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ORIGINAL ARTICLE

Relationship between dry mouth and hypertension

Makiko Kawamoto[1] · Shin-ichi Yamada[1] · Takahiko Gibo[1] · Ryo Kajihara[1] · Sachiho Nagashio[1,2] · Hirokazu Tanaka[1] · Junichi Yajima[1,3] · Atsushi Takizawa[1,4] · Eiji Kondo[1] · Hironori Sakai[1] · Tomoki Kaneko[5] · Takeshi Uehara[6] · Hiroshi Kurita[1]

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Abstract

Objectives Salivary dysfunction, such as reduced salivary flow and an altered salivary composition, is caused by several diseases, medical conditions, and medications. The purpose of the present study was to clarify the relationship between hypertension and morphological changes in the submandibular glands.

Materials and methods An epidemiological study was conducted to elucidate the relationship between hypertension and dry mouth. The effects of hypertension on morphological changes and the intima thickness of arteries in the submandibular glands were histopathologically investigated.

Results Among 1933 subjects in the epidemiological study, 155 (8.0%) had dry mouth. A multivariate analysis revealed that dry mouth correlated with age ($p < 0.001$), sex ($p < 0.001$), and hypertension ($p < 0.05$). No significant differences were observed in the size of the submandibular glands between patients with or without hypertension. The average area of acinar cells was smaller in patients with than in those without hypertension (0.366 ± 0.153 vs. 0.465 ± 0.178, $p < 0.05$). The arteriosclerotic index was significantly higher in patients with than in those without hypertension (0.304 ± 0.034 vs 0.475 ± 0.053, $p < 0.05$).

Conclusions Hypertension may contribute to the degeneration of the submandibular glands by decreasing the number of acinar cells and promoting fatty infiltration and stenosis of the arteries.

Clinical relevance There may be a correlation between hypertension and the degeneration of the submandibular glands by decreasing the number of acinar cells and promoting fatty infiltration and stenosis of the arteries.

Keywords Dry mouth · Submandibular glands · Hypertension · Arteriosclerosis · Xerostomia · Intima

Introduction

Saliva plays various roles in maintaining homeostasis in the oral cavity. Salivary dysfunction, such as reduced salivary flow and an altered salivary composition, is caused by several diseases, medical conditions, and medications [1–4].

Hypertension is a major risk factor for cardiovascular disease, and its prevention represents a major medical and social issue [5, 6]. Arterial stiffness due to macrovascular [7–9] or microvascular damage [10, 11] plays a critical role in the development of hypertension. Hypertension may be caused by sclerosis and stenosis of the arterioles, while high blood pressure may result in arteriosclerosis. Sclerosis and stenosis of the arterioles may be responsible for the degeneration and hypofunction of some organs. The salivary flow rate and its pH were shown to be affected by hypertension [12]. A previous study reported that the salivary flow rate was lower in borderline hypertensives than in normotensives [13].

✉ Shin-ichi Yamada
yshinshin@shinshu-u.ac.jp

1 Department of Dentistry and Oral Surgery, Shinshu University School of Medicine, 3-1-1, Asahi, Matsumoto 390-8621, Japan

2 Department of Dentistry and Oral Surgery, JA Nagano Koseiren Kakeyu-Misayama Rehabilitation Center Kakeyu Hospital, Ueda, Japan

3 Department of Dentistry and Oral Surgery, North Alps Medical Center Azumi Hospital, Ikeda, Japan

4 Department of Dentistry and Oral Surgery, Shinshu Ueda Medical Center, Ueda, Japan

5 Department of Radiology, Shinshu University School of Medicine, Matsumoto, Japan

6 Department of Laboratory Medicine, Shinshu University School of Medicine, Matsumoto, Japan

Furthermore, hyposalivation was more prevalent in hypertensive patients receiving anti-hypertensive medication [3]. However, in a study on the influence of hypertension on saliva in the elderly, no correlations were observed between hypertension or the administration of anti-hypertensive medication and unstimulated or stimulated salivary flow [3].

