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A Cross-Sectional Study for Association between Periodontitis and Benign Prostatic Hyperplasia Using the Korean Genome and Epidemiology Study Data

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Abstract: Recently, several studies have suggested the relationship between periodontitis and prostatic disease. However, epidemiological studies on the association between periodontitis and benign prostatic hyperplasia (BPH) are scarce. Hence, we aimed to identify the association between the two diseases using data from the Korean Genome and Epidemiology Study. Among the 173,209 participants, 3297 men with periodontitis and 35,292 controls (without periodontitis) were selected. The history of BPH in participants with periodontitis and the controls were also investigated. Two-tailed analyses, independent *t*-tests, and chi-square tests were used for statistical analysis. The adjusted odds ratio (OR) for BPH was 1.50 (95% confidence interval, 1.35–1.68; $p < 0.001$) after adjusting for past medical histories. The adjusted OR for BPH was 1.57 (95% confidence interval, 1.41–1.76; $p < 0.001$) after adjusting for anthropometric and laboratory data. Collectively, this study provides evidence that periodontitis is associated with BPH. This finding supports the use of regular dental checkups and periodontal treatments to reduce the prevalence and progression of BPH.

Keywords: microbiology; oral medicine; periodontitis; prostate; urology

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1. Introduction

Periodontitis is an inflammatory disease that develops in intraoral sites, such as the gingiva, teeth, and surrounding bone [1]. Aggravation of periodontitis can lead to the severe resorption of anatomic structures [2]. In the United States, approximately 50% of individuals above the age of 30 years are affected by periodontitis, and approximately 10% of the population has severe periodontal disease [3,4]. Bacteria are commonly thought to be the main etiological factor of periodontitis. Periodontal bacteria cause an imbalance in immunological and inflammatory responses [5]. Bacterial microorganisms, including *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, have been shown

to be associated with chronic periodontitis [6]. Furthermore, microbial dysbiosis plays a key role in determining the activity of periodontitis [1,6]. Periodontitis is difficult to treat, but periodontal treatment can control the disease by preventing severe progression and maintaining the current condition. Biofilms should be cleansed, and oral hygiene should be practiced to prevent the production of new biofilms [7]. In addition, smoking is the most important risk factor for periodontitis. This could be due to several effects of smoking on immune response, including amplifying inflammatory responses to the microbial challenge and decreased wound healing [8,9].

Benign prostatic hyperplasia (BPH) is a disease associated with enlargement of the prostate gland. BPH is common among aging men [10]. BPH occurs in 30–40% of men in their fourth decade of life, and the occurrence of BPH increases to 70–80% in men above 80 years of age [11]. This prostatic enlargement may accelerate urination, including frequent urination, weak stream, or loss of urination control [12]. Aggravation of these lower urinary tract symptoms can lead to chronic kidney problems, bladder stones, and urinary tract infections [13].

Despite the high prevalence of BPH, its pathophysiology has not yet been completely identified. The androgen hormone system is known to be involved in the development of BPH. There is an increased expression of androgen receptors in BPH that are triggered by androgen dihydrotestosterone [14]. Moreover, recent studies have shown that metabolic parameters and prostatic inflammation are associated with BPH development [11,15]. Prostatic inflammation may be activated by bacterial or viral infections that induce the production of inflammatory cytokines and growth factors, resulting in the spontaneous growth of stromal and epithelial prostatic cells [16]. Infection is associated with the increased severity of BPH symptoms, and dysbiosis of urine microbiota is involved in the pathogenesis of BPH [17,18].

BPH, and the severity and prevalence of periodontal disease, are associated with age [19,20]. Hypertension and diabetes are also associated with BPH [21,22]. The Baltimore Longitudinal Study of Aging cohort reported that each 1-kg/m^2 increase in body mass index (BMI) corresponded to a 0.4-mL increase in prostate volume [23]. Obese participants (BMI > 35 kg/m^2) showed a 3.5-fold increased risk of prostate enlargement compared with non-obese participants (BMI < 25 kg/m^2) [23]. Metabolic syndrome is associated with a higher BPH growth rate and increased sympathetic activity [16,24]. The pathophysiological mechanisms of metabolic factors associated with BPH are not fully understood, but increased sympathetic activity, pelvic ischemia, and systemic inflammation may play essential roles in BPH [16,25].

