Japanese Dental Science Review (2015) 51, 34—40

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Review Article

How masticatory function and periodontal disease relate to senile dementia

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Received 23 April 2014; received in revised form 18 July 2014; accepted 8 September 2014

KEYWORDS
Masticatory function;
Dementia;
Periodontal disease;
Elderly persons

Summary This study reviews the research of dementia, a pathology for which numerous studies have found associations with masticatory function in the elderly. These issues are presently major problems in geriatric medical and welfare settings, and we discuss the prospects for future research into mastication. Dementia and masticatory function have been examined in a range of epidemiological and neuroscientific studies, and associations between the two have been reported. However, a causal relationship has not been satisfactorily established. Biochemical studies have also clarified the basis of the association between dementia and periodontal disease, but have not yet yielded sufficient evidence. Studies offering a high level of evidence, such as intervention studies and meta-analyses, are expected to be undertaken in this area in the future. Maintenance and recovery of masticatory function is of great importance with respect to achieving healthy longevity. Dental science will have considerable obligations and will have to take on an important role in this regard. For dental treatment to take on such important roles in the fields of health, medicine and welfare, it is necessary to provide information that will be understood not just by other medical and healthcare professionals, but also by the general public.

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http://dx.doi.org/10.1016/j.jdsr.2014.09.002
1882-7616

Contents

1. Introduction

Japan has become a super-aged society, reaching this situation before any other country [1]. The 2012 Survey of Dental Diseases found that the proportion of elderly individuals with at least 20 of their own teeth at 80 years of age was 38.3% [2]. At the same time, an increase has been seen in the number of elderly people who have many of their own teeth but have decreased masticatory function [3]. Masticatory function may therefore be conjectured to be affected not only by reductions in the number of teeth, but also by increasing age [4].

Mastication, in which food is crushed and mixed with saliva to form a bolus for swallowing, is a complex process involving the repeated opening and closing of the jaw, the secretion of saliva and the mixing of food with the tongue. Mastication is a rhythmic, automatic movement similar to breathing or walking, and is a characteristic movement that can intentionally be made faster, slower or even stopped [5]. In addition, mastication and swallowing of solid food differs from command swallowing of fluid or semi-solid food. With solid food, the masticated bolus is transported to the oropharynx (stage II transport) before the swallowing reflex begins, and bolus formation within the mouth continues. This transport to the oropharynx is not gravity-dependent, but takes place as a result of active movement of the tongue during mastication. The bolus sent to the pharynx is swallowed while the next bolus is masticated in the mouth and then is sent to the pharynx. Swallowing also occurs sequentially while food that has not been fully masticated remains in the mouth [6]. For this reason, humans are able to efficiently form, divide and swallow boluses of food while masticating and tasting them, even when large amounts of food are placed in the mouth, and can thus ingest abundant nutrition within a short period. This complex feeding and swallowing function is essential for humans to be able to ingest nutrients of the quality and in the quantity necessary for an intellectually and physically active life [7].

The neural circuits for mastication, together with those for the regulation of breathing, walking, posture and blood circulation, exist within the lower brainstem. The rhythmic movement of the jaw and tongue is regulated by the lower brainstem, mainly as a mechanism of rhythm formation based on information generated during mastication from sensory receptors in the oral cavity and masseter muscles [5]. In addition, control is achieved via regulatory mechanisms in areas of the upper brain, including the cerebral cortex, amygdala, basal ganglia, midbrain reticular formation, hypothalamus and cerebellum, which are involved in arousal, higher mental activity, emotion, instinct, homeostasis, taste, motivation to eat, food discrimination, saliva secretion, elicitation of swallowing and movement [8]. Moreover, there are many integrative effects, including health maintenance by the stimulation of saliva secretion, promotion of digestion and appetite regulation by stimulation of digestive juices and hormonal secretion, elicitation of a sense of safety and euphoria via the secretion of pleasure-related substances in the brain by the jaw and oral cavity sensation during mastication, brain activation, and promotion of faciocranial growth and development [8]. In other words, mastication is not only directly involved in digestive function in the oral cavity, but also plays very important and broad-ranging roles in maintaining vital functions.

