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Evaluation of Vascular Complication and Lack of Glycemic Control as Factors in the Development of Ovarian Cancer in Female Nigerian Type 2 Diabetic Population

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ABSTRACT: Hypertension and diabetes are important medical conditions that are responsible for a significant number of deaths globally. Therefore, the objective of this study was to assess the human epididymis protein-4 in patients with untreated and treated uncomplicated and complicated type 2 diabetes with hypertension at a teaching hospital in Ido-Ekiti, Ekiti State, Nigeria using blood samples and appropriate standard techniques. The results (mean ± SD) obtained showed that the glucose level (mmol/L) in untreated DM, Treated DM and Control was 9.13±1.51, 5.05±0.84 and 4.71±0.81, while HE4 (nmol/L) was 59.52±9.85, 30.49±5.12 and 24.78±4.18 respectively. Furthermore, the glucose (mmol/L) level in untreated DM/HTN subjects and treated DM/HTN subjects was 10.02±3.46 and 4.99±1.04, while HE4 (nmol/L) was 103.33±34.58 and 50.32±5.02 respectively. In conclusion, this research found that HE4 was significantly increased ($p<0.05$) in T2DM subjects with uncomplicated and complicated type 2 diabetes with hypertension compared to control and therefore it can be considered that ovarian cancer can be associated with type 2 diabetes and HE4 can be used as a marker of early detection in both uncomplicated and complicated type 2 diabetes.

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Type 2 Diabetes mellitus (T2DM) is a chronic, metabolic illness, characterized by high blood glucose levels (DeFronzo *et al*., 2015). Type 2 diabetes mellitus is a group of dysfunctions characterized by hyperglycemia and brought on by confluence of inadequate insulin secretion, excessive or incorrect glucagon secretion and resistance to insulin secretion (Galicia-Garcia *et al*., 2020). Despite the complexity of the pathogenesis of T2DM, a number of risk factors for the disease have been identified which includes non-modifiable risk factors like age, ethnicity, comorbid diseases, family history and genetic predisposition, and modifiable risk factors such as body mass index (BMI), physical inactivity, diet and high blood pressure (Deshpande *et al*., 2008). Patients with T2DM have a variety of pathophysiological anomalies, clinical presentations, and disease progressions, which might delay diagnosis and alter a patient's vulnerability to consequences. T2DM complications can be categorized as macrovascular or microvascular, including cardiovascular, cerebrovascular, and peripheral vascular disease. Microvascular problems include retinopathy, neuropathy, and nephropathy (Harding *et al*., 2019). Hypertension (HTN) is a common disorder characterized by high blood pressure which generates

vascular impairment (endothelial dysfunction, altered contractility, and vascular remodeling) (Pena-Sánchez *et al.,* 2014). The diagnosis of hypertension is dependent on the most recent classification of a consistent systolic blood pressure (SBP) greater than or equal to 130 mmHg and diastolic blood pressure (DBP) greater than or equal to 80 mmHg (Whelton *et al.,* 2017). Blood pressure (BP) values vary vastly and tend to increase with age in the population (Malyszko *et al.,* 2016). The pathogenesis of essential hypertension may include a number of factors such as heredity, increased fluid volume, renal sodium transport deficiency, increased sympathetic activity and increased vascular tone, involvement of renin aldosterone system, chronic stress, diminished activity of vasopressor hormones (PGs, ANF) etc (Jha *et al.,* 2014). In addition, factors such as obesity, physical inactivity, occupation, smoking, alcoholism etc. may also contribute (Jha *et al.,* 2014). Human epididymis protein 4 (HE4) is a secretory protein that is member of the whey acidic protein domain family, bearing a conserved motif found in a number a protease inhibitors (Drapkin et al., 2005). HE4 also known as WAP four-disulfide core domain protein 2 is a protein that in humans is encoded by the WFDC2 gene. This gene is expressed in pulmonary epithelial cells and was also found to be expressed in some ovarian cancers. The encoded protein is a small secretory protein, which may be involved in sperm maturation (James et al., 2018). HE4 was initially suggested to be involved in the innate immune defense of multiple epithelia and has also been found to function in epithelial host defense (Kumarasamy *et al.,* 2019). In ovarian tissue, HE4 is highly over-expressed in epithelial ovarian carcinomas (EOCs) compared normal tissue. Clinically, HE4 has been identified as a novel therapeutic biomarker for EOC and has also proven useful in detection of recurrent disease (James et al., 2018). Serum HE4 level predicts EOC with equal sensitivity to the established biomarker CA125 and is less likely to be elevated in benign disease (Kumarasamy *et al.,* 2019).

