치의학석사학위논문

Association of salivary nitric oxide metabolites with dry mouth and hyposalivation among Korean adults

한국 성인에서 구강건조증과 타액분비저하에 대한 타액 산화질소 대사산물의 연관성

2014 년 8 월

서울대학교 대학원

치의과학과 예방치학전공

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이 논문을 치의학석사학위논문으로 제출함
2014년 8월

서울대학교 대학원
치의과학과 예방치학전공
Sukhbaatar Munkhzaya

Sukhbaatar Munkhzaya의 석사학위논문을 인준함
2014년 8월

위 원 장 _____ **(인)**

부 위 원 장 _____ **(인)**

위 원 _____ **(인)**

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②본인의 논문을 디지털화하여 인터넷 등 정보통신망을 통한 논문의 일부 또는 전부의 복제·배포 및 전송 시 무료로 제공하는 것에 동의합니다.

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①서울대학교는 본 논문을 외부에 제공할 경우 저작권 보호장치(DRM)를 사용하여야 합니다.

②서울대학교는 본 논문에 대한 공개의 유보나 해지 신청 시 즉시 처리해야 합니다.

논문제목: Association of salivary nitric oxide metabolites with dry mouth and hyposalivation among Korean adults

학위구분: 석사 ☑ · 박사 □

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제 출 일: 2014 년 8 월 1 일

서울대학교총장 귀하

-ABSTRACT-

Association of salivary nitric oxide metabolites with dry mouth and hyposalivation among Korean adults

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Objective:

Dry mouth (DM) and hyposalivation are common problems among older adults. They can affect quality of life, nutritional status, the tolerance for dental prostheses, the susceptibility to dental caries and the loss of dentition. However, the relationship between hyposalivation and DM remains still controversial. Nitric oxide (NO) participates in a vast number of physiological functions including nerve transmission, host defense and could affect the pathogenesis of DM and hyposalivation. Therefore, we proposed three hypothese; firstly, hyposalivation is associated with DM, secondly, salivary NO is associated with DM and finally, salivary NO is associated with hyposalivation. The aim of this study was to evaluate these three hypothese among Korean adults.

Materials and Methods:

The study sample consisted of 293 participants from Sunchang Longevity Cohort. DM was assessed by single question and Visual Analog Scale (VAS). Hyposalivation was determined by resting salivary flow rate < 0.1 ml/min. Salivary NO metabolites (total, nitrite [NO_2^-], nitrate [NO_3^-]) were measured via the Griess reaction. Age, sex, economic level, exercise, smoking, drinking, obesity, diabetes and food habits were considered as confounders. Multivariable logistic regression analysis was applied to estimate the association. Stratified analysis by age, sex, economic level, exercise, smoking, drinking, obesity, diabetes, sour and salty food was also applied.

Results:

The association between DM and hyposalivation was not significant (p=0.473). High level of nitrate compared to low level of nitrate was associated with low prevalence of DM (adjusted OR= 0.51, 95% CI: 0.27-0.97). The link was highlighted on males (OR= 0.27), non-obese people (OR= 0.40), non-diabetic people (OR=0.40) and drinkers (OR=0.20). High level of nitrate compared to low level of nitrate was associated with high prevalence of hyposalivation (adjusted OR= 2.05, 95% CI: 1.05-4.00). The link was highlighted on elders under 70 years (OR=3.00), non-exercisers (OR=2.48) and obese people (OR=4.17).

Conclusions:

Our data showed that there was no significant association between dry mouth and hyposalivation. High level of nitric oxide metabolite is independently associated with low prevalence of dry mouth discomfort and high prevalence of hyposalivation among Korean adults. Further studies will be needed to clarify the causality and mechanism of this link.

Keywords: nitric oxide, dry mouth, hyposalivation, adult, epidemiology

Student No: 2012-24051

Contents

I. INTRODUCTION

Oral symptoms such as dry mouth (DM) and hyposalivation are common complaints and often lead patients to consult to dentist. DM is a symptom that has been defined as the subjective impression of oral dryness [1]. DM was more likely to report problems with respect to oral function and activities of daily life such as speech and the chewing and swallowing of food, communication and relationships with others. Therefore, people suffering from DM are less satisfied with their oral health status. When symptoms of DM are associated with a reduction in saliva, it may signal the onset or presence of a potentially serious disease, disorder or condition.