Previous studies histometrically investigated arteriosclerosis in various arteries in the oral and maxillofacial regions [14–20]. However, only one of these studies examined arteries in the submandibular glands [20]. In addition, although aging in the submandibular glands has been morphologically assessed [20–24], the relationship between hypertension and morphological changes in the submandibular glands remains unclear. Moreover, the effects of hypertension on the salivary glands have not yet been evaluated in detail. Therefore, the purpose of the present study was to elucidate the relationship between hypertension and the salivary gland secretion. The relationship between dry mouth and hypertension was initially examined based on a large epidemiological study, and the effects of hypertension on arterial and morphological changes in the submandibular glands were then histopathologically investigated.

Materials and methods

The protocol of the present study was approved by the Committee on Medical Research of Shinshu University (#4003 and #4264).

Epidemiological study

Individuals who underwent health check-ups (health check-ups for metabolic syndrome (MetS) and a medical examination for the elderly) in the Japanese cities Azumino and Shiojiri in 2017 were subjects in the present study. All individuals, who included self-employed workers, farmers, and the elderly, were insured by the Japanese national health insurance system and were ≥ 25 years old. All subjects provided written informed consent prior to the study. Health check-ups were performed according to the standard program provided by the Ministry of Health, Labour and Welfare of Japan (2013) [25]. This health check-up includes an interview on lifestyle and the systemic disease treatment status (including recent smoking habits and whether any medication is being taken to treat hypertension, lipid abnormalities, or hyperglycemia); height, weight, abdominal circumference, and blood pressure measurements; and blood tests (on triglycerides, high-density lipoprotein cholesterol [HDL-C], blood sugar, hemoglobin A1c [HbA1c], and the estimated glomerular filtration rate [eGFR]). A dental examination was conducted in addition to the health check-up, and dry mouth was assessed as one of the dental examination items. Dryness of the mouth was judged by the independent two dentists with abundant clinical experience and classified into four categories according to the clinical classification reported by Kakinoki et al. (normal: non-dry, slight: saliva shows viscosity, moderate: saliva shows tiny bubbles on the tongue, and severe: dry tongue with little or no saliva present) [26]. Prior to the dental examination, the unification of diagnostic criteria was conducted among the examiners.

The relationships between the presence/absence of dry mouth and the results of the health check-up, such as hypertension, hyperlipidemia, diabetes mellitus, renal dysfunction, and medication, were statistically examined. In the health check-up, hypertension was defined by a systolic pressure of higher than 130 mmHg and/or a diastolic pressure of higher than 85 mmHg or the use of anti-hypertensive medication.

Histopathological study

To investigate morphological and histological changes in the salivary glands associated with hypertension, medical records and surgical specimens of the submandibular glands were obtained from 49 patients who underwent neck dissection for the treatment of oral cancer (18 women and 31 men, mean age of 67 years) without any presurgical treatments.

To investigate the grade of atrophy of the submandibular glands, their volume (mm^3) was calculated on T2-weighted magnetic resonance images (MRI) obtained from 43 patients before neck dissection using a medical image diagnosis support system (EV Insite net®, PSP Co., Ltd., Tokyo, Japan). Additionally, 4-μm-thick serial sections were cut from paraffin-embedded tissue blocks of the submandibular glands. A representative center section was stained with hematoxylin and eosin, and the percent area of acinar cells was measured using ImageJ [27]. The percent area of acinar cells was measured at any 5 locations at a magnification of × 20 and used as the average value. The volume (mm^3) of the submandibular glands and histopathological acinar cell percentage were compared between patients with and without a medical history of hypertension in their medical records.

