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Association between Serum Alkaline Phosphatase and Nocturia: A Cross-Sectional Study in a Diabetic Population

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Abstract: ***Nocturia in the diabetic population is a serious public health condition that is becoming increasingly common worldwide. Limited data on the association of alkaline phosphatase (ALP) with Nocturia warrants further attention. We analyzed data using the National Health and Nutrition Examination Survey (NHANES) from 2009-2018. Indicators related to ALP, Nocturia, Diabetes mellitus, and related covariates were extracted and analyzed. Logistic regression models were used to explore the independent correlation between serum ALP and Nocturia. We then assessed whether there was a non-linear relationship between the two using Restricted Cubic Splines (RCS) and performed subgroup analyses. The study population comprised 4479 diabetic patients (2353 males and 2126 females) aged 20 years or older. The prevalence of nocturia in the diabetic population was 49.2% (2202/4479). Multifactorial logistic regression analysis shows positive association between ALP and nocturia. Interaction tests demonstrated that the positive association between ALP and Nocturia interacted with age (interaction p < 0.05). Based on a representative sample of the US diabetic population, we found that higher levels of ALP were significantly associated with the risk of nocturia, even when ALP levels were within the normal range. This finding requires further prospective studies to provide additional evidence.***

Keywords: Alkaline phosphatase, Nocturia, Diabetes, NHANES, Cross-Sectional study.

1. Introduction

Nocturia is defined as one or more nocturnal sleep interruptions due to the need to urinate. Currently, the definition of nocturia is the subject of considerable controversy, with the prevailing consensus being that one nocturnal micturition is normal, whereas two or more nocturnal micturitions are more clinically significant. It has also been suggested [1] that it may be more appropriate to define nocturia based on nocturnal urine production or nocturnal voiding, rather than based on diurnal urine production patterns. As indicated by the Third National Nutrition and Health Survey, the prevalence of nocturia has been documented to be 15.5 percent among male subjects and 20.9 percent among female subjects. It is noteworthy that this figure has exhibited an upward trend in recent years [2]. Nocturia has been demonstrated to increase the risk of falls and related injuries. In addition, it has been shown to contribute indirectly to reduced productivity and absenteeism, which is estimated to cost the economy up to $61 billion per year [3]. The risk factors for nocturia vary between different populations [4]. In the case of older males, for instance, nocturia is predominantly associated with age-related urological conditions such as benign prostatic hyperplasia and prostate cancer [5,6].

Nocturia is frequently observed in individuals with diabetes. A study of 5,506 adults aged between 30 and 79 years, recruited through a multistage stratified sample, found nocturia to be prevalent among 1,872 respondents (28.4%). A positive correlation exists between the prevalence of nocturia and an elevated body mass index, with a statistically significant association ($p<0.001$). Moreover, the probability of experiencing nocturia is increased in individuals with type 2 diabetes, as evidenced by an odds ratio of 1.67 (95% confidence interval, 1.20 to 2.33) [7]. Evidence suggests a potential link between nocturia and both central hemodynamic indices and vascular sclerosis biomarkers in the context of type 2 diabetes mellitus (T2DM) [8]. Numerous factors influence the occurrence of nocturia, including sleep, obesity, hypertension, cardiovascular disease, all-cause mortality, and poor lifestyle habits [9-11]. Given the high prevalence of nocturia and its negative impact on health and the economy, it is particularly important to study in depth the factors influencing nocturia.

The present study centered on the investigation of alkaline phosphatase ALP, an enzyme that is present in many living organisms [12], with notably high expression levels observed in the liver, kidneys, and bones. ALP has been reported as an independent risk factor for coronary heart disease, myocardial infarction, chronic kidney disease, and even death [13]. Elevated levels of ALP have been associated with an increased risk of all-cause and cardiovascular mortality, potentially through the influence of intermediary factors including gamma-glutamyl transferase, vitamin D, and C-reactive protein [14]. It has also been reported that ALP levels are lower in the type 2 diabetes mellitus (T2DM) population than in the non-T2DM population [15], however, whether ALP influences nocturia production in patients with type 2 diabetes mellitus is still a question worth exploring.

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative, population-based study within the United States. It is executed by the National Center for Health Statistics, which is part of the Centers for Disease Control and Prevention. To date, no studies have used NHANES data to investigate the relationship between ALP and nocturia in a diabetic population. In this research, we employed data from the NHANES spanning the years 2009 to 2018 to explore the correlation between ALP levels and the incidence of nocturia. We subsequently conducted sensitivity

analyses to validate our findings.