Hyposalivation is a different concept from DM, hyposalivation requires objective evidence of reduced salivary output [2]. Fluid secretion from many exocrine glands including salivary, lacrimal and submucosal glands is dependent on signalling from parasympathetic autonomic nerves evoking increases in acinar cell calcium concentration mediated by muscarinic receptors and, to a lesser extent, other non-cholinergic receptors [3]. Patients with hyposalivation may have complaints that include difficulties in eating, swallowing and speaking also. There is some experimental evidence to suggest that stress has an effect which increase or decreases salivary flow rates [4]. Furthermore, decreased salivary production can lead to oral mucosal infection with Candida and increase the risk of dental caries which eventually accelerate tooth loss. Salivary gland dysfunction and reduced salivary flow rates may or may not be related to DM [5, 6]. Because DM and hyposalivation are not identical but seems like closely related entities. Most dentists are thinking that they are usually associated with each other. There are some studies focusing on significant correlation between DM and hyposalivation in adults [7-9]. However, other studies have suggested that DM does not always associated with hyposalivation [10, 11]. Eventually, the relationship between hyposalivation and DM is remains still controversial. Therefore, we stated our first hypothesis (H1) that**,** hyposalivation is associated with DM.

Since NOS has been found to control the function of many organs of the body by its distribution in the non-adrenergic, non-cholinergic branch of the autonomic nervous system. NO is a soluble gas that is produced not only by the endothelial cells, but also by macrophages and specific neurons in the brain. There are three different types of NOS: endothelial (eNOS), neuronal (nNOS), and cytokine-inducible (iNOS) [12]. Neurons produce nNOS which acts as a neurotransmitter and a signaling molecule. Under normal conditions, the brain has the highest concentration of NO among different tissues. Since NO is produced extensively in the nervous system, it is not unexpected that imbalance in NO metabolism can lead to pathologic conditions in the brain. Indeed, a number of neurodegenerative diseases are suspected to be caused in part by an increase in nitrosative stress in neurons. This is because nitrated protein aggregates are consistently observed in brain tissues of patients with various neurodegenerative neurodegenerative disorders such as Alzheimer's disease , Parkinson's disease, Amyotrophic lateral sclerosis and Huntington's disease [13, 14]. Thus, nitrosative stress may also related mucosal sensation by causing inhibition of neurotransmition pathways. Due to decrease of oral mucosa patients can not feel the oral dryness. Therefore, we proposed our second hypothesis (H2) that the increased NO metabolite is associated with DM.

NO is synthesized from L-arginine and other cofactors by the enzyme nitric oxide synthase (NOS). eNOS and nNOS are expressed constitutively at low levels and can be activated rapidly by an increase in cytoplasmatic calcium. The influx of calcium into the cell leads to a rapid production of NO. In contrast, iNOS is induced when macrophages are activated by cytokines [12]. Salivation caused by chewing and in response to taste increases the flow of saliva and decreases the salivary nitrate concentration, although the overall salivary nitrate output is increased [15]. The parasympathetic nervous system is the main controller of salivary secretion via impulses in the chorda tympani nerve that innervates the acini and releases acetylcholine. It combines with and activates muscarinic receptors that evoke secretion of large quantities of serous fluid [16]. Finally, we

proposed our last hypothesis (H3) that NO metabolite is associated with hyposalivation.

Overall, this study aimed to evaluate these three hypothesis among Korean adults: first, DM is associated with hyposalivation, second, NO metabolite is associated with DM, last, NO metabolite is associated with hyposalivation. In addition we evaluated these links within subgroups based on age, sex, economical level, frequency of exercise, obesity, diabetes, smoking, drinking and dietary habits.

II.MATERIALS AND METHODS

Study design and ethical consideration

This cross-sectional study was conducted using participants and salivary samples from the Sunchang Elderly Cohort Study (SECS). The SECS has been conducted in Sunchang country, a rural area in which the elderly reportedly have the longest life expectancy in Korea. The SECS is an ongoing population-based prospective cohort study that began in 2009. The goal of the SECS is to uncover the genetic and lifestyle factors responsible for the remarkable longevity among the Sunchang elderly population. This study was approved by the Institutional Review Board for Human Subjects at the Seoul National University School of Dentistry (approval no. S-D20090003). All participants provided written in- formed consent.

Participant recruitment

A total of 293 participants aged from 48 to 93 years: mean age was 70.04±8.04 years. Selection criteria for this study included the following: 1) the ability to produce saliva; 2) completion of the health assessment and questionnaires, including information about potential confounders; and 3) the presence of ≥6teeth. A total of 293 participants fulfilled these selection criteria.

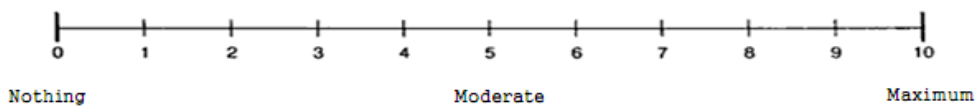
Determination of DM

The subjects answered a questionnaire assessing their subjective sensation of a DM. The questions suggested by Fox *et al* and subjects answering "yes" to the question: " Does your mouth dry?" , each was further asked “How severe is the discomfort?”, which has scoring range of 0 to 10 points.

Question 1: “Does your mouth dry?” Yes and No

If yes, go to question 2

Question 2: How severe is the discomfort?