To assess arteriosclerosis in the submandibular glands, 4-μm-thick sections of paraffin-embedded submandibular gland specimens at the representative center slice were also stained with Elastica van Gieson staining. The severity of arteriosclerosis was measured as a ratio of the thickness of the intima to the media (the intima/media ratio = arteriosclerosis index: AI) based on the modified method of Satoh et al. (Fig. 1) [17]. The severity of arteriosclerosis was compared between patients with and without a medical history of hypertension. All slides were evaluated by two independent authors (M.K, R.K, and T.U) blinded to any information on patient characteristics. Each specimen was observed under an optical microscope at a magnification of × 100 for any three medium-

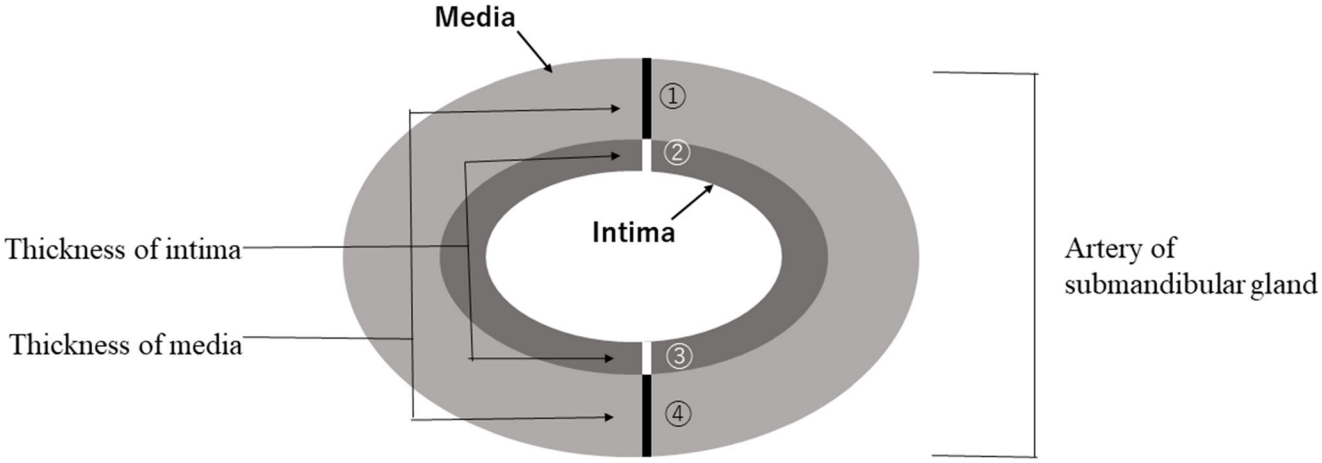

Fig. 1 Method to measure the arteriosclerotic index. The arteriosclerosis index was calculated as a ratio of the thickness of the intima to the media (arteriosclerosis index (the intima/media ratio) = ② + ③/① + ④). ① and ④: media, ② and ③: intima

and small-sized arteries, as well as in three areas of the submandibular glands.

Statistical analysis

Statistical analyses were performed using JMP ver.13 (SAS Institute Inc., NC, USA). The relationships between dry mouth and the results of health check-ups were examined with the chi-squared test and a logistic regression analysis. The significance of differences in morphological changes and arteriosclerosis in the submandibular glands between patients with and without hypertension or other systemic diseases were examined with the Wilcoxon, Fisher's exact probability test, or Student's *t* test according to the distribution of data. *p* values <0.05 were considered to indicate a significant difference.

Results

Relationship between dry mouth and results of health check-ups

Among the 7848 individuals who underwent health check-ups, 1933 (24.6%) consented to dental check-ups and participated in the present study. There were 1038 women and 895 men with a mean age of 64.9 years. Among 1933 subjects, 129 (6.8%) had dry mouth (slight 110, moderate 18, and severe 1; no data 26). Subject characteristics and the relationships between dry mouth and the results of health check-ups are summarized in Table 1. In a univariate analysis, dry mouth correlated with sex (chi-squared test, $p < 0.01$), age (chi-squared test, $p < 0.01$), hypertension (chi-squared test, $p < 0.01$), any medication (chi-squared test, $p < 0.01$), and anti-hypertensive medication (chi-squared test, $p < 0.01$). Low eGFR was associated with dry mouth (chi-squared test, $p = 0.08$). The results of the multivariate analysis are shown in Table 2. Dry mouth correlated with sex (female/male; odds ratio (OR): 1.475, 95% confidence interval (CI): 1.215–1.804, $p < 0.01$), age (≧70/< 70; OR: 1.051, 95% CI: 1.030–1.072, $p < 0.01$), hypertension (yes/no; OR: 1.346, 95% CI: 1.018–1.749, $p < 0.05$), and hyperlipidemia (yes/no; OR: 0.707, 95% CI: 0.558–0.883, $p < 0.01$). Medication had no significant impact on the presence of dry mouth.