2. Materials and Methods

2.1 Data Source

NHANES is a cross-sectional, stratified, multistage epidemiological investigation conducted across the United States. The objective of the study is to evaluate the health and nutritional status of both adult and pediatric populations. For this analysis, NHANES data from 2009 to 2018 were utilized, which corresponds to five distinct cycles of data collection within the survey. Of the 49,693 participants, we excluded 44,130 nondiabetics based on fasting glucose, glycosylated hemoglobin, oral glucose tolerance test, and diabetes questionnaire (which asked if they had ever had diabetes), and then excluded 444 individuals who lacked data on serum ALP levels, and 460 who lacked data on nocturia; ultimately, 4,479 subjects (2,353 men and 2,161 women) participated in this retrospective study (Figure 1). NHANES was approved by the Institutional Review Board of the National Center for Health Statistics, thereby ensuring ethical compliance. Participants in the study provided their informed consent, thereby granting permission for the utilization of their data in future research endeavors. Further details regarding this process can be found on the CDC website (https://www.cdc.gov/nchs/nhanes/irba98.htm).

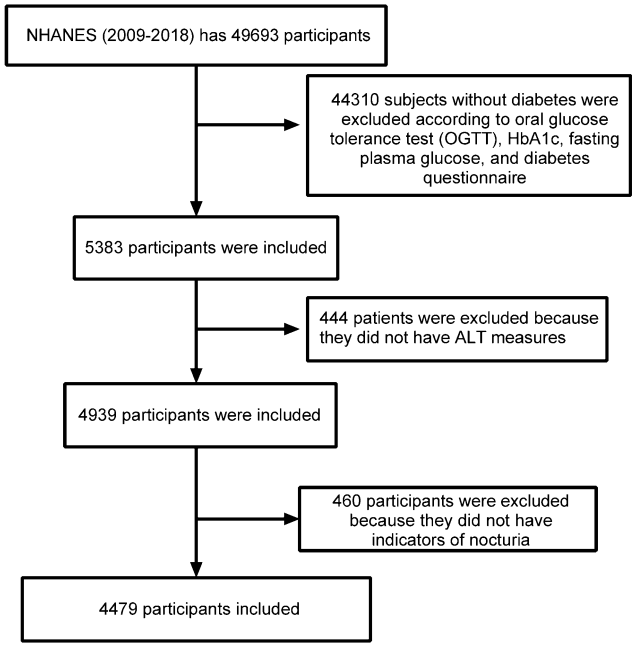

Figure 1: Participants inclusion flowchart.

2.2 Exposure Variable

In the present study, the exposure variable under investigation was the serum level of ALP, an enzyme found in osteoblasts, hepatocytes, kidneys, spleen, placenta, prostate, and small intestine. Serum ALP was measured by Beckman UniCel® DxC800 Synchron, which uses a kinetic rate method using an AMP buffer to measure ALP activity in serum or plasma.

2.3 Outcome Variable

In this research, nocturia was identified as the outcome variable. This was determined through a questionnaire on renal conditions, which was administered in the participants' residences by a trained interviewer utilizing a computer-assisted personal interview (CAPI) system. "During the past 30 days, how many times per night did you most typically get up to urinate from the time going to bed at night to waking up in the morning?" The participants' responses regarding nocturnal urination were meticulously categorized into six groups: 0, 1, 2, 3, 4, and 5 or more voids per night. For this study, individuals reporting two or more voids per night were classified as experiencing nocturia.

2.4 Covariates

The following covariates were analyzed: gender, age, race, body mass index (BMI), smoking status, alcohol status, alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol (TC), triglycerides (TG), creatinine (Scr), urea nitrogen (BUN), uric acid (SU A), urinary albumin/creatinine ratio (UACR), hypertension, diabetes mellitus, albumin (ALB), serum glucose, glycosylated hemoglobin (HbA1c), oral glucose tolerance test (OGTT), estimated glomerular filtration rate (eGFR), hemoglobin (Hb), white blood cell count (WBC). Ethnicity was divided into five groups: Mexican Americans, other Hispanics, non-Hispanic whites, non-Hispanic blacks, and others; drinkers were defined as those who had at least 12 alcoholic beverages in 1 year; smokers were defined as Individuals who had smoked at least 100 cigarettes during their lifetime; and hypertension was defined by asking patients if they had hypertension; we defined diabetes mellitus based on 4 criteria: fasting blood glucose $\geqslant$7.0 mmol/L, 2-hour blood glucose $\geqslant$11.1 mmol/L during OGTT, HbA1c $\geqslant$6.5%, and asking patients whether they had ever had diabetes. These covariates were examined by trained medical specialists for physiological, clinical, and laboratory parameters. Further information regarding the measurement of these variables can be found on the NHANES website (NHANES Questionnaires, Datasets, and Related Documentation).