Hypertension and diabetes are important medical conditions that are responsible for a significant number of deaths globally. Complications from hypertension are estimated to cause 9.4 million deaths every year and about 4 out of every 10 deaths among people with diabetes is as a result of raised blood pressure (Anyanti *et al.,* 2020). According to World Health Organization (2023), the number of people with diabetes rose from 108 million in 1980 to 422 million in 2014 and it is predicted that 366 million individuals will suffer from diabetes by 2030 (type 2 in 90% of the cases) (WHO, 2023). The coexistence of diabetes and hypertension has become an emerging epidemic and public health challenge globally. Poor management of diabetes mellitus complicated with hypertension has placed a great economic burden on many countries, especially on families with diabetes individuals and those complicated with hypertension (Kenore *et al.,* 2022). Therefore, early detection to prevent complication and management of this condition is very crucial. Despite the ongoing research on human epididymis protein 4 in hospitals and research institutions globally, no work has been done on the relationship between human epididymis protein 4 and complicated and uncomplicated type 2 diabetes with hypertensive patients. Therefore, the objective of this study was to assess the human epididymis protein-4 in patients with untreated and treated uncomplicated and complicated type-2 diabetic with hypertension at a teaching hospital in Ido-Ekiti, Ekiti State, Nigeria.

METHODS AND METHODS

Study Area*:* The research was conducted in Ado-Ekiti and its immediate environs. Ado-Ekiti is a town and capital of Ekiti State, southwestern Nigeria. It lies in the Yoruba Hills, at the intersection of roads from Akure, Ilawe Ekiti, Ilesha, Ila Orangun, and Ikare, and is situated 92 miles (148 km) east of Ibadan.

Study Design: The study is a cross-sectional study design using a stratified random sampling method. Stratification was done by age, gender, family medical history and therapy that involved human subjects and assessing the level of human epididymis protein-4 in patients with uncomplicated and complicated diabetes with hypertension.

Sample Size: The minimum sample size (N) was calculated by single proportion formula based on 3% (0.03) estimated prevalence of type 2 diabetes patients complicated with hypertension in Ekiti State. Allowance for error was 0.05 at 95% confidence interval (z). Sample size was calculated using the formular:

$N = Z\, q(1-p) / w^2$ (Adeloye *et al*., 2017)

Where Z = confidence level at 95, N = Minimum sample size, W = allowance for error= 0.05, P = estimated prevalence of type 2 diabetes patients complicated with hypertension at 3%

$q = 1 - p = 1 - 0.03 = 0.97$

$N = (1.96^2)\,(0.03)\,(0.97) / (0.05^2) = 44.72.$

Meanwhile, expected attrition rate is 10%. Therefore, final size was calculated using the following formula:

(100)(Calculated sample size) / (100-Attrition rate)

= (100)(44.72) / (100-10) = 49.68

However, the final sample size was increased to 80 for better representation.

Inclusion Criteria*:* Women aged 20 years and above who are newly diagnosed with uncomplicated and complicated type 2 diabetes with hypertension on therapy who gave their consent were recruited for this study. Diabetes mellitus subjects recently diagnosed of the disease without treatment yet and those who have been receiving treatment for a while were also included.

Exclusion Criteria*:* Females below 20 years, those using oral contraceptives, hormone replacement therapy and tobacco/alcohol, those with personal history of breast cancer, pregnant women and those with other disease conditions were excluded from the study.

Ethical Clearance*:* Ethical Clearance for this research was obtained from the Ethics and Health Research Committee, Federal Medical Centre, Ido-Ekiti, Ekiti State. Informed consent was also obtained from each subject who participated in the study before sample collection.

Sample Collection*:* Anthropometric data including body weight was obtained using bathroom scales, height was measured using a height gauge and blood pressure was obtained using a digital sphygmomanometer. From each subjects, three millimeters (3ml) of venous blood was collected from the cubital fossa using 23G needle and syringe. The blood samples were centrifuged to obtain serum and samples were frozen at −20°C until analysis.