Morphological and histopathological analyses of submandibular glands in patients with hypertension

Forty-nine patients participated in the present study and their characteristics are summarized in Table 3. There were 31 males and 18 females with a median age of 67 years (range 30–88 years). Twenty-two out of 49 patients had a medical history of hypertension. No significant differences were observed in the distribution of sex or age between patients with and without a medical history of hypertension. A correlation was noted between a medical history of hyperlipidemia and that of hypertension. Hyperlipidemia was more frequently observed in patients with hypertension (2/27 vs 9/22, Fisher's exact probability test, $p < 0.01$).

Preoperative T2-weightd MRI of the submandibular glands was available for 34 patients (13 with hypertension and 21 without). No significant differences were observed in sex, age, or body mass index (BMI) between patients with and without hypertension. The median volumes of the submandibular glands in patients with and without hypertension were 7636.8 mm^3 and 6787.7 mm^3, and did not significantly differ (the Wilcoxon test, $p = 0.47$; Fig. 2).

The histopathological analysis of the submandibular glands revealed a decrease in acinar cells and their replacement with adipose tissue in most patients with hypertension (Fig. 3). The percent area of acinar cells was significantly lower in patients

Table 1 Patient characteristics and results of a univariate analysis ($n = 1933$)

	Xerostomia (%)			*p* value (chi-squared test)
	No	Yes	*No data*	
	1778 (92.0)	129 (6.7)	26 (1.3)	
Sex				
Female	934 (48.3)	87 (4.5)	*17 (0.9)*	*p*<0.01
Male	844 (43.7)	42 (2.2)	*9 (0.5)*	
Age				
<70	1091 (56.4)	42 (2.2)	*14 (0.7)*	*p*<0.01
≥70	687 (35.5)	87 (4.5)	*12 (0.6)*	
Hypertension				
Yes	668 (34.6)	72 (3.7)	*12 (0.6)*	*p*<0.01
No	1105 (57.2)	57 (2.9)	*14 (0.7)*	
No data	*5 (0.3)*			
Hyperlipidemia				
Yes	616 (31.9)	36 (1.9)	*11 (0.6)*	*p*=0.13
No	1157 (59.9)	93 (4.8)	*15 (0.8)*	
No data	*5 (0.3)*			
Diabetes mellitus				
Yes	178 (9.2)	9 (0.5)	*3 (0.2)*	*p*=0.36
No	1595 (82.5)	120 (6.2)	*23 (1.2)*	
No data	*5 (0.3)*			
eGFR				
< 60 ml/min/1.73 m^2/dl	266 (13.8)	27 (1.4)	*3 (0.2)*	*p*=0.08
≥ 60 ml/min/1.73 m^2/dl	1507 (78.0)	102 (5.3)	*23 (1.2)*	
No data	*5 (0.3)*			
Any medication				
Yes	643 (33.3)	64 (3.3)	*11 (0.6)*	*p*<0.01
No	1126 (58.3)	65 (3.4)	*15 (0.8)*	
No data	*9 (0.5)*			
Polypharmacy				
Yes	216 (11.2)	18 (0.9)	*6 (0.3)*	*p*=0.56
No	1553 (79.3)	111 (5.8)	*20 ((1.0)*	
No data	*9(0.5)*			
Anti-hypertensive medication				
Yes	462 (23.9)	51 (2.6)	*8 (0.4)*	*p*<0.01
No	1307 (67.6)	78 (4.0)	*18 (0.9)*	
No data	*9 (0.5)*			

p value in italics

eGFR, estimated glomerular filtration rate

with than in those without hypertension (36.6% vs. 46.5%, the Student's *t* test, $p < 0.05$; Fig. 4).