Determination of hyposalivation

Experienced dentists performed calibrated before the start of the study. The patients were instructed to refrain from smoking, eating, or drinking for at least 1 h before the test session. Unstimulated whole saliva was collected at the clinical examination appointment by the "spit" method [17]. Some five minutes before collection, participants were instructed to sit quietly while administrative procedures were attended to. Immediately prior to saliva collection, each was asked to clean the mouth by swallowing, and then to actively spit saliva into a pre-weighed plastic collection tube. At the end of that time, a beeper sounded, and the participant was asked to spit any remaining saliva into the tube. Those whose unstimulated flow rate was <0.1 ml/min were placed in the hyposalivation group, and those whose unstimulated flow rate exceeded this values were placed into normal group.

NO metabolite measurement

According to the instructions of the manufacturer for the total NO/nitrite/nitrate assay kit, salivary NO levels were measured using the Griess colorimetric reaction [18]. In measuring NO levels, 50 mL reaction diluent, 25 mL nicotinamide adenine dinucleotide, and diluted nitrate reductase were added to each sample, and this mixture was subsequently incubated for 30 minutes at 37℃. After incubation, 50 mL of both Griess reagents I and II were added and incubated for 10 minutes at room temperature. The optical density of the characteristic purple color of each well was then determined using a microplate reader set at 540 nm under wavelength correction at 690 nm.

Confounders

Confounders were socio-demographic factors, such as age [19], sex [8], and income [20]. Behavioral factors were smoking, drinking [21] and frequency of physical activity [22]. Dietary factors were sour and salty food habits [20]. The information about socio-demographic factors, behavioral factors and dietary factors were obtained by questionnaire. In systemic factors, obesity was defined by body mass index (BMI: $\geq$25 kg/m^2 for male, $\geq$24 kg/m^2 for female) and diabetes defined by fasting plasma glucose (FPG: $\geq$126mg/dL).

Statistical Analyses

The association between NO (independent variable) with DM and hyposalivation (dependent variable) was evaluated. DM and saliva flow rate were not normally distributed (P=<0.001 by Kolmogorov-Smirnov test), NO metabolites showed not normal distributions also (P =<0.001, by Kolmogorov-Smirnov test). Mann-

Whitney U test, Spearman correlation were utilized to assess the differences between DM discomfort and saliva flow rate. The adjusted relationship between DM and NO metabolites was determined using logistic regression models that were adjusted for confounders such as age, sex, income, physical activity, smoking status, drinking, obesity, diabetes and dietary factor. In addition, we did subgroup analysis by age, sex, income, physical activity, smoking status, drinking, obesity, diabetes and dietary factor to find out the effect modifier. All statistical significance were decided by the type Ⅰ error at 0.05.

III.RESULTS

Of the 293 participants evaluated, 106 (36.2%) were male and 187(63.8%) were female. Mean ages were 70.59±8.17 years for male subjects and 69.73±7.9 years for female subjects. More females belonged to the DM group than males (76.2% for females versus 23.8% for males). The prevalence of DM was more in less exercisers compare to those with more exercisers (80% versus 20%). The prevalence of DM was more in participants without diabetes compare to those with diabetes (83.1% versus 11.3%). The prevalence of DM was higher in non-smokers than smokers (67.5% and 32.5%) In case of hyposalivation, there was no significant association with other variables (Table 1). The relation between DM and hyposalivation was further examined using logistic regression model. There was no significant association between DM and hyposalivation (p=0.794) (Table 2). We did subgroup analysis because the association can be modified by groups. However, we did not find any association between DM and hyposalivation. No practice variables were significantly accosiated with DM and hyposalivation (Table 3).

After controlling for age, sex, and income, as well as health related behaviours, such as smoking drinking, and frequency of physical activity, obesity, diabetes, food habits NO metabolite was significantly different between DM and hyposalivation. Among three NO metabolites only nitrate level was associated with

DM. As hypothesized, high level of nitrate compare to low level of nitrate was significantly associated with low prevalence of DM with impact of 49% reduction of prevalence of DM. The link was in dose response relationship (Table 4). The association between medium and high level of nitrate and non-dry mouth was highlighted in males, non-exercise group, non-obese group, subjects without diabetes, drinking group, subjects who use more salty food and less sour food (Table 5). According to subsequent stratified analyses, the link between medium and high nitrite level and non-dry mouth shows a dose response relationship only in drinking groups (Table 6). The link between medium and high total NO level and non-dry mouth shows a dose response relationship in drinking group and subjects who use more salty food and less sour food (Table 7).

Among three NO metabolites only nitrate was associated with hyposalivation. High level of nitrate compare to low level of nitrate was associated with high prevalence of hyposalivation with impact of 100.5% increase of prevalence of hyposalivation (Table 8). Consistent with the stratified analysis, the association between high level of nitrate and hyposalivation existence was highlighted in subjects under 70 years, non-exercise group and obese group (Table 9). In hyposalivation, there was no significant association between nitrite metabolite and hyposalivation.