One important factor inhibiting masticatory function in elderly people is periodontal disease, and numerous reports in recent years have examined relationships between the sustained chronic inflammation in periodontal disease and pathologies such as dementia, diabetes, cardiovascular disease, cancer, premature birth and low birth weight [9]. Associations of periodontal disease with these conditions are supported by a large body of epidemiological data [10], but no causal relationships have been adequately established [11]. This review summarizes the findings on dementia [12—15], which numerous recent studies have reported to be associated with masticatory function in the elderly. This issue is presently a major problem in geriatric medical and care-giving settings, and we consider the prospects for future research into mastication.

2. Relationship between masticatory function and dementia in the elderly

According to results published by a study group of the Japanese Ministry of Health, Labor and Welfare, an estimated 4.62 million people with dementia lived in Japan in 2012. A further 4.0 million people had mild cognitive impairment (MCI), which has a high probability of developing into dementia [16]. Altogether, one in four people $\geq$65 years old in Japan has or is at risk of dementia [17]. The prevalence of dementia increases with age, so the number of individuals with dementia is expected to continue rising.

Dementia and its associated problem behaviors lead to the need for more intensive levels of care and are major factors preventing independent living [18]. Consequently, prevention of dementia and protection against aggravation of the condition are enormously important. This review examines the relationship between masticatory function and dementia in the elderly.

2.1. Studies of masticatory function and dementia

Activity levels are higher in elderly individuals with good chewing ability compared to those without, and in particular, marked differences in items related to cognitive ability have been demonstrated. Kondo et al. reported that the loss of teeth, which can markedly impair masticatory function, is a significant risk factor for Alzheimer's disease (AD) [19]. Moreover, the risk of developing AD increases as the number of intact teeth decreases. Kusaga et al. observed a relationship between chewing score and dementia level, and stated that the number of remaining teeth, molar occlusion, and chewing habits may exert influences on dementia [20]. Moreover, chewing scores decreased rapidly from the mild dementia group to the moderate dementia group. Chewing scores thus did not gradually decrease with dementia progression, but rather decreased rapidly with loss of teeth after mild dementia started, suggesting some degree of influence on cerebral function. Encouraging the prevention of tooth loss and adjustment of dentures is of course important when subjects are healthy, but is particularly essential in individuals with mild dementia.

In a separate study, in addition to blood pressure measurements, blood testing and electrocardiography, magnetic resonance imaging (MRI) was performed on volunteers to comprehensively evaluate overall function, including cognitive function, motor function and mental status. The relationship between intraoral status, masticatory function and number of remaining teeth was examined. Elderly individuals who underwent testing were divided into three groups: a ''healthy group'' ($n = 652$, 55.8%), an ''age-associated cognitive decline group'' ($n = 460$, 39.4%) and a ''suspected dementia group'' ($n = 55$, 4.7%). The healthy elderly group had a mean of 14.9 teeth remaining, whereas the 55 elderly individuals with suspected dementia had a significantly lower mean of 9.4 teeth. This suggested a relationship between the number of teeth and dementia. In addition, a total of 195 individuals in the healthy and age-associated cognitive decline groups underwent MRI of the brain to clarify the relationships between both the number of remaining teeth and number of occlusions with the volume of gray matter in the brain. In individuals with a smaller number of teeth, the volume near the hippocampus was decreased. The volume of the frontal lobes, associated with higher brain functions such as volition and thought, was also decreased [21]. Similarly, in a study of 155 people who had undergone MRI, the prevalence of lacunar infarction from asymptomatic cerebrovascular disease and leukoaraiosis, which represent high risk factors for dementia onset, increased with the decreasing number of remaining teeth [22].

A study of 218 elderly individuals in Brazil found that edentulous participants who did not use any dental prostheses scored significantly lower on the Mini-Mental State Examination [23]. People hospitalized with dementia also showed a significantly increased risk of AD as the number of lost teeth increased [24]. Numerous other reports have found associations between tooth loss and decreased cognitive function [25,26].