Sample Analysis*: Body mass index*, expressed in kg/m^2 was calculated for each individual by using the formula: weight (kg) / height (m^2)

Systolic and diastolic blood pressure of the participants was measured using a blood pressure monitor.

Glucose was determined by the GOPD method by using glucose Randox kit.

Principle: Glucose oxidase catalyzes the oxidation of glucose to give hydrogen peroxide and gluconic acid. In the presence of peroxidase, the hydrogen peroxide is broken down to oxygen and water. Oxygen reacts with 4-aminophenazone and phenol to give a pink color and absorbance of the color produced is measured at 505nm wavelength using a spectrophotometer. The intensity of the light path is directly proportional to the amount of glucose concentration present in the sample.

Human Epididymis Protein-4 was estimated using the Sandwich-ELISA based biogenic® patented kits.

Principle: Plate is coated with a capture antibody; sample is added, and any antigen present binds to capture antibody; detecting antibody is added, and binds to antigen; enzyme-linked secondary antibody is added, and binds to detecting antibody; substrate is added, and is converted by enzyme to detectable form.

Statistical Analysis: The data generated were expressed as mean ± SD. Analysis was done using SPSS 23. Student t-test and ANOVA were used to compare the serum levels of all variables between hypertensive and known diabetic subjects. Values were compared and significance was tested at $p<0.05$.

RESULTS AND DISCUSSION

Table 1 showed the mean value of BMI, Glucose and HE4 in Untreated DM and Treated DM subjects compared with control. The results obtained showed that Glucose, SBP and HE4 levels were significantly higher ($p<0.05$) in untreated diabetic subjects compared with control. HE4 was significantly higher ($p<0.05$) in treated diabetic subjects in comparison with control. Glucose, SBP, DBP and HE4 levels were significantly higher ($p<0.05$) in untreated diabetic subjects compared with treated group. Table 2 showed the mean value of BMI, Glucose and HE4 in Untreated DM/HTN subjects compared with control. The results obtained showed that. BMI, Glucose, SBP, DBP and HE4 levels were significantly higher ($p<0.05$) in untreated complicated diabetic subjects compared with control. BMI, SBP, DBP and HE4 levels were significantly higher ($p<0.05$) in treated complicated diabetic subjects compared with control. Glucose, SBP, DBP and HE4 levels were significantly higher ($p<0.05$) in untreated complicated diabetic subjects compare with treated group. Figure 1 is a bar chart showing the Glucose and HE4 in treated and untreated subjects and control according to age. From the results obtained, the glucose and HE4 in age groups up to 50 years and above 50 years were all significantly lower ($p<0.05$) in treated uncomplicated and complicated diabetics with hypertension when compared with untreated uncomplicated and complicated diabetics. Figure 2 is a bar chart showing the mean HE4 in treated and untreated uncomplicated subjects relative to treated and untreated complicated subjects. The result obtained showed that HE4 was significantly higher ($p<0.05$) in both treated and untreated complicated diabetics relative to their uncomplicated counterparts. Figure 3 showed the mean Glucose in treated and untreated uncomplicated subjects relative

to treated and untreated complicated subjects. The results obtained showed that Glucose was significantly lower ($p<0.05$) in treated complicated diabetics relative to their uncomplicated counterparts.

Table 1: Mean value of BMI, Glucose and HE4 in untreated DM subjects compared with control

Parameters	UNTREATED DM Mean ± SD (n = 13)	TREATED DM Mean ± SD (n = 17)	CONTROL Mean ± SD (n = 19)	p-value
BMI (kg/m^2)	22.93 ± 3.00	21.87 ± 5.61	21.25 ± 0.80	0.265
SBP (mmHg)	125.27±9.19^c	104.61±7.99^f	109.09 ± 4.44	0.000
DBP (mmHg)	78.45±5.87^c	71.87±3.09^f	73.82 ± 8.40	0.001
Glucose (mmol/L)	9.13 ± 1.51^c	5.05 ± 0.84^f	4.71 ± .81	0.000
HE4 (nmol/L)	59.52 ± 9.85^c	30.49 ± 5.12^f	24.78 ± 4.18	0.000