Interestingly, some studies have examined the relationship between periodontitis and prostatic disease [26–28]. Several common risk factors, such as age, metabolic disorders, and psychological factors are related to both periodontitis and prostatic disease [29,30]. Both diseases affect middle-aged and elderly people, and chronic inflammation is related with pathogenesis of both diseases [31,32]. Furthermore, emerging evidence suggests possible roles of periodontitis in prostatic disease [33]. Microbiome dysbiosis, bacterial infections, immune dysfunction, and proinflammatory cytokines are considered to the development of BPH. The oral microbiota may move to prostatic area through hematogenous spread [34]. Oral pathogens could also induce the prostatic inflammatory process through the increase in proinflammatory cytokines, such as interleukin (IL) 1 and 6, tumor necrosis factor α (TNF-α), and interferon γ (IFN-γ) [31,35]. Then, prostatic inflammation may be exacerbated by metabolic disorders [25,36].

Epidemiological studies on the association between periodontitis and BPH are scarce [37]. Therefore, we examined the association between BPH and periodontitis using data from the Korean Genome and Epidemiology Study (KoGES). We hypothesized that periodontitis may be associated with the prevalence of BPH.

2. Materials and Methods

2.1. Study Population and Data Collection

The ethics committee approved the use of data from the KoGES, conducted from 2004 to 2016, for this prospective cohort study (2019-02-020, approval date: 19 March 2019). The requirement for written informed consent was waived by the Institutional Review Board. A detailed description of these data has been explained previously [38–40]. Among the KoGES Consortium, we used the KoGES Health Examinees Study data, which consisted of urban residence participants aged 40 years or older and constituted the baseline data from 2004 to 2013, as well as the follow-up data from 2012 to 2016 [39,40]. Although we did not have any criteria for the study population, this study included all subjects who had participated in the KoGES.

2.2. Participants Selection

Of the 173,209 participants, we excluded: women; those who lacked a record of height or weight, periodontitis, or BPH; those with a history of smoking and/or alcohol use; and those with a medical history of hyperlipidemia, ischemic heart disease, cerebral stroke, hypertension, or diabetes mellitus. Many participants were excluded because their history of periodontitis was not investigated between 2004 and 2006. BPH was not investigated between 2006 and 2008. Finally, 3297 participants with periodontitis and 35,292 controls (without periodontitis) remained (Figure 1). This study compared the periodontitis and control groups based on the history of BPH with adjustment for age, sex, smoking, alcohol consumption, financial status, obesity, hyperlipidemia, cerebral stroke, ischemic heart disease history, hypertension, and diabetes mellitus.