2.5 Statistical Analyses

The data were analyzed using the 4,479 diabetic subjects included in the NHANES database, and the study participants were divided into three groups based on serum ALP levels: high, medium, and low. To analyze the demographic and clinical data, the mean $\pm$ standard deviation was employed to represent normally distributed continuous variables, the median $\pm$ interquartile range was used for skewed continuous variables, and the frequency (expressed as a percentage) was used for categorical variables. The t-test was used to perform statistical comparisons between groups for normally distributed continuous variables, while the Kruskal-Wallis test was applied for skewed distributions. Categorical variables were compared across groups using the chi-square test. The significance of differences between groups grouped by ALP tertiles was assessed using the Kruskal-Wallis test or one-way ANOVA. One-way and multifactorial logistic regression models were used to analyze the association between serum ALP and nocturia. In multivariate logistic regression analyses, ALP was considered both as a continuous variable (denoted as Log2ALP), a dichotomous variable (with a threshold of 72 U/L), and a tertiary variable (Q1, Q2, Q3). To assess the independent risk between ALP and nocturia, 3

models were developed. Model 1 adjusted for sex and age; Model 2 made additional adjustments for smoking status, alcohol intake, and ethnicity in Model 1; and Model 3 further refined Model 2 to include creatinine, uric acid, alanine aminotransferase (ALT), osmolality, and hemoglobin. To explore potential interactions, we used a stratified logic by sex (female or male), age (<60 or ⩾60 years), body mass index (BMI; <25 kg/m^2, 2.5 to 30 kg/m^2, or ⩾30 kg/m^2), triglyceride levels (TG; <1.7 mmol/L or ⩾1.7 mmol/L), and smoking, alcohol use, and hypertension status were grouped. Stratified logistic regression and likelihood ratio tests were used for grouping. All analyses were performed using the statistical software package R (http://www.R-project.org, R Foundation). Statistical tests were performed using two-sided tests with a significance level of p=0.05.

3. Results

3.1 Characteristics of the Study Population

Table 1 presents the baseline characteristics of the participants. The total sample included 4,479 diabetic patients, aged 20 years or older, with a mean age of 61.26 ± 13.35 years. Of these, 2,353 (52.5%) were male. The prevalence of nocturia in this population was 49.2% (2202/4479). Categorization of the participants was performed based on serum ALP tertiles (Q1: <62 U/L, Q2: 63-82 U/L, Q3: ⩾83 U/L), it was observed that several demographic and physiological variables exhibited significant disparities across the spectrum of serum ALP levels. These variables encompassed gender, age, waist circumference, BMI, race, alcohol consumption, UACR, ALB, Scr, BUN, SUA, TC, TG, osmolality, bicarbonate, serum glucose, WBC, Hb, HbA1c, and frequency of nocturia (p<0.05).

Table 1: Characteristics of the study participants according to the triple categorical variable ALP