IV. DISCUSSION

DM is defined as the subjective feeling of oral dryness perceived by the patient, and classification is based on the presence or absence of a reported sensation of oral dryness [21]. Hyposalivation is inadequate flow of the saliva fluid. This is a less subjective, more quantifiable condition that is sometimes assumed to be the cause of DM. A reduced flow rate may result in increased prevalence of oral disease and complaints. But, not all patients who report DM symptoms actually

have insufficient salivary flow. Moreover, in many studies the distinction between subjective and objective feeling is not clear. These symptoms reflect the impact of reduced salivary flow on the maintenance of the health of the oral tissues. The cause of a reduced saliva flow rate is still unknown, but it has been suggested that the side effects of medication and psychological processes play an important role [23]. Patients with less saliva often have difficulty talking, chewing, and swallowing, and are at increased risk for developing cavities and yeast infections. Therefore the hyposalivation and DM can have a devastating effect on the physiology of patient. There have been few reports on the association between hyposalivation and DM. Two studies considered the significant association between saliva flow rate and DM [9, 24]; however, some studies reported non-association between stimulated saliva flow rate and DM [10, 25]. Nevertheless, the mechanism of the association of hyposalivation and sensation of DM is still unclear. On the other hand, most of the previous evidence had been obtained from small numbers of hospitalized patients without adjusting for confounders except age and sex [7, 9, 11]. But our data were from the population that fully represent the general population and valid enough to meet the aim of our study. And present study exhibits major strengths enrollment of participants from a community-based cohort and adjustment of results for possible confounders, including socio-demographic factors (age, sex, and education), general health-related behavioral factors (smoking, drinking and physical activity), and systemic health factors (obesity and diabetes). Our results are supportive of the fact that DM does not always associated with hyposalivation [10, 25].

We found the proportion of study participants reporting prevalence of DM to be 23.8% for males and 76.2% for females. This was confirmed in this study, females had much high subjective oral dryness than males. The functional outcome of the increased NO production in patients with DM, as well as the mechanisms by which NO contributes to pathophysiology, are still not resolved. With regard to the secondary research hypothesis (H2), there has only been one study that has attempted to determine the involvement of oxidative stress on patients with Sjogren's syndrome [26]. In this study the diagnosis of Sjogren's syndrome was

based on the DM and other options. Patients with unstimulated salivary test result values of <1.5 ml/15 min, and stimulated values of <10 ml/10 min were diagnosed as DM, whereas patients with values of ≥10 ml/min were excluded from this study, despite subjective symptoms otherwise suggestive of DM. The definition of DM is based on the presence or absence of an individual's reported sensation rather than the measurement of actual salivary flow rate [27]. In this study DM was measured as objective feeling of participant. This indicates that further studies are needed to establish the role of NO in the pathogenesis of DM.

Nitrate and nitrite are compounds that contain a nitrogen atom joined to three or two oxygen atoms, respectively. In nature, these two compounds are readily interconverted. NO signaling is partially regulated by its short half-life in biologic systems because it is rapidly oxidized to nitrite or nitrate. For this reason, these inorganic anions have been considered stable end metabolites of NO production, and scientific interest in these anions has primarily been as markers of NO activity [28]. We determined NO production by measuring total NO, nitrite, and nitrate using the Griess reaction and assessed the link between outcome and concentrations of NO metabolites. The parotid gland is the main contributor to salivary nitrate with its saliva containing approximately three times more nitrate compared with mixed whole saliva. NO is an important signalling molecule in mediating salivary secretion, since it modifies acinar cell calcium signalling in response to autonomic stimulation [29]. Thus, it can be hypothesized (H3) that up-regulation of NOS expression may lead to hyposalivation , possibly by interfering release of calcium inside the cell. Very few evidence regarding to association between NO and hyposalivation in the general population has been reported. According to the paper of Correia *et al*, up-regulation of glandular iNOS can increase salivary secretion in inflamed gland [30]. According to our data we found opposite result in compare with Correia's animal study. However, the present study is relevant to imply about this association which is more valid because our study was done on general population.

Three limitations should be mentioned. First, this study is based on a cross-sectional design that does not allow inferring the causative effect of the variables

effectively. Second, retrospective self-reports of DM symptoms may have uncertain accuracy. To minimize such uncertainty, we used a multiple-item questionnaire in conjunction with DM severity ratings. And third, there may have been selection bias during the interview when asking the potential participants for their cooperation. Because of the limited sample size used in the stratified analyses of the present study, larger studies will be necessary to further support this data. Since we have considered three kind of hypothesis simultaneously, in addition to adding several confounders, the present study permits such a distinction.

V. CONCLUSION

The data of the present study showed that there was no significant association between dry mouth and hyposalivation. Our data suggested that high level of nitric oxide metabolite was associated with low level of dry mouth, and high level of nitrate was associated with high prevalence of hyposalivation. More comprehensive and detailed prospective studies will be indicated to clarify this link.