Keys: a = Statistically significant relative to control at P<0.05; b = Statistically significant relative to control at P<0.005; c = Statistically significant relative to control at P<0.0001; d= Statistically significant relative to treated and untreated at P<0.05; e= Statistically significant relative to treated and untreated at P<0.005; f= Statistically significant relative to treated and untreated at P<0.0001

Table 2: Mean value of BMI, Glucose and HE4in Treated DM subjects compared with control

GROUP	UNTREATED DM/HTN Mean ± SD (n = 19)	TREATED DM/HTN Mean ± SD (n = 16)	CONTROL Mean ± SD (n = 19)	p-value
BMI(kg/m^2)	25.36 ± 4.07^a	25.30 ± 4.21^{ad}	21.25±4.58^{ba}	0.000
Glucose (mmol/L)	10.02 ± 3.46^c	4.99 ± 1.04^f	4.75±0.70^c	0.000
SBP (mmHg)	152.06 ± 10.79^{cd}	142.66 ± 7.99^c	108.88±4.89^c	0.000
DBP (mmHg)	96.79 ± 5.95^c	93.00 ± 3.09^c	72.87±7.97^c	0.365
HE4 (nmol/L)	103.33 ± 34.58^f	50.32 ± 5.02^f	24.58±3.64^c	0.001

***Keys**: a = Statistically significant relative to control at P<0.05; b = Statistically significant relative to control at P<0.005; c = Statistically significant relative to control at P<0.0001; d= Statistically significant relative to treated and untreated at P<0.05; e= Statistically significant relative to treated and untreated at P<0.005; f= Statistically significant relative to treated and untreated at P<0.0001*

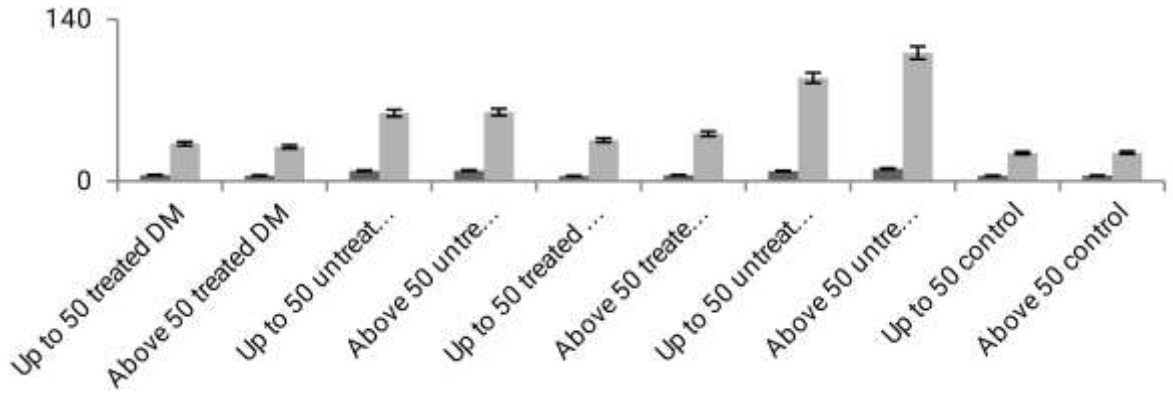

Fig 1: Glucose and HE4 in treated and untreated subjects and control according to age