Variable	Total(n=4479)	ALP Tertiles			P-value
		Q1:<62U/L	Q2:63-82U/L	Q3:≥83U/L	
Gender					< 0.001
Male	2353 (52.5)	838 (58)	797 (53.1)	718 (46.9)	
Female	2126 (47.5)	607 (42)	705 (46.9)	814 (53.1)	
Age (years)	61.3 ± 13.4	62.1 ± 13.7	61.0 ± 13.3	60.7 ± 13.0	0.011
Waistline (cm)	109.2 ± 16.0	108.1 ± 16.1	109.6 ± 16.0	109.7 ± 15.9	0.015
BMI (kg/m^2)	32.4 ± 7.5	31.8 ± 7.3	32.5 ± 7.2	32.9 ± 8.1	< 0.001
Race group					< 0.001
Mexican American	599 (16.7)	134 (11.8)	208 (17.3)	257 (20.6)	
Other Hispanic	407 (11.3)	110 (9.7)	128 (10.6)	169 (13.5)	
Non-Hispanic White	1176 (32.8)	403 (35.6)	395 (32.8)	378 (30.3)	
Non-Hispanic Black	908 (25.3)	270 (23.8)	322 (26.7)	316 (25.3)	
Other Race	496 (13.8)	216 (19.1)	151 (12.5)	129 (10.3)	
Smoking status					0.314
Non-smoker	2278 (50.9)	747 (51.7)	776 (51.7)	755 (49.3)	
Smoker	2201 (49.1)	698 (48.3)	726 (48.3)	777 (50.7)	
Drinking status					< 0.001
Non drinker	1712 (40.1)	496 (35.2)	566 (39.4)	650 (45.5)	
Drinker	2560 (59.9)	912 (64.8)	870 (60.6)	778 (54.5)	
Hypertension					0.408
No	1535 (34.3)	496 (34.4)	532 (35.5)	507 (33.2)	
Yes	2935 (65.7)	947 (65.6)	967 (64.5)	1021 (66.8)	
ALT (U/L)	21.0 (16.0, 30.0)	21.0 (16.0, 29.0)	22.0 (17.0, 30.0)	22.0 (16.0, 31.0)	0.08
AST (U/L)	22.0 (19.0, 28.0)	22.0 (19.0, 28.0)	23.0 (19.0, 28.0)	22.0 (18.0, 29.0)	0.262
UACR (mg/g）	12.5 (6.8, 39.7)	11.1 (6.1, 30.2)	11.9 (6.5, 35.3)	16.1 (7.7, 58.3)	< 0.001
ALB (g/L)	41.1 ± 3.5	41.9 ± 3.2	41.3 ± 3.4	40.3 ± 3.8	< 0.001
ALP (U/L)	77.3 ± 30.5	51.7 ± 7.9	71.9 ± 5.6	106.6 ± 33.6	< 0.001
Scr (umol/L)	78.7 (64.5, 97.2)	80.4 (67.2, 99.9)	78.7 (65.4, 95.5)	76.0 (61.9, 98.1)	< 0.001
BUN (mmol/L)	5.9 ± 3.0	5.8 ± 2.4	5.7 ± 2.7	6.2 ± 3.6	< 0.001
SUA (umol/L)	344.4 ± 94.0	346.7 ± 88.9	348.9 ± 92.8	337.8 ± 99.2	0.003
eGFR (mL/min)	82.9 ± 25.0	82.4 ± 23.3	83.5 ± 24.0	82.7 ± 27.4	0.469
TG (mmol/L)	1.7 (1.2, 2.5)	1.6 (1.1, 2.4)	1.7 (1.2, 2.5)	1.8 (1.2, 2.7)	< 0.001
TC (mmol/L)	4.8 ± 1.2	4.6 ± 1.2	4.8 ± 1.3	4.8 ± 1.2	< 0.001
Osmolality (mmol/kg)	281.7 ± 6.0	281.0 ± 5.5	281.6 ± 5.7	282.6 ± 6.7	< 0.001
Bicarbonate (mmol/L)	25.2 ± 2.5	25.3 ± 2.4	25.2 ± 2.5	25.1 ± 2.6	0.019
Glucose (mmol/L)	8.3 ± 3.9	7.6 ± 2.9	8.0 ± 3.4	9.3 ± 4.9	< 0.001
WBC (×10^9/L)	7.6 ± 2.2	7.3 ± 2.2	7.6 ± 2.1	7.9 ± 2.4	< 0.001
Hb (g/dL）	13.8 ± 1.6	13.8 ± 1.6	13.8 ± 1.6	13.7 ± 1.7	0.034
HbA1c (%)	7.3 ± 1.7	6.9 ± 1.4	7.2 ± 1.6	7.7 ± 2.1	< 0.001
Fasting Glucose (mmol/L)	8.5 ± 3.3	7.8 ± 2.5	8.2 ± 2.9	9.3 ± 4.0	< 0.001
Nocturia frequency, n (%)					0.004
0 times per night	760 (17.0)	258 (17.9)	264 (17.6)	238 (15.5)	
1 times per night	1517 (33.9)	509 (35.2)	507 (33.8)	501 (32.7)	
2 times per night	1086 (24.2)	336 (23.3)	377 (25.1)	373 (24.3)	
3 times per night	658 (14.7)	196 (13.6)	226 (15)	236 (15.4)	
4 times per night	271 (6.1)	101 (7)	72 (4.8)	98 (6.4)	
≥5 times per night	187 (4.2)	45 (3.1)	56 (3.7)	86 (5.6)	

Data for continuous variables are expressed as the mean ± standard deviation (SD) or the median with interquartile range. Categorical variables are represented as counts (percentages). BMI, body mass index; WBC, white blood cell; ALB, albumin; UACR, Urinary Albumin/Creatinine Ratio; BUN, Blood Urea Nitrogen; eGFR, Estimated Glomerular Filtration Rate; SCR, Serum Creatinine; SUA, Serum Uric Acid; HbA1c, Hemoglobin A1c; Hb, Hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TC, total cholesterol; TG, triglyceride; Q1, Q2, and Q3 are tertiles of ALP. For continuous variables, P-values were calculated using Student's t-test, and for categorical variables, P-values were computed using chi-square tests.

3.2 Univariate Logistic Regression Analysis between ALP and Nocturia

Table 2 presents the findings of the one-way logistic regression analysis, wherein ALP was utilized as a continuous variable. Our analysis identified several factors significantly associated with the risk of nocturia., including age, gender, waist circumference, BMI, ethnicity, smoking, alcohol consumption, hypertension, eGFR, UACR, ALB, ALT, TG, TC, BUN, SUA, osmolality, glucose, Hb, HbA1c, and fasting glucose. An inverse relationship was observed between serum albumin concentrations and the likelihood of nocturia, with an odds ratio (OR) of 0.95 (95% CI: 0.94 - 0.97, p < 0.001).

