG	64.5	10.7-132	0.000*
2hrPPG	32.1	4.0-62.4	0.000*
TC	0.15	0.1-2-1	0.572
TG	2.9	0.1-5.2	0.016*
HBA1c	14.8	2.0-19.5	0.000*

AAD = Age at diagnosis, DOD = Duration of diabetes, WHR= waist hip ratio, WC = Waist circumference, BMI = body mass index FPG = Fasting plasma glucose, 2hrPPG = Two hours post prandial glucose, TC = Total cholesterol, TG = Triglycerides, HbA1c – Glycated haemoglobin A1c, * = Significant p value

Of the 22(30.5%) GAD positive in OHA failure there were 18 males and 4 females. Chi sq = 1.97, p < 0.05.

Risk factors estimate for secondary OHA failure among the study population

Table 5 depicts an odds ratio estimate, corresponding to relative risk estimation, of any of the variables of greater than 1.0 indicated an increased risk of developing OHA failure. The BMI, WC, FPG, 2hr PPG and HBA1c, GAD positivity, AAD, TG, DOD with odds ratio, greater than 1.0 were significantly found to be associated with OHA failure, p < 0.05.

A logistic regression analysis was done to ascertain the effects of the variables above on the likely hood that the subjects have failure of OHA. The logistic regression was statistically significant with Chi sq = 27.6, p < 0.05. The model explained 19% (Nagelkerke R² of the variance in secondary failure and correctly classified 67% of cases. The GAD positivity, less c-peptide and lean subjects correctly predicted secondary failure in this study.

Discussion

The prevalence of secondary OHA failure in this study population was 36%. This finding is lower than that of Mathews *et al.* [11] as documented in UKPDS 26 study, where he reported 48% failure rate in newly diagnosed T2DM, 6 years after initiation of sulphonylurea therapy. A lower percentage was reported by Donnan *et al.* [26] and Binerjee *et al.* [27] in their work among Caucasians and Indian migrants found the prevalence of OHA failure to be 10% and 15% respectively. The finding of a higher prevalence of OHA failure of 36% in this study could be due to genetic variability or the lower cut off value of FPG > 8.0 mmol/L used to define OHA failure as compared to Donnan *et al.* [26] and Binerjee *et al.* [27] who used FPG > 15.0 mmol/L and > 10.0 mmol/L respectively.

It was observed in this study that there were more female subjects with OHA failure. This may be due to a slight female preponderance in the diabetic population generally [1,2]. However Pantiroli *et al.* [8] in Italy and Donnan *et al.* [26] found more males among the Caucasians with OHA failure.

It was found that the β -cell functional reserve is compromised as evidence by the significant lower plasma c-peptide level. In UKPDS 26 study, Mathew *et al.* [11] showed in a model that gradual and continuous decline in β -cell function in T2DM patients results in the secondary failure of sulphonylureas. The rate of the failure is dependent on the phenotype at presentation and other intrinsic host factors or perhaps the agent used initially [14].

The prevalence of GAD antibody among the OHA failure subjects was 30.5%. Our result is in concordance with similar studies elsewhere. Aviles-Santa *et al.* [28] in the United States had earlier reported a 30% prevalence rate of GAD positivity among T2DM migrant Asians with OHA failure. Fukai *et al.* [16] in Japan, found a significant GAD

positive among those with failure of sulphonylurea therapy than in those without. Davies *et al.* [14] in UKPDS-70 reported positive association between the failure of sulphonylurea therapy with GAD positivity, leaner subjects and younger age group. This means that significant number of our T2DM patients with OHA failure could be having slowly developing T1DM or latent autoimmune diabetes in adults (LADA), hence a significant failure rate.

That 55.6% of the subjects with OHA failure and 54.7% of those without OHA failure had no formal education. Goudswaard *et al.* [29] in the Netherlands found lower educational level to affect OHA failure significantly. The reason why we did not observe any differences between the two groups may be due to smaller sample size in this study.

The mean duration of diabetes was higher and the subjects were younger among those with OHA failure than those without OHA failure Goudswaard *et al.* [29] in the Netherlands and Mathews *et al.* [11] among Caucasians have found that the duration of diabetes in subjects with OHA failure was significantly longer and were also younger than those without OHA failure. Our findings did not attain statistical significance perhaps because of the small sample size.

In this study it was found that the means of BMI and WC were significantly lower in those with OHA failure. Charlton *et al.* [30] in South Africa and Pontiroli *et al.* [8] in Italy found that lower BMI and WC were significantly associated with development of OHA failure. Davies *et al.* [14] in UKPDS-70 have shown that lean T2DM have less pancreatic reserve than obese T2DM subjects, this leads to reduced insulin release and early development of secondary OHA failure in lean T2DM subjects.

The subjects with OHA failure, in this study, had significant poor glycaemic control than those without OHA failure. Guillausseau *et al.* [31] in France found that post prandial hyperglycaemia is a consistent finding in those with OHA failure while Goudswaard *et al.* [29] in the Netherlands reported that fasting hyperglycaemia among T2DM patients, is an independent risk factor for the development of secondary OHA failure. The chronic hyperglycaemia and excessive free fatty acids found in long standing diabetes are known to cause toxicity to pancreatic β -cells, (known as glucotoxicity and lipotoxicity), with resultant poor diabetes control.

The means of TC, LDL-C and TG were lower in those subjects with OHA failure than in those without OHA failure. This result is in conformity with similar previous studies [25,32]. In lean T2DM there is less central obesity with reduced metabolically active fat tissues and hence less dyslipidaemia.

We conclude that secondary failure to OHA among our diabetic subjects is high (36%) and it constitutes a huge challenge in the management of the T2DM patients. It is common in females subjects with poor glycaemic control and GAD positivity, long duration of diabetes, lean subjects and β -cell failure are predictors. Early identification of those at risk and introduction of insulin and newer therapies may reduce the magnitude and consequences of the chronic complications that follows poor management of diabetes.

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