Table 1. Characteristic of subjects according to hyposalivation and dry mouth

Variables	Dry mouth*		P-value	Hyposalivation†		P-value
	No (n=133)	Yes (n=160)		No (n=207)	Yes (n=86)	
Age(year),mean(SD)	69.11(8.61)	70.82(7.46)	0.07	69.72(7.79)	70.81(8.6)	0.292
Sex, n(%)						
Male	68(51.1)	38(23.8)	< **0.001**	74(35.7)	32(37.2)	0.894
Female	65(48.9)	122(76.2)		133(64.3)	54(62.8)	
Income‡, n(%)						
Low	66(49.6)	88(55.0)	0.411	112(54.1)	42(48.8)	0.442
High	67(50.4)	72(45.0)		95(45.9)	44(51.2)	
Exercise, n(%)						
No	89(66.9)	128(80.0)	**0.016**	159(76.8)	58(67.4)	0.108
Yes	44(33.1)	32(20.0)		48(23.2)	28(32.6)	
Obesity§, n(%)						
No	93(69.9)	102(63.8)	0.320	138(66.7)	57(66.3)	1.000
Yes	40(30.1)	58(36.2)		69(33.3)	29(33.7)	
DM¶, n(%)						
No	94(70.7)	133(83.1)	**0.040**	161(77.8)	66(76.7)	0.401
Yes	26(19.5)	18(11.3)		33(15.9)	11(12.8)	
Missing	13(9.8)	9(5.6)		13(6.3)	9(10.5)	
Smoking**, n(%)						
No	70(52.6)	108(67.5)	**0.012**	125(60.4)	53(61.6)	0.896
Yes	63(47.4)	52(32.5)		82(39.6)	33(38.4)	
Drinking, n(%)						
No	78(58.6)	108(67.5)	0.144	132(63.8)	54(62.8)	0.895
Yes	55(41.4)	52(32.5)		75(36.2)	32(37.2)	
Sour food, n(%)						
No	74(55.6)	105(65.6)	0.092	126(60.9)	53(61.6)	1.000
Yes	59(44.4)	55(34.4)		81(39.1)	33(38.4)	
Salty food, n(%)						
No	62(46.6)	78(48.8)	0.726	101(48.8)	39(45.3)	0.610
Yes	71(53.4)	82(51.2)		106(51.2)	47(54.7)	

Bold values denote statistical significance ($p<0.05$).
*Dry mouth denotes subjective NO symptom.
†Hyposalivation denotes unstimulated saliva flow rate <0.1 ml/min.
‡Low income is defined as lower middle and lower classes, high income is defined as upper middle and upper classes.
§Obesity denotes body mass index (BMI) ≥25 for males and ≥24 for females.
¶Diabetes denotes fasting plasma glucose (FPG) ≥126 mg/dL or on medication due to DM.
**Smokers including past smokers.

Table 2. Association of dry mouth with hyposalivation

Variables		N	Dry mouth	
			OR*(95% CI)	p-value*
Hyposalivation				
	No	207	1	
	Yes	86	0.929(0.537-1.609)	0.794
Age		293	1.029(0.995-1.065)	0.096
Sex				
	Male	106	1	
	Female	187	**4.188(1.918-9.145)**	**<0.001**
Income				
	Low	154	1	
	High	139	1.041(0.623-1.737)	0.879
Exercise				
	No	217	1	
	Yes	76	**0.520(0.293-0.923)**	**0.025**
Obesity				
	No	195	1	
	Yes	98	1.284(0.715-2.306)	0.403
DM				
	No	227	1	
	Yes	44	0.539(0.265-1.094)	0.087
	Missing	22	0.544(0.213-1.385)	0.202
Smoking				
	No	178	1	
	Yes	115	1.304(0.605-2.811)	0.499
Drinking				
	No	186	1	
	Yes	107	1.116(0.639-1.950)	0.700
Sour food				
	No	179	1	
	Yes	114	0.835(0.499-1.397)	0.492
Salty food				
	No	140	1	
	Yes	153	0.762(0.457-1.271)	0.298

Bold values denote statistical significance ($p<0.05$)
*Odds ratio and p-value were obtained from logistic regression model adjusted by age, sex, income, exercise, obesity, diabetes, smoking, drinking, sour and salty food.