Table 2: Association of covariates and risk of Nocturia

Variable	Nocturia	
	OR(95%CI)	P-value
Gender		
Male	1	
Female	1.19 (1.06~1.33)	0.004
Age (years)	1.02 (1.02~1.03)	<0.001
Waistline (cm)	1.01 (1~1.01)	<0.001
BMI (kg/m^2)	1.02 (1.01~1.02)	<0.001
Race group		
Mexican American	1	
Other Hispanic	1.04 (0.81~1.33)	0.776
Non-Hispanic White	0.79 (0.65~0.96)	0.02
Non-Hispanic Black	1.2 (0.98~1.48)	0.084
Other Race	0.69 (0.55~0.88)	0.003
Smoking status		
Non-smoker	1	
Smoker	1.22 (1.08~1.37)	0.001
Drinking status		
Non-drinker	1	
Drinker	0.82 (0.73~0.93)	0.002
Hypertension		
No	1	
Yes	1.69 (1.49~1.91)	<0.001
ALP (U/L)	1 (1~1.01)	0.001
eGFR (mL/min)	0.99 (0.99~0.99)	<0.001
eGFR≥60	1	
eGFR＜60	1.53 (1.32~1.79)	<0.001
UACR (mg/g）	1 (1~1)	0.041
ALB (g/L)	0.95 (0.94~0.97)	<0.001
ALT (U/L)	1 (0.99~1)	0.006
AST (U/L)	1 (1~1)	0.949
TG (mmol/L)	0.96 (0.93~0.99)	0.015
TC (mmol/L)	0.89 (0.85~0.93)	<0.001
Scr (umol/L)	1 (1~1)	0.305
BUN (mmol/L)	1.05 (1.03~1.07)	<0.001
Bicarbonate (mmol/L)	0.99 (0.97~1.01)	0.396
SUA (umol/L)	1 (1~1)	0.001
Osmolality (mmol/kg)	1.02 (1.01~1.03)	0.001
Glucose (mmol/L)	1.03 (1.01~1.04)	0.001
WBC (×10^9/L)	1.02 (0.99~1.05)	0.141
Hb (g/dL）	0.86 (0.83~0.9)	<0.001
HbA1c (%)	1.06 (1.02~1.09)	0.002
Fasting Glucose (mmol/L)	1.03 (1~1.05)	0.022

Data presented are ORs and 95% CIs. BMI, body mass index; WBC, white blood cell; ALB, albumin; UACR, Urinary Albumin/Creatinine Ratio; BUN, Blood Urea Nitrogen; eGFR, Estimated Glomerular Filtration Rate; Scr, Serum Creatinine; SUA, Serum Uric Acid; HbA1c, Hemoglobin A1c; Hb, Hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TC, total cholesterol; TG, triglyceride.

3.3 Multifactorial Logistic Regression Analysis between ALP and Nocturia

Table 3 presents a summary of the odds ratios (ORs) and their 95% confidence intervals (CIs) for serum ALP (calculated as log2), ALP tertiles (Q1:<62 U/L, Q2:63-82 U/L, and Q3:≥83 U/L), and ALP dichotomies (ALP ≥72 U/L and ALP <72 U/L) concerning the risk of nocturia. After adjusting for potential confounders, we found that when ALP was analyzed as a continuous variable (log2ALP), there was a statistically significant association between log2ALP and the risk of nocturia in all three models (P < 0.05). Conversely, when ALP was analyzed as a dichotomous variable with an ALP cutoff of 72 U/L, no statistically significant difference was observed between the ALP ≥ 72 U/L group and nocturia in models 2 and 3, compared with ALP < 72 U/L (P > 0.05). Subsequent analysis by ALP tertiles revealed that, in model 3, compared to group Q1, group Q2 (OR: 1.05, 95%CI: 0.88-1.24, P > 0.05) and group Q3 (OR: 1.21, 95%CI: 1.01-1.44, P < 0.05) demonstrated a statistically significant trend, and the test of trend between them remained significant in all models (test of trend P < 0.05).