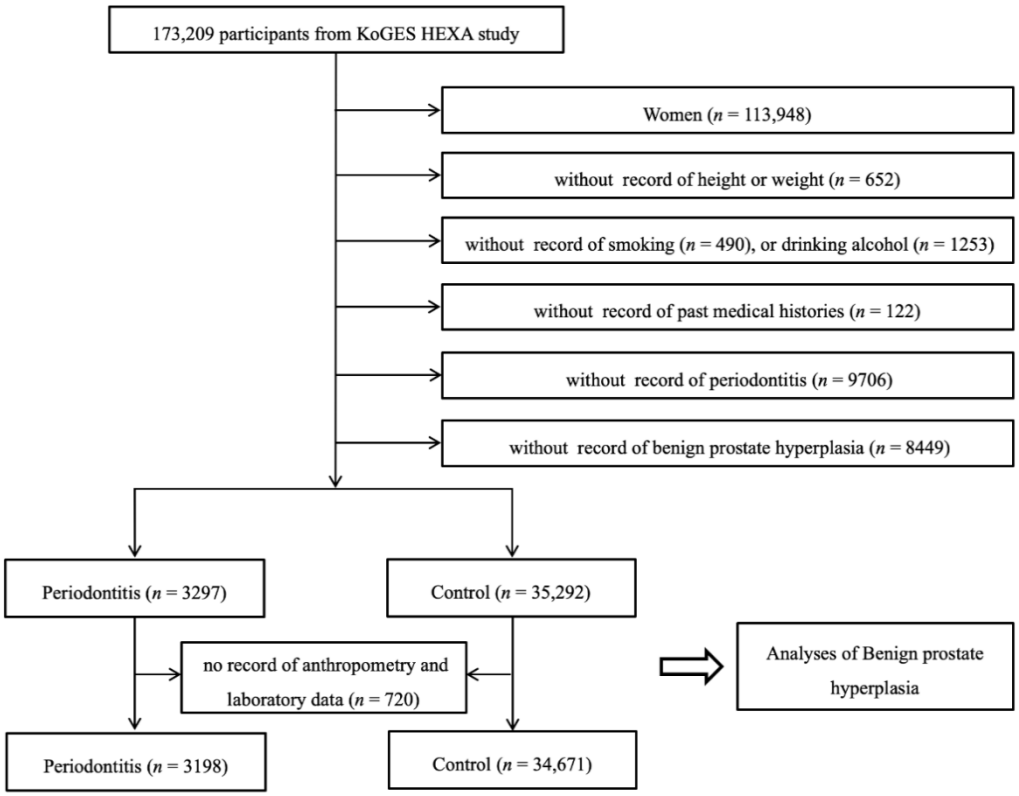

Figure 1. Participant selection diagram. KoGES–HEXA Study, Korean Genome and Epidemiology Study—Health Examinees Study; BPH, benign prostatic hyperplasia.

We then compared the history of BPH between the two groups. In this analysis, we adjusted for age, BMI, income group, smoking status, alcohol consumption, and anthropometric and laboratory data (secondary objective) to use objective data rather than the

medical histories of the participants. In both groups, 720 participants were excluded due to a lack of anthropometric and laboratory data.

2.3. Survey

Smoking history was divided into non-smokers (<100 cigarettes in the entire life), past smoker (quit > 1 year ago), and current smokers. Alcohol consumption was divided into nondrinkers, past drinkers, and current drinkers. Trained interviewers surveyed the participants' history of diabetes mellitus, periodontitis, hypertension, alcohol consumption, hyperlipidemia, and smoking. The income group was divided into non-respondent, low income (<~$2000 per month), middle income ($2000–$3999 per month), and high income (≥$4000 per month) based on household income.

BMI (kg/m^2) was calculated using the health checkup data. Fasting blood sugar (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), triglyceride (mg/dL), uric acid (mg/dL), total cholesterol (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), creatinine (mg/dL), and blood urea nitrogen (mg/dL) were acquired from the health checkup data.

2.4. Statistical Analyses

A logistic regression model was used to analyze the odds ratio (OR) of periodontitis for BPH. Crude and adjusted models were used for age, smoking, alcohol consumption, financial income, BMI, and past medical history. Subgroup analysis was performed according to age. The age range was divided by the median age (≤53 and >53 years).

Independent *t*-tests were used to compare systolic blood pressure, diastolic blood pressure, fasting blood sugar, age, BMI, blood urea nitrogen, creatinine, uric acid, total cholesterol, triglyceride, and HDL cholesterol. Chi-square tests were performed to compare the financial income groups, smoking, alcohol consumption, hyperlipidemia, cerebral stroke, ischemic heart disease, hypertension, and diabetes mellitus.

The adjusted model was utilized for smoking, alcohol consumption, age, financial income, BMI, and anthropometric and laboratory data (systolic blood pressure, diastolic blood pressure, fasting blood sugar, total cholesterol, triglyceride, HDL cholesterol, blood urea nitrogen, creatinine, and uric acid variables).

Two-tailed analyses were also performed. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS (version 24.0; IBM Corp., Armonk, NY, USA).