The intima of arteries in the submandibular glands was relatively flat in patients without hypertension, but was thicker in patients with hypertension (Fig. 5). A comparison of AI between patients with and without hypertension is shown in Fig. 6. AI was significantly higher in patients with than in those without hypertension (0.39 vs. 0.28, the Wilcoxon test, $p < 0.05$).

Discussion

To the best of our knowledge, this is the first study to examine the relationship between hypertension and dry mouth. The results obtained indicated that hypertension followed by arteriosclerosis might induce the degeneration of the salivary glands.

In daily clinical practice, we sometimes observe dry mouth in patients with chronic and metabolic diseases. Therefore, we

Table 2 Results of a multivariate analysis

Factors	Odds ratio	95% confidence interval	*p* value*
Sex (female/male)	1.475	1.215–1.804	< 0.01
Age (≥ 70/< 70)	1.051	1.030–1.072	< 0.01
Hypertension (yes/no)	1.346	1.018–1.749	< 0.05
Hyperlipidemia (yes/no)	0.707	0.558–0.883	< 0.01
Diabetes mellitus (yes/no)	0.720	0.482–1.016	0.082
eGFR (< 60 ml/min/1.73m^2/dl/≥ 60 ml/min/1.73m^2/dl)	1.056	0.828–1.328	0.651
Anti-hypertensive medication (yes/no)	1.224	0.801–1.828	0.334
Any medication (yes/no)	1.256	0.856–1.806	0.228

*Logistic regression analysis

eGFR, estimated glomerular filtration rate

conducted the present epidemiological study to examine the relationship between dry mouth and metabolic diseases. Diagnostic criteria for dry mouth have not yet been established. In the present study, dryness of the mouth was judged by an inspection according to the clinical criteria reported by Kakinoki [26]. These criteria correlate with the subjective symptoms of dry mouth, the amount of saliva, and the wetness of the oral mucosa. In the epidemiological study based on health check-ups for MetS, the multivariate analysis showed that dry mouth correlated with sex, age, hyperlipidemia, and hypertension. Furthermore, dry mouth was more prevalent in woman, the elderly, individuals without hyperlipidemia, and those with hypertension. In a previous study, sex, age, and medication were identified as independent risk factors for the development of dry mouth [28]. Our results were consistent with these findings, except for the factor of medication. A correlation was also previously reported between the use of medication and xerostomia in older adults [29]. The findings of this study showed that urological medication, antidepressants, and psycholeptics had a significant impact on xerostomia and salivary gland hypofunction. Furthermore, hyposalivation was reported in hypertensive patients receiving anti-hypertensive medication [3]. In the present study, the univariate analysis revealed a correlation between dry mouth and medication. However, in the multivariate analysis, medication did not have a significant impact on dry mouth when the prevalence of hypertension was included in the model. Moreover, the majority of hypertensive subjects (70.8%) were receiving anti-hypertensive medication. These results suggest that not only anti-hypertension medication but also hypertension itself are responsible for dry mouth.

Although the effects of aging on morphological changes in the submandibular glands were previously demonstrated [20–24], those of hypertension remain unclear. In the present study, the volume of the submandibular glands was compared between patients with and without hypertension using MRI. No significant difference was observed in the volume of the submandibular glands, age, or BMI between the groups examined. In a previous study, the volume of the submandibular glands was shown to decrease with age [22]; however, hypertension did not have any effect.

The effects of hypertension on histopathological changes in the salivary glands were also assessed in the present study. The results obtained revealed a significant difference in the number of acinar cells (percentage) in the submandibular glands between patients with and without hypertension. The percentage of acinar cells decreased in patients with hypertension and the fatty degeneration of the submandibular glands was detected. Fatty infiltration, fibrosis, and lymphoplasmacytic infiltration have been reported to generally reflect the degeneration of the submandibular

Table 3 Characteristics of patients in morphological and histopathological analyses of submandibular glands ($n = 49$)