Table 3: Multivariate Logistic Regression Analysis of ALP and Nocturia

Variable	Non-adjusted		Model 1		Model 2		Model 3	
	OR(95%CI)	P-value	OR(95%CI)	P-value	OR(95%CI)	P-value	OR(95%CI)	P-value
Log_2ALP	1.22 (1.08~1.38)	0.002	1.24 (1.09~1.4)	0.001	1.19 (1.02~1.38)	0.023	1.19 (1.02~1.38)	0.024
Categories								
ALP＜72	Ref		Ref		Ref		Ref	
ALP≥72	1.17 (1.04~1.32)	0.007	1.19 (1.06~1.34)	0.004	1.14 (0.99~1.31)	0.066	1.14 (0.99~1.32)	0.063
Triplets								
Q1(<62)	Ref		Ref		Ref		Ref	
Q2(63~82)	1.07 (0.93~1.24)	0.342	1.09 (0.94~1.27)	0.236	1.04 (0.88~1.24)	0.628	1.05 (0.88~1.24)	0.604
Q3(≥83)	1.21 (1.05~1.4)	0.008	1.24 (1.07~1.43)	0.004	1.21 (1.02~1.44)	0.032	1.21 (1.01~1.44)	0.035
Trend.test	1.1 (1.03~1.18)	0.008	1.11 (1.03~1.2)	0.004	1.1 (1.01~1.2)	0.031	1.1 (1.01~1.2)	0.035

Model 1 adjusted for sex and age; Model 2 made additional adjustments for smoking status, alcohol intake, and ethnicity in Model 1; and Model 3 further refined Model 2 to include Hb, SCR, SUA, Osmolality, and ALT.

3.4 Restricted Cubic Spline (RCS) Curves of Serum ALP Levels and Nocturia

We proceeded to investigate the possible non-linear association between ALP and nocturia in the diabeticpopulation using RCS curves. The outcomes are presented in Figure 2. However, our findings revealed no substantial non-linear correlation between ALP levels and nocturia (nonlinear p-value of 0.523).

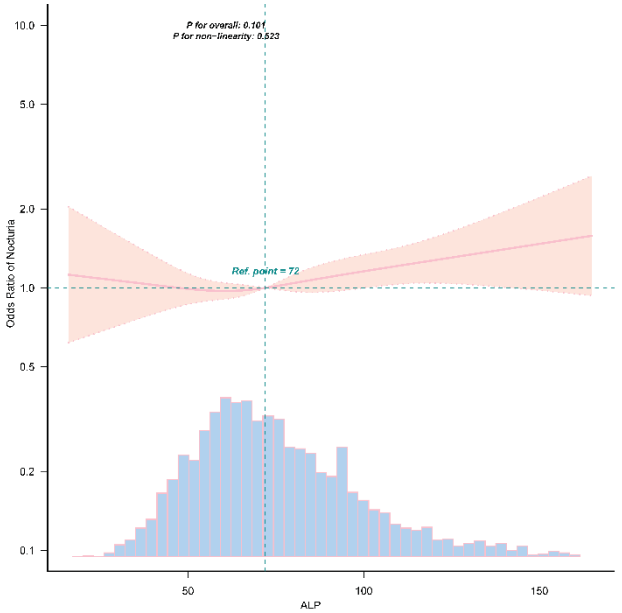

Figure 2: RCS curves between ALT and nocturia

RCS curves of ALP versus nocturia, adjusted for confounders according to model 3, with the solid red line indicating the OR of nocturia, the red area indicating the corresponding 95% Cis, and the blue histogram indicating the distribution of ALP, with the y-axis being the OR of nocturia and the x-axis being the value of ALP. A p-value of >0.05 for total association indicates no significant association. A p-value of >0.05 for non-linear association indicates that no significant non-linear association was found between ALP levels and nocturia.

3.5 Subgroup Analysis

To elucidate the association between serum ALP levels and nocturia risk across various demographic and lifestyle subgroups, stratified and interaction analyses were conducted. These analyses were adjusted for multiple factors, including age (<40 years, 40-60 years, ⩾60 years), gender (male or female), ethnicity, BMI (<25.0, 25.0-29.9, or ⩾30.0 kg/m²), smoking status (yes or no), drinking status (yes or no), triglycerides (TG, <1.7 or ⩾1.7 mmol/L), and hypertension (yes or no). Subsequently, we evaluated the impact of serum ALP, expressed as log2ALP for each 1-unit increment, on the risk of nocturia within the defined subgroups. Subgroup analyses revealed significant differences between age groups (interaction P = 0.001), suggesting an age interaction between serum ALP and nocturia. Significant interactions were observed for other variables related to the relationship between serum ALP and nocturia. In diabetic individuals with a BMI of 30 kg/m² or more, elevated serum ALP levels were found to be significantly associated with an elevated risk of nocturia (OR = 1.34, 95% CI: 1.1 to 1.65). The covariates incorporated in this subgroup analysis were consistent with those considered in Model 3 (Supplementary Table S1). The corresponding forest plot is presented in Figure 3.