3. Results

The general characteristics were significantly different between the participants with periodontitis and the controls (Table 1). The mean age was higher (55.5 vs. 53.9) in the periodontitis group than in the controls. The proportions of past smokers (44.7% vs. 41.5%), current smokers (33.4% vs. 30.8%), past drinkers (8.1% vs. 7.1%), and current drinkers (74.3% vs. 72.9%) were higher the periodontitis group than in the controls. Interestingly, the prevalence rates of underlying diseases, including hypertension (33.2% vs. 27.8%), diabetes mellitus (14.9% vs. 11.4%), hyperlipidemia (20.8% vs. 14.6%), ischemic heart disease (6.9% vs. 4.7%), and stroke (2.9% vs. 1.9%) were significantly higher in the periodontitis group than in the controls. The prevalence of benign prostatic hyperplasia was also higher (14.1% vs. 9.0%) in the periodontitis group than in the controls.

We then analyzed the crude and adjusted ORs (95% confidence interval: CI) of periodontitis for BPH after adjusting for past medical histories (Table 2). The adjusted ORs for BPH were 1.50 (95% CI, 1.35–1.68; $p < 0.001$) in all participants, 1.65 (95% CI, 1.30–2.10; $p < 0.001$) in subjects 53 years or younger, and 1.46 (95% CI, 1.29–1.65; $p < 0.001$) in subjects older than 53 years.

Table 1. Demographic and anthropometric characteristics of subjects.

Characteristics	Total Participants		
	Periodontitis	**Control**	***p*-Value**
Age (mean, SD, y) †	55.5 (8.1)	53.9 (8.6)	<0.001 *
BMI (mean, SD, kg/m^2) †	24.5 (2.7)	24.4 (2.7)	0.174
Income (*n*, %) ‡			<0.001 *
Missing, no response	181 (5.5)	2171 (6.1)	
Lowest	924 (28.0)	8391 (23.8)	
Middle	1369 (41.5)	14,791 (41.9)	
Highest	823 (25.0)	9939 (28.2)	
Smoking status (*n*, %) ‡			<0.001 *
Nonsmoker	722 (21.9)	9774 (27.7)	
Past smoker	1474 (44.7)	14,639 (41.5)	
Current smoker	1101 (33.4)	10,879 (30.8)	
Alcohol consumption (*n*, %) ‡			0.001 *
Non-drinker	581 (17.6)	7045 (20.0)	
Past drinker	266 (8.1)	2503 (7.1)	
Current drinker	2450 (74.3)	25,744 (72.9)	
Hypertension ‡	1094 (33.2)	9803 (27.8)	<0.001 *
Diabetes mellitus ‡	491 (14.9)	4019 (11.4)	<0.001 *
Hyperlipidemia ‡	686 (20.8)	5136 (14.6)	<0.001 *
Ischemic heart disease ‡	226 (6.9)	1668 (4.7)	<0.001 *
Stroke ‡	94 (2.9)	672 (1.9)	<0.001 *
Anthropometry data (mean, SD) †			
Systolic blood pressure (mmHg)	125.5 (14.1)	125.4 (14.2)	0.649
Diastolic blood pressure (mmHg)	78.3 (9.4)	78.4 (9.7)	0.167
Fasting blood sugar (mg/dL)	101.0 (24.8)	98.9 (23.6)	<0.001 *
Total cholesterol (mg/dL)	191.3 (34.4)	193.0 (34.9)	0.009 *
Triglyceride (mg/dL)	153.9 (111.2)	150.3 (107.1)	0.069
HDL cholesterol (mg/dL)	48.8 (11.6)	49.5 (11.9)	0.002 *
Blood urea nitrogen (mg/dL)	15.4 (3.4)	15.2 (4.1)	0.001 *
Creatinine (mg/dL)	0.97 (0.30)	0.96 (0.24)	0.264
Uric acid (mg/dL)	5.6 (1.3)	5.7 (1.3)	0.012 *
Benign prostatic hyperplasia (*n*, %) ‡	466 (14.1)	3179 (9.0)	<0.001 *

SD, standard deviation; HDL, high-density lipoprotein. * Independent *t*-test or chi-square test. Significance was set at $p < 0.05$. † Continuous variables. ‡ Categorical variables.

Table 2. Data of crude and adjusted odds ratios (95% confidence interval) of periodontitis for benign prostatic hyperplasia.