	Patients without a medical history of hypertension (n=27)	Patients with a medical history of hypertension (n=22)	*p* value
Sex (female:male)	10:17	8:14	p=1.00*
Age (median, range)	65, 30–85 years	70, 46–88 years	p=0.33†
BMI (median, range)	21.8, 15.5–28.0 kg/m^2	22.2, 16.7–29.8 kg/m^2	p=0.62†
Medical history of hyperlipidemia (yes:no)	2:25	9:13	p<0.01*
Medical history of diabetes (yes:no)	6:21	4:18	p=1.00*

*The chi-squared test (Fisher's exact probability test)

† The Wilcoxon test

BMI, body mass index

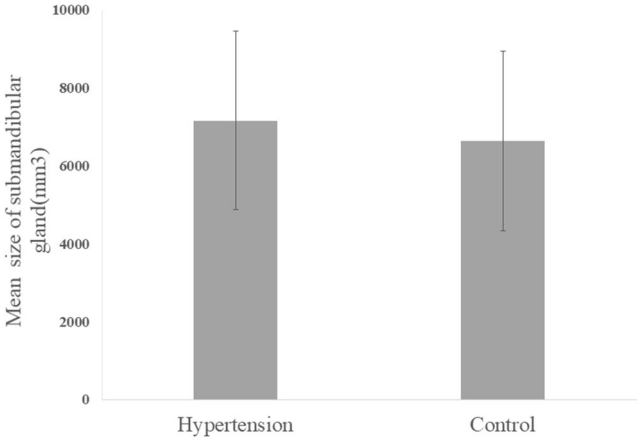

Fig. 2 Comparison of the volume of submandibular glands between patients with and without a medical history of hypertension. No significant differences were observed in the volume of the submandibular glands between patients with and without hypertension and controls (the Wilcoxon test, $p = 0.47$). BMI: body mass index

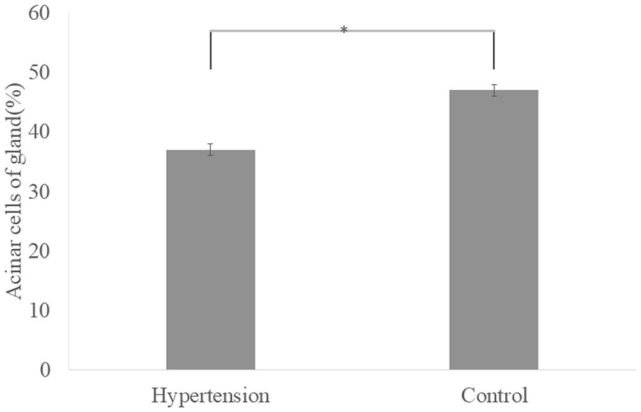

Fig. 4 Comparison of percent areas of acinar cells between patients with and without hypertension. The percent area of acinar cells was lower in patients with than in those without hypertension (the Student's t test, $p < 0.05$)

glands with aging [20, 30]. A decrease in the amount of the parenchyma and increases in those of ductal, vascular, and adipose tissues were noted in the submandibular glands with aging [20, 21, 23, 24]. Additionally, the atrophy and disappearance of acini and increases in adipose tissue were detected [20]. The histopathological changes observed in the present study were similar to those associated with aging. The mechanisms underlying age-related changes in the salivary glands currently remain unclear. Ishikawa et al. investigated age-related changes in the submandibular glands and reported that arterial stenosis was associated with aging and also correlated with fatty infiltration and fibrosis [20]. The aging process is commonly associated with increased vascular rigidity and decreased vascular compliance. These changes are caused by the aging process and are also attributable to hypertension and arteriosclerosis [31]. In the present study, significant differences in histological findings were associated with the presence of hypertension regardless of aging (no significant difference was noted in the age of patients with and without hypertension). Physiological aging is considered to be promoted by a number of risk factors, including high blood pressure, diabetes, hyperlipidemia, obesity, and smoking [32, 33]. These findings suggest that the vascular pathology, particularly the arterioles, plays an important and promoting role in the degeneration of the salivary glands.