The forest plot presents the results of subgroup analyses examining the relationship between ALP and nocturia. The odds ratios (ORs) were derived from multivariate logistic regression models, with adjustments made according to Model 3. It is important to note that in these analyses, the stratification variable was not included in the model's adjustments. The ORs are denoted by circles, while the solid lines indicate the corresponding 95% confidence intervals (CI).

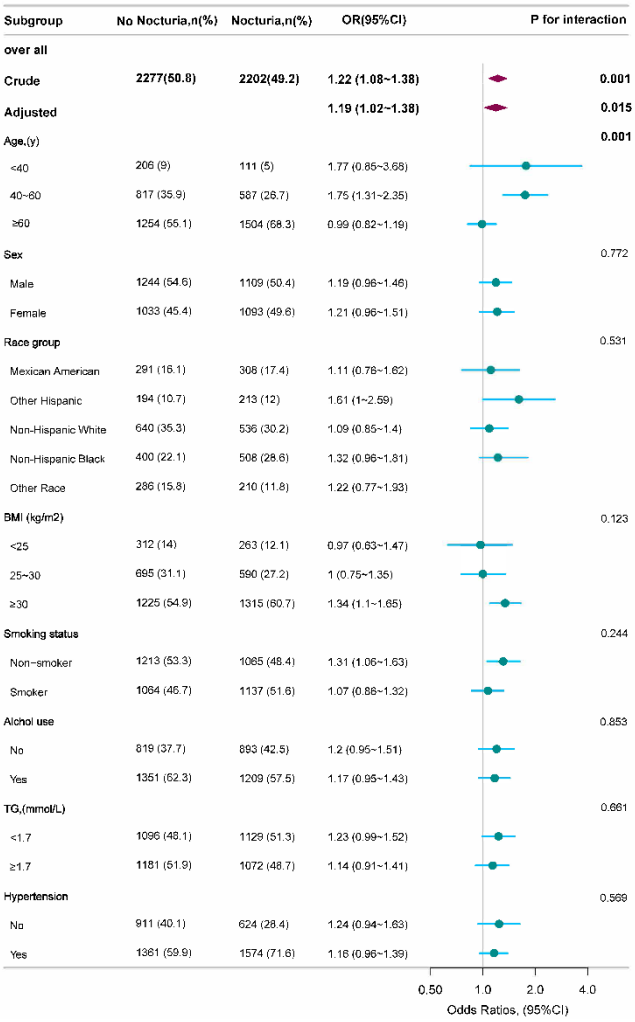

Figure 3: Forest Plot

3.6 Discussion

To elucidate the association between ALP and nocturia in the diabetic population, we conducted a cross-sectional analysis of 4479 diabetic patients, including 2353 men and 2126 women from NHANES 2009-2018, with a prevalence of nocturia as high as 49.2% in the diabetic population. The results of the study showed that in the diabetic population, glycated hemoglobin and fasting glucose levels tended to increase with increasing serum ALP tertiles (especially in the Q2 and Q3 groups), suggesting that serum ALP levels are strongly associated with diabetes progression. In patients with type 2 diabetes, baseline serum ALP levels were positively correlated with age, waist circumference, triglycerides, and serum leukocyte count, and negatively correlated with estimated glomerular filtration rate (eGFR) and serum albumin levels. The risk of nocturia was higher in those with eGFR <60 mL/min compared with those with eGFR ⩾60 mL/min. This is consistent with the results of a previous cross-sectional study on nocturia [16]. After controlling for confounders such as sex, age, race, smoking, alcohol consumption, Scr, SUA, ALT, osmolality, and Hb, we found that the risk of nocturia was 21% higher in patients with serum ALP greater than 83 U/L than in patients with ALP less than 62 U/L. In addition, when log2ALP was considered as a

continuous variable, the risk of nocturia increased by 19% for each 1-unit increase in log2ALP levels. To assess whether this relationship was linear, we performed an RCS curve analysis, and the results confirmed a linear relationship between ALP levels and nocturia.

Current studies on ALP have focused on bone metabolism and renal metabolism, with relatively few studies involving both diabetes mellitus and nocturia. A study in patients with type 1 diabetes found that serum ALP levels were independently correlated with renal function in patients with normal urinary albumin levels [17]. Another study showed an association between renal ultrafiltration and ALP levels [18]. In a retrospective cohort study of peritoneal dialysis patients, researchers found that serum ALP levels were positively correlated with hemoglobin levels and gradually increased with the duration of peritoneal dialysis, a trend that was particularly evident in diabetic patients [19]. In addition, a cohort study in northern Iran also showed a significant association between serum ALP levels and metabolic syndrome [20]. A study on diabetes mellitus and nocturia showed that diabetes mellitus is an independent risk factor for nocturia [21], and osmotic diuresis secondary to hyperglycemia significantly increased nocturnal urine output [22]. However, these studies did not explore the correlation between ALP and nocturia in diabetic patients. Consequently, we initiated a retrospective observational study using the NHANES database to elucidate the correlation between serum ALP levels and the incidence of nocturia among adult diabetic patients.