Table 3. Association between dry mouth and hyposalivation by subgroups

Subgroup	Category	N	Crude	Adjusted
			OR (95% CI)	OR* (95% CI)
Age				
≤70	Normal	149	1	1
	Hyposalivation		0.956(0.463-1.975)	1.358(0.586-3.146)
≥70	Normal	144	1	1
	Hyposalivation		0.755(0.370-1.540)	0.787(0.359-1.724)
Sex				
Male	Normal	106	1	1
	Hyposalivation		1.108(0.469-2.618)	1.252(0.479-3.275)
Female	Normal	187	1	1
	Hyposalivation		0.777(0.403-1.497)	0.871(0.432-1.757)
Income				
Low	Normal	154	1	1
	Hyposalivation		1.144(0.557-2.351)	1.295(0.556-3.016)
High	Normal	139	1	1
	Hyposalivation		0.689(0.336-1.413)	0.785(0.351-1.756)
Exercise				
No	Normal	217	1	1
	Hyposalivation		0.889(0.484-1.635)	0.837(0.434-1.612)
Yes	Normal	76	1	1
	Hyposalivation		1.050(0.409-2.696)	0.961(0.297-3.110)
Obesity				
No	Normal	195	1	1
	Hyposalivation		1.019(0.549-1.890)	0.985(0.504-1.928)
Yes	Normal	98	1	1
	Hyposalivation		0.648(0.270-1.556)	0.809(0.277-2.361)
DM				
No	Normal	227	1	1
	Hyposalivation		0.726(0.407-1.293)	0.854(0.456-1.599)
Yes	Normal	44	1	1
	Hyposalivation		2.100(0.527-8.369)	9.334(0.550-158.508)
Missing	Normal	22	1	1
	Hyposalivation		1.280(0.228-7.187)	0.581(0.053-6.380)
Smoking				
No	Normal	178	1	1
	Hyposalivation		0.704(0.367-1.350)	0.778(0.383-1.581)
Yes	Normal	115	1	1
	Hyposalivation		1.203(0.353-2.704)	1.540(0.591-4.013)
Drinking				
No	Normal	186	1	1
	Hyposalivation		0.700(0.370-1.325)	0.697(0.346-1.403)
Yes	Normal	107	1	1
	Hyposalivation		1.295(0.565-2.969)	1.245(0.478-3.241)
Sour food				
No	Normal	179	1	1
	Hyposalivation		0.990(0.516-1.899)	1.092(0.538-2.214)
Yes	Normal	114	1	1
	Hyposalivation		0.719(0.318-1.626)	0.731(0.275-1.942)
Salty food				
No	Normal	140	1	1
	Hyposalivation		0.586(0.278-1.233)	0.610(0.252-1.473)
Yes	Normal	153	1	1
	Hyposalivation		1.252(0.626-2.502)	1.529(0.705-3.314)

Bold values denote statistical significance ($p<0.05$).
*Odds ratio and p-value were obtained from logistic regression model adjusted by age, sex, income, exercise, obesity, diabetes, smoking, drinking, sour and salty food.

Table 4. Association of nitric oxide metabolites with dry mouth

Variables	N	Dry mouth[II]	
		OR*(95% CI)	p-value*
Total NO[†]			
Low	97	1	0.282
Medium	98	0.642(0.344-1.196)	0.162
High	98	0.636(0.334-1.214)	0.170
Trend-p		0.167	
Nitrite[‡]			
Low	98	1	0.494
Medium	97	0.691(0.372-1.280)	0.240
High	98	0.794(0.428-1.474)	0.465
Trend-p		0.459	
Nitrate[§]			
Low	97	1	0.076
Medium	99	0.547(0.294-1.019)	0.057
High	97	**0.510(0.268-0.970)**	**0.040**
Trend-p		**0.039**	

Bold values denote statistical significance ($p<0.05$).

*Odds ratio and p-value were obtained from multivariable logistic regression model adjusted by age, sex, income, exercise, obesity, diabetes, smoking, drinking, sour and salty food.

[†]Total nitric oxide levels classified into tertile group - low (< 166.5 umol/L), medium (166.6-689.4 umol/L) and high (> 689.5 umol/L).

[‡]Nitrite levels classified into tertile group - low (< 73.8 umol/L), medium (73.9-331.1 umol/L) and high (> 331.2 umol/L).

[§]Nitrate levels classified into tertile group - low (<31.8 umol/L), medium (31.9-260.1 umol/L) and high (>260.2 umol/L).

[II]Dry mouth denotes subjective dry mouth symptom.