In the kidneys, arterial intimal thickening has been associated with more frequent and severe hypertension [34]. There is currently no information on arterial intimal thickening in the submandibular glands of patients with hypertension, except for the effects of aging [20]. The ratio of the intima to the media in the common carotid artery was previously reported to high and associated with hypertension and arteriosclerotic disease [14]. In the present study, the intimal medial thickness of arterioles in the submandibular glands was significantly greater in individuals with hypertension. Furthermore, the prevalence of hyperlipidemia was higher in patients with hypertension, which may be associated with increases in intimal medial thickness. However, as described above, the epidemiological study showed a negative correlation between hyperlipidemia and dry mouth. These results suggested that hypertension was associated with an increase in the intimal medial

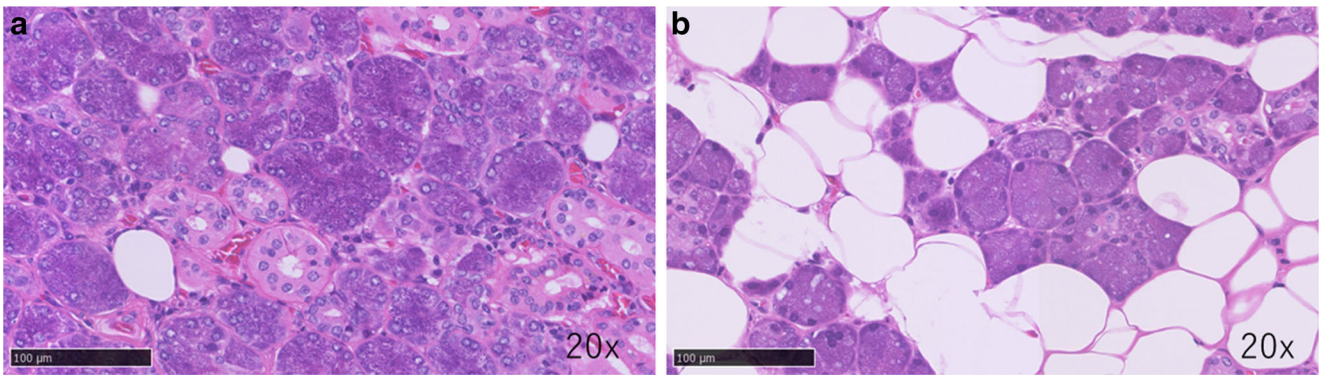

Fig. 3 Hematoxylin and eosin staining of submandibular (SM) glands. **a** SM glands in a patient without hypertension (× 20). **b** SM glands in a patient with hypertension (× 20). A decrease in acinar cells and their replacement with adipose tissue were observed in most patients with hypertension

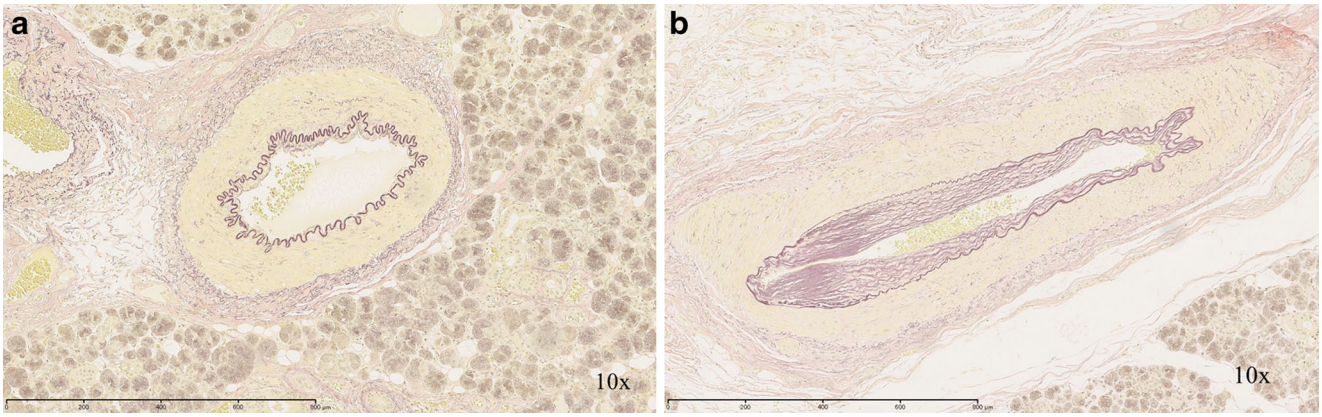

Fig. 5 Elastica van Gieson staining of arteries in submandibular glands. **a** Submandibular glands in a patient without hypertension (× 10). **b** Submandibular glands in a patient with hypertension (× 10). The intima in arteries was thicker in patients with hypertension