Some studies have identified correlations between ALP and insulin resistance, glucose metabolism, and metabolic syndrome. This suggests that ALP could serve as a potential biomarker for tracking diabetes progression [23-25]. Nevertheless, the specific mechanism of ALP's role in diabetic patients' nocturia production has not been fully elucidated and warrants further investigation. Available studies have shown that diabetic patients with hyperfiltration tend to have higher serum ALP levels and increased urinary ALP excretion in the presence of compensatory hyperfiltration [26]. In hyperglycemic states, glomerular filtration is enhanced, leading to a rise in intraglomerular pressure, which is closely associated with the development of glomerular inflammation and fibrosis, ultimately affecting tubular reabsorption and potentially leading to the development of nocturia. In addition, ALP plays a key role in calcification, as ALP can hydrolyze pyrophosphate (an endogenous anti-calcification factor within the arterial wall), thereby promoting vascular calcification [27], and therefore, prevention or treatment of vascular calcification may be achieved by regulating ALP activity [28]. In the diabetic patient population, vascular calcification is a strong independent predictor closely associated with the progression of cardiovascular disease and renal pathology [29,30]. Increased arterial stiffness leads to increased blood pressure and decreased resistance in glomerular capillaries, further exacerbating intraglomerular hypertension and ultrafiltration. Several studies have identified a potential link between nocturia and abdominal aortic calcification, which is particularly significant in women [31]. Therefore, future studies need to explore the potential mechanisms between the two in-depth to develop effective preventive and intervention measures.

Subgroup analyses showed that the effect of ALP on nocturia differed significantly between age groups, with a p-value of 0.001 for the interaction after adjustment for various confounders, including sex, race, body mass index, smoking, alcohol consumption, triglyceride, hemoglobin, and hypertension, and this was particularly evident in diabetic patients between the ages of 40 and 60. However, a systematic evaluation of diabetes and nocturia showed a strong correlation between diabetes mellitus and nocturia, but this correlation was not related to age [32]. Therefore, further research is needed to investigate how age affects the association between ALP and nocturia in the diabetic population. In the diabetic population with body mass index (BMI) ⩾30 kg/m2, serum ALP levels were associated with a higher risk of nocturia, which is consistent with the results of a previous cross-sectional study [9]. The mechanism of action behind this association is currently unclear, with some studies suggesting that centrally obese patients may have increased intra-abdominal pressure and thus may contribute to nocturia [33]. Therefore, future studies are needed to further investigate how age and body mass index affect the association between ALP and nocturia risk, and no other confounders were found to be involved in the interaction at this time, suggesting that the previously established positive association between ALP and nocturia is reliable.

The present study has several strengths. In particular, our analysis used a large, nationally representative dataset of American adults, which strengthens the external validity of our findings. Second, our study focused on the relationship between serum ALP and nocturia in a diabetic population, which, to our knowledge, is one of the earliest studies in this area. In addition, we included a variety of potential risk factors for nocturia and adjusted them to ensure the accuracy of our results. Third, we examined ALP in different forms: continuous variables (log2ALP), dichotomous variables (with a cutoff value of 72 U/L), and tertiary variables. We performed ROC curves and subgroup analyses to further explore the association between ALP and nocturia.

This study is not without its limitations. First, the cross-sectional nature of the study precludes the ability to make direct causal inferences; therefore, longitudinal studies are necessary to determine causality. Second, the NHANES program is based primarily on the U.S. population, and the data are reliant on self-report, which may lead to misinterpretation of questions or recall bias, thus limiting the generalizability of the findings to other populations. Third, the inability to distinguish between type 1 and type 2 diabetes, due to limitations inherent to the NHANES database, necessitated the uniform categorization of all study participants as diabetic. Despite the use of multistage stratified probability sampling techniques by NHANES to reduce selection bias, there is a need for a well-designed multicenter randomized controlled trial to confirm the findings.

4. Conclusion

The present study found that the prevalence of nocturia increased with elevated serum ALP levels and that even

moderate ALP levels within the normal range were associated with a significantly increased risk of nocturia. Furthermore, age and body mass index affect the relationship between ALP and the risk of nocturia. Future studies may prioritize randomized controlled trials or cohort studies to confirm these observations and explore the detailed mechanisms of action of this association.

Data Availability

All datasets provided in this study are derived from the National Health and Nutrition Examination Survey (NHANES) and are accessible on the NHANES official website at https://www.cdc.gov/nchs/nhanes/index.htm.

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