Table 5. Stratified association between nitrate metabolite and dry mouth

Subgroup	Nitrate grade	N	Dry mouth	
			OR (95% CI)	p-value
Age				
≤70	Low	53	1	0.127
	Medium	44	0.499(0.201-1.239)	0.134
	High	52	0.407(0.163-1.017)	0.054
Trend-p			0.053	
Sex				
Male	Low	29	1	0.115
	Medium	35	**0.273(0.079-0.943)**	**0.040**
	High	42	0.442(0.143-1.372)	0.158
Trend-p			0.211	
Exercise				
No	Low	73	1	0.083
	Medium	72	**0.444(0.211-0.935)**	**0.033**
	High	72	0.513(0.237-1.110)	0.090
Trend-p			0.088	
Obesity				
No	Low	62	1	0.054
	Medium	69	**0.395(0.184-0.848)**	**0.017**
	High	64	0.523(0.235-1.162)	0.111
Trend-p			0.105	
Yes	Low	35	1	0.271
	Medium	30	1.055(0.320-3.477)	0.929
	High	33	0.447(0.138-1.453)	0.181
Trend-p			0.174	
DM				
No	Low	80	1	0.053
	Medium	81	0.589(0.294-1.181)	0.136
	High	66	**0.401(0.190-0.846)**	**0.016**
Trend-p			**0.016**	
Drinking				
Yes	Low	38	1	**0.020**
	Medium	32	0.324(0.100-1.048)	0.060
	High	37	**0.203(0.065-0.635)**	**0.006**
Trend-p			**0.006**	
Sour food				
No	Low	59	**1**	**0.015**
	Medium	62	**0.388(0.170-0.887)**	**0.025**
	High	68	**0.293(0.122-0.700)**	**0.006**
Trend-p			**0.005**	
Salty food				
Yes	Low	51	**1**	**0.008**
	Medium	52	0.407(0.164-1.014)	0.054
	High	50	**0.213(0.080-0.566)**	**0.002**
Trend-p			**0.002**	

Bold values denote statistical significance ($p<0.05$).

Table 6. Stratified association between nitrite metabolite and dry mouth

Subgroup	Nitrite grade	N	Dry mouth	
			OR (95% CI)	p-value
Exercise				
Yes	Low	25	1	0.058
	Medium	27	**0.177(0.042-0.739)**	**0.018**
	High	24	0.376(0.097-1.101)	0.156
Trend-p			0.162	
DM				
Yes	Low	12	1	0.090
	Medium	14	**0.046(0.003-0.721)**	**0.028**
	High	18	0.199(0.021-1.910)	0.162
Trend-p			0.251	
Drinking				
Yes	Low	31	**1**	**0.048**
	Medium	45	**0.271(0.087-0.849)**	**0.025**
	High	31	**0.280(0.080-0.978)**	**0.046**
Trend-p			**0.035**	

Bold values denote statistical significance ($p<0.05$).

Table 7. Stratified association between total nitric oxide and dry mouth

Subgroup	Total Nitric oxide	N	Dry mouth	
			OR (95% CI)	p-value
Drinking				
Yes	Low	34	**1**	**0.006**
	Medium	37	**0.196(0.056-0.690)**	**0.011**
	High	36	**0.141(0.040-0.495)**	**0.002**
Trend-p			**0.003**	
Sour food				
No	Low	61	1	0.057
	Medium	62	**0.438(0.192-0.995)**	**0.049**
	High	56	**0.367(0.152-0.888)**	**0.026**
Trend-p			**0.026**	
Salty food				
Yes	Low	50	**1**	**0.015**
	Medium	52	**0.273(0.107-0.698)**	**0.007**
	High	51	**0.324(0.125-0.840)**	**0.020**
Trend-p			**0.020**	

Bold values denote statistical significance ($p<0.05$).

Table 8. Association of nitric oxide metabolites with hyposalivation

Variables	N	Hyposalivation[¶]	
		OR*(95% CI)	p-value*
Total NO[†]			
Low	97	1	0.307
Medium	98	0.897(0.467-1.723)	0.745
High	98	1.467(0.758-2.837)	0.255
Trend-p		0.263	
Nitrite[‡]			
Low	98	1	0.877
Medium	97	0.849(0.450-1.600)	0.612
High	98	0.905(0.481-1.703)	0.756
Trend-p		0.748	
Nitrate[§]			
Low	97	1	0.107
Medium	99	1.355(0.705-2.606)	0.362
High	97	**2.049(1.048-4.004)**	**0.036**
Trend-p		**0.036**	

Bold values denote statistical significance (p<0.05).

*Odds ratio and p-value were obtained from multivariable logistic regression model adjusted by age, sex, income, exercise, obesity, diabetes, smoking, drinking, sour and salty food.

[†]Total nitric oxide levels classified into tertile group - low (< 166.5 umol/L), medium (166.6-689.4 umol/L) and high (> 689.5 umol/L).

[‡]Nitrite levels classified into tertile group - low (< 73.8 umol/L), medium (73.9-331.1 umol/L) and high (> 331.2 umol/L).

[§]Nitrate levels classified into tertile group - low (<31.8 umol/L), medium (31.9-260.1 umol/L) and high (>260.2 umol/L).

[¶]Hyposalivation denotes unstimulated saliva flow rate <0.1 ml/min.