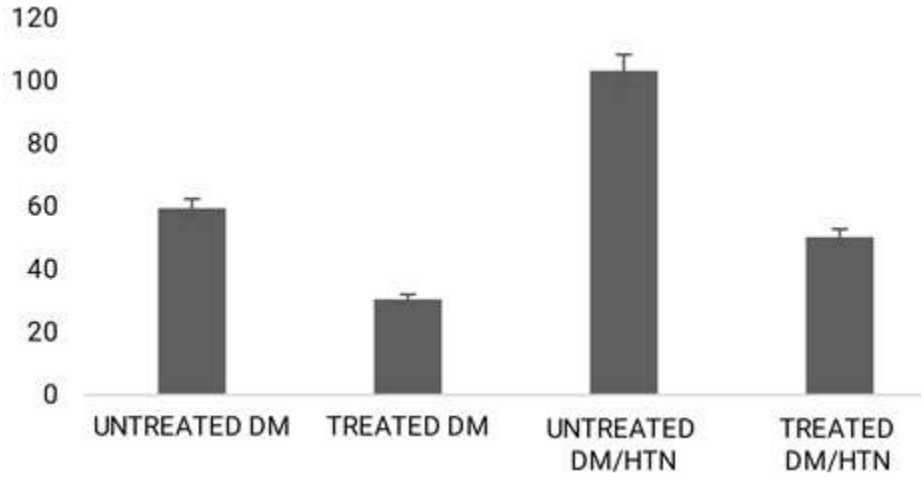

Fig 2: Mean values of HE4 in treated and untreated uncomplicated subjects relative to treated and untreated complicated subjects

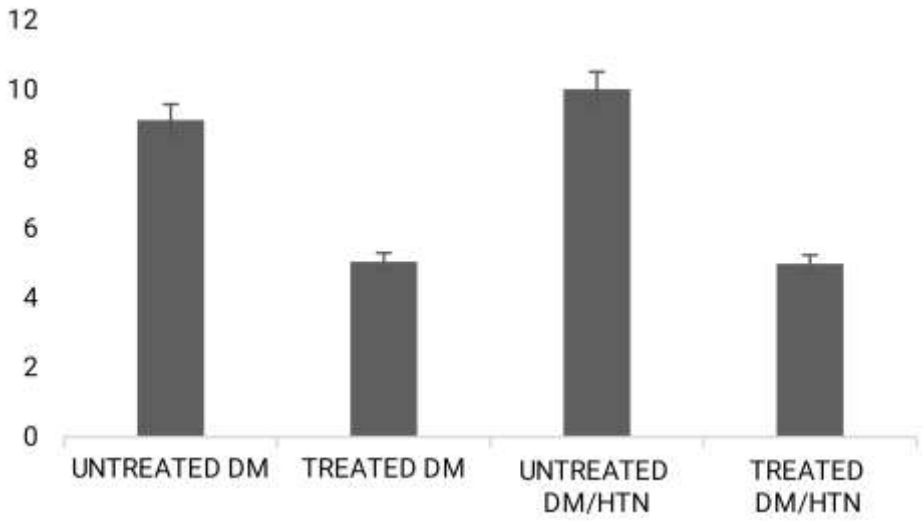

Fig 3: Mean value of Glucose in treated and untreated uncomplicated subjects relative to treated and untreated complicated subjects.

Type-2 diabetes and coexistence of type 2 diabetes with hypertension has been hypothetically linked to a change in several biochemical markers. Hence, this research was carried out to determine the serum level of Human Epididymis Protein-4 (HE4) concentration in treated and untreated uncomplicated type 2 diabetes and complicated type 2 diabetes with hypertension respectively. In this study, BMI was significantly higher ($p<0.05$) in untreated and treated uncomplicated diabetes compared with control. The higher BMI among females can be attributed to short intervals between pregnancies, hormonal imbalance related to menopause, use of oral contraceptive pills, dietary habit and sedentary lifestyle. Generalized obesity, as measured by BMI, has been established as an independent risk factor for type 2 diabetes (Olebu *et al.*, 2014). An explosion in the rates of obesity and high blood pressure has been reported with a concomitant rise in deaths from cardiovascular disease, diabetes, cancer and chronic respiratory disease which has become faster in Africa than anywhere else in the world (Ayogu *et al.*, 2022).This finding is in line with the works of Gezawa *et al.* (2019), where body mass index was seen to be significantly higher ($p=0.001$) in treated and untreated diabetics when compared to control. Similarly, BMI was significantly higher ($p<0.05$) in treated and untreated complicated hypertensive diabetics compared to control. This could be as a result of applied obesity criteria (BMI, WC, or waist/hip ratio), physical inactivity, lack of adequate sleep, poor diet amongst others. This agrees with previous studies (Sonmeza *et al.*, 2019; Ayogu *et al.*, 2022) where BMI was reported to be significantly higher in complicated diabetics compared to uncomplicated diabetics. For prevention of DM complications, keeping a healthy weight, among other things, may be more important to women than to men at lower levels of excess weight, since for women DM complications are associated even with just slightly overweight status (Gray *et al.*, 2015). The result of this study showed that glucose level was significantly higher ($p<0.001$) in untreated uncomplicated diabetes compared to control. It has been reported that increase in BMI increases insulin resistance which results in hyperglycemia in the body (Akalu & Belsti, 2020). Studies observed that individuals with T2DM have two to three folds greater risk of cardiovascular events compared with subjects without diabetes, and CVD is responsible for almost 80% of the mortality in T2DM (Bizuayehu *et al.*, 2022). This finding is in agreement with previous studies (Akalu & Belsti, 2020; Bizuayehu *et al.*, 2022). Furthermore, glucose level was significantly higher ($p<0.0001$) in untreated hypertensive diabetics compared to control. Also, glucose level was significantly lower ($p<0.001$) in treated diabetics compared with untreated uncomplicated diabetics. This is because insulin treatments have a significance contribution to the minimization of the blood glucose level of the diabetes mellitus patient as opposed to the patients not on treatment. This finding is in line with previous studies (Ali & Hassan, 2019; Yordanos *et al.*, 2021) where glucose level of complicated diabetics was significantly higher ($p<0.05$) than uncomplicated diabetic subjects. The BMI of subjects was found to be associated with the change in blood glucose level. This result revealed that with the increase of patients' weight, they are more exposed to the risks of having diabetes and/or its complications; this is consistent with other studies (Yordanos *et al.*, 2021).