Animal experiments have reported significant effects on learning and significant extension in memory time as a result eating of hard food [27,28]. Studies using aged animals have shown that hard food delays the decline in learning effectiveness brought on by old age when compared to soft food, which suggests that hard food may curtail senile deterioration [29]. Also, the results of an experiment in which masticatory function disorder was caused by tooth extraction in senescence-accelerated mice suggested an association between masticatory function disorder and declines in cognitive function [30]. Studies using animal models of AD show that soft food causes declines in memory and learning ability compared to hard food, suggesting that the hardness of food affects cognitive function [31]. Studies using animal models of cerebral infarction have also reported that hard food is associated with significantly greater recovery from learning and memory defects than soft food [32].

2.2. Studies of periodontal disease and dementia

The greatest cause of impaired masticatory function among elderly individuals is periodontal disease. In one study of periodontal disease and dementia, the relationship between a serological marker for periodontal disease (*Porphyromonas gingivalis* serum immunoglobulin G antibody titer) and cognitive function was investigated in 2355 individuals $\geq$60 years old as part of the National Health and Nutrition Examination Survey III in the United States. That study reported impairments of recent memory and calculation ability as associated with detection of a serological marker for periodontal disease [33,34]. A separate study looking at AD also found that AD patients show high levels of inflammatory mediators such as tumor necrosis factor (TNF)-α and antibodies to bacteria related to periodontal disease in their sera, suggesting a statistically independent association between periodontal disease and AD [35].

A number of reviews of the literature [36—38] concerning AD and bacterial infections found significant correlations between AD and the presence of *P. gingivalis*. In a brain analysis study of patients with AD, bacteria of the genus *Treponema*, one type of bacteria related to periodontal disease, were observed in $\geq$90% of the cases [39]. In vitro experiments have also suggested an association between neurospirochetosis and AD. A research group in the UK recently carried out an analytic study of brain samples from 10 AD patients, and found traces of *P. gingivalis* in four of them. However, bacteria were not detected in brain samples from 10 people of the same age range who did not display symptoms of dementia [40]. In a recent study, we examined AD model mice (J20 mice) with periodontal disease caused by oral inoculation of *P. gingivalis*. Compared to mice not inoculated with the bacteria, the mice with periodontal disease showed lower maintenance of cognitive function, increased deposition of senile plaques in the hippocampus and cortex of the brain tissue, and increased levels of interleukin 1β and TNF-α in the brain tissue [41]. These findings suggest the possibility that persistent infection in a localized area of the host, such as periodontal tissue, and the resulting inflammatory response may spill over to the whole body, including the brain, and may be involved in systemic inflammation and the development of AD [42]. Lexomboon et al. reported that persons with multiple tooth loss and/or difficulty of chewing hard food had significantly higher odds of cognitive impairment, in a cross-sectional survey of 557 people who were nationally representative of the Swedish population aged 77 or older [43]. When adjusted for sex, age and education, the odds of cognitive impairment were not significantly different between persons with natural teeth and with those multiple tooth loss, but the odds of impairment remained significantly higher for persons with chewing difficulty even when adjusted for sex, age, education, depression and mental illness.

In response to that report, Savikko et al. sent a response letter stating that people with dementia differed from those without dementia in several characteristics although dementia was not related to dentition status or chewing difficulty in a cross-sectional survey that included 3164 people living in long-term care facilities (nursing homes and service housing) in Helsinki [44]. Individuals with dementia were more likely to have malnutrition than those without. It may be that in this frail, highly selected older population residing in long-term institutional care, lifetime risk factors, such as cardiovascular disease, depression, inflammation, use of alcohol or tobacco, and nutrition, have had more of an effect on the prevalence of dementia than dentition or chewing ability at this late point in life. It may also be that these risk factors have had their effect on cognitive impairment and chewing abilities. Savikko et al. further commented that these results may imply that chewing difficulties alone do not lead to cognitive decline, but may be a marker of comorbidities and nutritional status partly responsible for initiating processes that lead to the development of dementia. As yet, insufficient data has accumulated to verify a causal relationship [45], but the nature of the relationship will doubtless become clearer as the mechanisms involved are clarified and intervention studies are carried out in the future.

2.3. Neuroscientific studies of mastication

As discussed in the preceding section, a number of biochemical studies have reported factors linking periodontal disease and dementia. However, factors linking masticatory function and dementia are unclear. In light of studies showing that reduced masticatory function affects cognitive function, we reviewed the current neuroscientific findings on masticatory function and examined factors that link masticatory function and dementia.