Table 9. Stratified association between nitrate metabolite and hyposalivation

Subgroup	Nitrate grade	N	Hyposalivation	
			OR (95% CI)	p-value
Age				
≤70	Low	53	1	0.119
	Medium	44	1.703(0.617-4.699)	0.304
	High	52	**3.000(1.057-8.511)**	**0.039**
Trend-p			**0.039**	
Sex				
Male	Low	29	1	0.108
	Medium	35	1.251(0.342-4.567)	0.735
	High	42	3.439(0.957-12.349)	0.058
Trend-p			0.048	
Exercise				
No	Low	73	1	0.096
	Medium	72	1.782(0.806-3.937)	0.153
	High	72	**2.481(1.083-5.685)**	**0.032**
Trend-p			**0.031**	
Obesity				
No	Low	62	1	0.407
	Medium	69	1.666(0.742-3.742)	0.216
	High	64	1.637(0.692-3.877)	0.262
Trend-p			0.263	
Yes	Low	35	1	0.067
	Medium	30	1.065(0.267-4.244)	0.928
	High	33	**4.170(1.071-16.234)**	**0.039**
Trend-p			**0.039**	
DM				
No	Low	80	1	0.256
	Medium	81	1.513(0.738-3.102)	0.258
	High	66	1.882(0.874-4.052)	0.106
Trend-p			0.103	
Drinking				
Yes	Low	38	1	0.178
	Medium	32	1.091(0.353-3.371)	0.880
	High	37	2.507(0.858-7.325)	0.093
Trend-p			0.092	
Sour food				
No	Low	59	1	0.273
	Medium	62	1.589(0.678-3.720)	0.286
	High	68	2.086(0.844-5.152)	0.111
Trend-p			0.110	
Salty food				
Yes	Low	51	1	0.226
	Medium	52	1.066(0.420-2.705)	0.893
	High	50	2.117(0.803-5.577)	0.129
Trend-p			0.127	

Bold values denote statistical significance ($p<0.05$).

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국문초록

한국 성인에서 구강건조증과 타액분비저하에 대한 타액 산화질소 대사산물의 연관성

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연구목적

구강건조증과 침분비저하는 노인에서 흔한 질환이다. 이 질환들은 삶의 질, 영양 상태, 구강 보철물에 대한 적응력, 치아우식증에 대한 민감도, 치열 상실 등에 영향을 미칠 수 있다. 그러나 구강건조증과 침분비저하 사이의 상관관계는 아직 명확하지 않다. 산화질소는 신경신호전달, 숙주 방어 등 다양한 생리적 기능을 가지고 구강건조증과 침분비저하의 발생에 영향을 미칠 수 있다. 그러므로 본 저자는 다음 세가지 가설을 제기하였다. 첫째, 침분비저하와 구강건조증은 관련이 있다. 둘째, 타액 산화질소는 구강건조증과 관련이 있다. 셋째, 타액 산화질소는 침분비저하와 관련이 있다. 이 연구의 목적은 이상의 세가지 가설을 한국 성인에서 평가하는 것이다.

연구대상 및 방법

본 연구의 대상자는 순창 장수 코호트 연구에 참여한 293명 중에 선정되었다. 구강건조증은 하나의 설문과 시각 아날로그 척도로 평가되었다.

침분비저하는 비자극성 타액 분비율 0.1ml/분 이하로 정의되었다. 타액 산화질소 대사산물 (total, nitrite [NO_2^-], nitrate [NO_3^-])은 Griess 반응을 통해 측정되었다. 연령, 성별, 경제 수준, 운동, 흡연, 음주, 비만, 당뇨, 식이습관은 혼란변수로 고려되었다. 연관성 분석을 위해 다변수 로지스틱 회귀 분석이 사용되었다. 연령별, 성별, 경제 수준별, 운동 상태별, 흡연 상태별, 음주 상태별, 비만 상태별, 당뇨 상태별, 신 음식 선호도별, 짠 음식 선호도별 층화분석을 시행하였다.

결 과

구강건조증과 침분비저하는 통계적으로 유의하게 연관 있지 않았다 (p=0.473). 고농도의 nitrate는 저농도일 때와 비교하여 낮은 구강건조증 유병률과 연관이 있었다(adjusted OR= 0.51, 95% CI: 0.27−0.97). 층화분석을 시행한 결과, 이 연관성은 남자(OR= 0.27), 비만이 없는 사람 (OR= 0.40), 당뇨가 없는 사람 (OR= 0.40), 음주자 (OR= 0.20)에서 더 강하게 나타났다. 고농도의 nitrate는 저농도일 때와 비교하여 높은 침분비저하 유병률과 연관이 있었다(adjusted OR= 2.05, 95% CI: 1.05−4.00). 층화 분석을 시행한 결과, 이 연관성은 70세 이하 성인 (OR=3.00), 운동 안 하는 사람(OR=2.48), 비만인 사람(OR=4.17)에서 더 강하게 나타났다.

결론

본 연구는 구강건조증과 침분비저하는 연관성이 없음을 보여 주었다. 또한 고농도의 산화질소 대사산물은 한국인 성인에서 낮은 구강건조증 유병률 및 높은 침분비저하 유병률과 연관성이 있었다. 이 연관성들의 인과관계와 기전을 규명하기 위한 후속 연구가 필요하다.

주요어: 산화질소, 구강건조증, 침분비저하, 성인, 역학

학 번: 2012−24051