Characteristics	Odds Ratios for Benign Prostatic Hyperplasia			
	Crude	***p*-Value**	**Adjusted †**	***p*-Value**
Total participants (*n* = 38,589)				
Periodontitis	1.66 (1.50–1.85)	<0.001 *	1.50 (1.35–1.68)	<0.001 *
Control	1.00		1.00	
Age ≤ 53 years (*n* = 18,646)				
Periodontitis	1.79 (1.41–2.28)	<0.001 *	1.65 (1.30–2.10)	<0.001 *
Control	1.00		1.00	
Age > 53 years (*n* = 19,943)				
Periodontitis	1.45 (1.29–1.64)	<0.001 *	1.46 (1.29–1.65)	<0.001 *
Control	1.00		1.00	

* Logistic regression model. Significance was set at $p < 0.05$. † Models adjusted for age, income group, body mass index, smoking, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, cerebral stroke, and ischemic heart disease history.

After adjusting for anthropometric and laboratory data, the adjusted ORs for BPH were 1.57 (95% CI, 1.41–1.76; $p < 0.001$) in all participants, 1.73 (95% CI, 1.36–2.21; $p < 0.001$) in subjects 53 years or younger, and 1.52 (95% CI, 1.35–1.72; $p < 0.001$) in subjects older than 53 years (Table 3).

Table 3. Data of crude and adjusted odds ratios (95% confidence interval) of periodontitis for benign prostatic hyperplasia.

Characteristics	Odds Ratios for Benign Prostatic Hyperplasia			
	Crude	*p*-Value	Adjusted †	*p*-Value
Total participants (n = 37,869)				
Periodontitis	1.66 (1.50–1.85)	<0.001 *	1.57 (1.41–1.76)	<0.001 *
Control	1.00		1.00	
Age ≤ 53 years (n = 18,336)				
Periodontitis	1.79 (1.41–2.28)	<0.001 *	1.73 (1.36–2.21)	<0.001 *
Control	1.00		1.00	
Age > 53 years (n = 19,533)				
Periodontitis	1.45 (1.29–1.64)	<0.001 *	1.52 (1.35–1.72)	<0.001 *
Control	1.00		1.00	

* Logistic regression model. Significance was set at $p < 0.05$. † Models adjusted for age, income group, body mass index, smoking, alcohol consumption, and anthropometric data (systolic blood pressure, diastolic blood pressure, fasting blood sugar, total cholesterol, triglyceride, high-density lipoprotein cholesterol, blood urea nitrogen, creatinine, and uric acid).

4. Discussion

In the present study, we found that periodontitis was related to BPH. Boland et al. [41] reported that periodontitis could increase the risk of BPH with or without urinary obstruction by 1.5 times in younger Americans after adjustment. Other studies on Asian individuals revealed an association between the two diseases and showed that periodontal disease could be a significant risk factor for BPH [26,37]. Joshi et al. [28] reported that subjects with periodontal disease and prostatitis had higher prostate-specific antigen levels than those with either condition alone.

Microbiome dysbiosis, bacterial movement, immune dysfunction, and proinflammatory cytokines are essential for understanding the link between periodontitis and BPH. The intraoral site is thought to be a reservoir of microorganisms [42]. Microorganisms related to biofilm and microbiota in the periodontium can act as an important factor in inflammation. Induced inflammation is linked to periodontitis [43]. *P. gingivalis* is an important microbiota in patients with chronic periodontitis. Chronic periodontitis can aggravate the environment of the bacterial biofilm by disrupting homeostasis [43]. A recent study showed that *Escherichia coli* and *Propionicimonas* could be associated with prostatic inflammation and BPH [44].

Oral bacteria can move to the extraoral site through body fluid and the bloodstream. Several previous studies showed that periodontal bacteria were found in atherosclerotic plaque [45], synovial fluid of subjects with arthritis [46], and mucosal tissue of subjects with inflammatory bowel disease [47]. If oral bacteria move to the prostatic area, prostatic inflammation may occur and lead to BPH. Estemalik et al. [34] found that at least one type of oral bacteria (*E. coli*, *T. denticola*, *Prevotella intermedia*, and *P. gingivalis*) was found in prostatic secretions in 9 out of 10 patients with BPH and periodontitis.