SBP and DBP was significantly higher ($p<0.05$) in treated and untreated hypertensive subjects compared with control. Systolic blood pressure (SBP) is due to the pumping of the heart and diastolic blood pressure (DBP) is measurement of the force that occurs when the heart relaxes to allow blood to flow into the heart. The increase in both systolic and diastolic blood pressure could play a significant role in increasing the progression of blood glucose levels among diabetic patients, which is consistent with previous studies (Dereje et al. 2020; Yordanos *et al.,* 2021). SBP and DBP was significantly lower ($p<0.05$) in treated hypertensive when compared with untreated hypertensive subjects. Adequate therapy, including the choice of the medication and the BP target, changes depending on the specific hypertensive emergency and the affected organ. Previous report have shown that use of ACE inhibitors including enalapril and lisinopril, Angiotensin-2 receptor blockers (ARBs) including losartan and telmisartan, Calcium channel blockers including amlodipine and felodipine and diuretics all relax blood vessels thereby reducing blood pressure (Maqsood *et al.,* 2023). This finding is in line with previous studies (Ayogu & Nwodo, 2021; Yordanos *et al.,* 2021), where blood pressure was reduced in treated hypertensive subjects compared to those not treated.

In this study, HE4 was significantly higher ($p<0.05$) in treated uncomplicated diabetics subjects compared with control. It was also significantly higher ($p<0.05$) in untreated uncomplicated diabetics compared with treated uncomplicated diabetics. Increased HE4 may be a valuable predictor for lupus nephritis (LN) development in SLE patient without LN (Ren *et al.,* 2018). In their study, Zhang *et al.* (2019) found that serum HE4 showed a strong, negative correlation with eGFR in T2DM patients, even though adjusting for various confounding factors such as age, urea, uric acid, blood glucose and blood fat. Therefore, we presumed that increased serum HE4 may be a reliable indicator to reflect renal dysfunction regardless of cause. With respect to age, HE4 significantly increased in above 50 untreated uncomplicated diabetics and shows a pattern of decrease in treated age group. This fining is in agreement with previous study by Zhang *et al.* (2019) who found that age is positively correlated with serum HE4, which has also been found in chronic heart failure, systemic lupus erythematosus and healthy individuals (Piek *et al.,* 2017). These results suggest that age should be considered when the clinical value of HE4 is investigated. Zang *et al.* (2019) found a positive relationship between serum HE4 and CRP, suggesting that HE4 may also be an inflammatory marker in T2DM.

Conclusion*:* This research found out that HE4 was significantly higher in type 2 diabetes patients and even much higher in diabetes with vascular complications which could be associated with decreased renal function and increased risks of Diabetic kidney disease (DKD) in patients with T2DM. Since serum HE4 has widely been used as a tumor marker in clinical practice, this indicator may be used in DKD screening. As it has been seen that complicated T2DM patients have likelihood of developing ovarian cancer/tumors, treatment of these patients should be personalized.

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