thickness of arterioles in the submandibular glands. Sclerosis and stenosis of the arterioles were associated with hypertension, which may cause degenerative changes in the submandibular glands.

The strength of the present study is that it is the first to investigate the relationship between hypertension and degenerative changes in the submandibular glands based on epidemiological and histopathological analyses. The limitation of this study is the effects of the age of subjects on degenerative changes in the submandibular glands. In the epidemiological study, a multivariate analysis revealed a correlation between age and dry mouth. The median age of subjects in the histological analysis was 67 years. Therefore, the present results may be limited to the elderly. The unstimulated saliva test is not suitable for large-population screening surveys because it takes time and effort. Therefore, Kakinoki's classification [26] based on the inspection was used, but the examination environment such as lighting might affect the results.

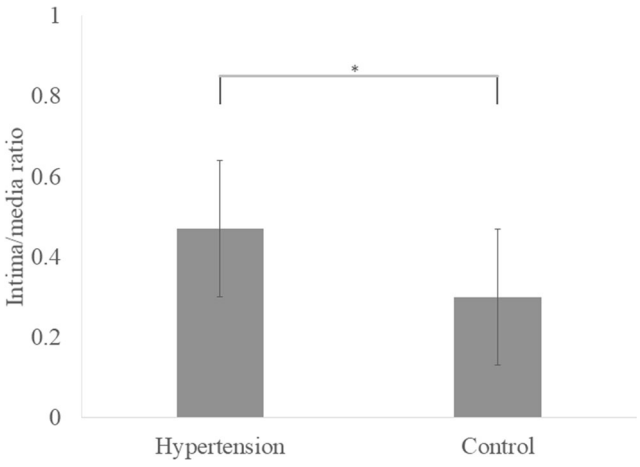

Fig. 6 Comparison of the arteriosclerotic index between patients with and without a medical history of hypertension. The arteriosclerotic index was higher in patients with than in those without hypertension (the Wilcoxon test, $p < 0.05$)

In conclusion, the results of the epidemiological study suggested that dry mouth was associated with sex, age, and hypertension. The results of the histopathological study indicated that degenerative changes in the submandibular glands (decease in the number of acinar cells, fatty infiltration, and the stenosis of arteries) were more evident in patients with hypertension. Based on these results, we speculate that the presence of hypertension may be synergic with aging and associated with sclerosis and stenosis of arterioles, which may result in the degeneration and hypofunction of the salivary glands. Further studies are needed to clarify the direct relationship between these factors.

Abbreviations MetS, Metabolic syndrome; HDL-C, High-density lipoprotein cholesterol; HbA1c, Hemoglobin A1c; eGFR, Estimated glomerular filtration rate; MRI, Magnetic resonance imaging; AI, Arteriosclerosis index; OR, Odds ratio; CI, Confidence interval

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Author contribution Conception and design of the study: Kurita H
Analysis and interpretation of data: Kawamoto M, Yamada S, and Kurita H
Collection and assembly of data: Sakurai A, Gibo T, Kajihara R, Hakoyama Y, Otagiri H, Hashidume M, Kubo K, Aizawa H, Tanaka H, Kondo E, Sakai H, Kaneko T, and Uehara T
Drafting of the article: Kawamoto M and Yamada S
Critical revision of the article for important intellectual content: Yamada S
Final approval of the article: Kurita H

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Declarations

Ethical approval The study protocol was approved by the Ethics Committee of the Shinshu University School of Medicine. (No. #4003 and #4264).

Informed consent Formal consent was not required for this type of study.

Conflict of interest The authors declare no competing interests.

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