The prostate gland is an immune-related anatomical organ with a complex immune system. Chronic inflammation can induce the formation of BPH nodules [48]. Previous studies have demonstrated that proinflammatory cytokines (IL-1 and IL-6) and TNF-α play a significant role in the pathogenesis of prostatic inflammation and BPH [49,50]. Bacteria from the oral site can cause epithelial cells to secrete cytokines (e.g., IL-1, IL-6, and TNF-α). These cytokines collect immune cells (eosinophils, T cells, macrophages, neutrophils, and dendritic cells) that can initiate inflammatory reactions and activate the pathogenesis

of chronic periodontitis [51]. A recent study revealed that periodontitis promotes BPH development through the regulation of oxidative stress and inflammatory processes [52].

These findings support the need for regular periodontal treatment and checkups. Moreover, BPH therapy should be accompanied by periodontal treatment, as such treatment would prevent the worsening of asymptomatic prostate inflammation in patients with BPH [53]. Further studies should be performed to confirm the association between periodontitis and BPH.

As with other systemic diseases, BPH and periodontitis are related to age and have become more prevalent in older populations [19,20]. Because the immune response and systemic conditions worsen with age, it could affect the ability of organs, such as the prostate and periodontium [54]. For example, periodontitis and BPH have been associated with insulin resistance and metabolic syndrome [11,55].

Age-related associations can easily be assumed between BPH and periodontitis. However, the present study revealed an association between BPH and periodontitis, with the exclusion of easily predictable factors. This study demonstrated that the association between BPH and periodontitis was statistically significant in male individuals of all ages, even after adjustment for various factors, including age, BMI, financial status, smoking, alcohol consumption, hypertension, diabetes, hyperlipidemia, ischemic heart disease, and stroke (Table 2). This study also adjusted for the potential effect of metabolic diseases on the association between BPH and periodontitis. Additionally, anthropometric and laboratory data were adjusted to reduce the influence of metabolic factors (Table 3). Anthropometric and laboratory data were objectively analyzed to confirm the presence of systemic disease in the KoGES survey. The present study could have adjusted both past medical histories and laboratory data simultaneously; however, simultaneous adjustments would result in multicollinearity. For example, both systolic and diastolic blood pressures are closely related to hypertension, and these data have the same meaning in this study. Therefore, this study evaluated the association using two different methods, with both methods showing a statistically significant association between BPH and periodontitis.

The present study had several limitations. First, these data were based on a questionnaire survey; thus, the data could not be objective. Second, it was impossible to adjust for all factors that could affect the results. Although this study tried to adjust for many factors to decrease surveillance bias, different systemic and local treatments of participants with periodontitis should be considered as potential variables. Third, this study has limitations as a cross-sectional study, because we did not have information on when participants were diagnosed with BPH or periodontitis. Lastly, the mechanisms of this association cannot be proven through one study alone; thus, further investigations are needed to confirm this association.

Nevertheless, this study has some advantages related to periodontitis and BPH. First, this study was conducted in a large Korean population. Therefore, the results can be meaningful in the fields of dentistry and urology. Second, this study included adjustments for many systemic factors and laboratory data to evaluate the independent relationship between periodontitis and BPH. If these adjustments were not performed in this study, the factors would be assumed to be pathophysiologic factors associated with periodontitis and BPH.

5. Conclusions

Through this research, we revealed that periodontitis is associated with BPH. Microbiome dysbiosis, bacterial movement, immune dysfunction, and proinflammatory cytokines seem to explain the relationship between periodontitis and BPH. This finding supports the use of regular dental checkups and periodontal treatment to reduce the prevalence and progression of BPH. Further studies should be performed to identify the pathophysiological mechanisms between periodontitis and BPH.

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Institutional Review Board Statement: The ethics committee of Hallym University (2019-02-020) approved the use of these data.

Informed Consent Statement: The requirement for written informed consent was waived by the institutional review board.

Data Availability Statement: The data that support the findings of this study are available from the database of Korean Genome and Epidemiology Study (KoGES) http://www.nih.go.kr/contents.es?mid=a40504010000 (accessed on 12 July 2021) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. However, data are available from the authors upon reasonable request and with permission of Korean Genome and Epidemiology Study (KoGES).

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