Increases in cerebral cortical activity with mastication have been studied using various devices measure brain function, and have been shown by increased blood flow and increased metabolic and nervous activity in various regions of the brain [46].

Cerebral blood flow (CBF) decreases with aging, and the brain atrophy index (BAI) increases when regional CBF decreases [47]. In elderly individuals, a positive correlation has been observed between carotid artery blood flow and intellectual and mental functions [48]. In addition, decreased CBF is a factor associated with cerebrovascular dementia [49].

Mastication causes an autonomic nervous system response that results in increased metabolic activity. This activity also stimulates oral tissues, resulting in increased blood flow not only to oral tissues, but also to the brain. Increases in regional CBF, by chewing sensory information sent to the brain via a sensory input subsystem from an effector subsystem of the masticatory system, and by a rise in carbon dioxide partial pressure produced by an increase in metabolic activity of feedback cortical sensorimotor neurons, are elicited as a result of the capillary lumens being dilated [50]. Based on these findings, sensory stimuli from the periodontal membrane and masseter muscle spindles are thought to reach cerebral blood vessels during chewing movements via trigeminal afferent pathways, leading to blood vessel dilation, and increasing CBF by an increase in heart rate [51]. A recent study using near-infrared spectroscopy (NIRS) evaluated differences in CBF during clenching in edentulous subjects and in those with implant prostheses. CBF was significantly increased with the implant prosthesis [52].

With measurement of brain function using functional MRI (fMRI), increased CBF in motor areas, sensory areas, supplementary motor areas, insula, thalamus and the cerebellum have been observed when chewing gum [53]. Moreover, gum chewing on both sides of the mouth has been reported to significantly increase CBF in the primary sensory area, motor area and prefrontal cortex on both sides, while gum chewing on only one side of the mouth preferentially increases CBF on one side [54—58]. Prefrontal cortical activation as a result of mastication was observed in a study using NIRS, and this increased activity was particularly marked in the elderly, suggesting that mastication may be useful in maintaining cognitive function [59].

Fibroblast growth factors released into the brain as a result of mastication regulate appetite and promote growth, and also are believed to promote brain cell repair and learning and memory formation [60—62].

In an electroencephalographic study, attention to language and processing speed were both increased by chewing, and effects on long-term memory were also suggested [63]. A study by Hirano et al. measured brain activity by fMRI when performing working memory tasks, and the effects of gum chewing were examined [64]. When gum was chewed before performing memory tasks, CBF was increased in the prefrontal area (Brodmann's areas 9 and 46). Furthermore, increased CBF was observed in the right premotor area, precuneus, thalamus, hippocampus and inferior parietal lobe. These findings suggest that chewing can stimulate arousal and may also accelerate the working memory process. Another study on working memory using magnetoencephalography was also conducted [65]. In that study, the magnetic field was measured when gum was chewed, when gum was not chewed and when the hands were opened and closed before performing the visual Sternberg task (working memory task). Under all conditions, in the occipital lobe during memory and in the calcarine and parieto-occipital sulci during memory maintenance, α waves were observed. After no gum chewing and after hand opening and closing, as compared to after gum chewing but before performing the tasks, the correct response rate decreased and α waves increased. This was attributed to decreases in concentration ability. The conclusion of that study was that chewing exerted effects on maintaining concentration and working memory acquisition. Neuroscientific studies have thus shown that mastication promotes CBF and cerebral metabolic and nervous activities, thus affecting cognitive function.

3. Prospects for research into mastication and dementia among the elderly

The above findings indicate a certain level of consensus that mastication affects dementia through the promotion of CBF and cerebral metabolic and nervous activities. However, very few studies have been carried out to verify the effects on dementia of the recovery of masticatory function in the elderly, and there is a need for intervention studies and large-scale prospective cohort studies in this area.

Dementia includes core symptoms of memory defects, disorientation, deterioration of judgment, aphasia, apraxia, agnosia, and behavioral and psychological symptoms of delirium, depression, agitation, wandering and delusions [66]. These symptoms can cause impaired eating and swallowing functions or impairments related to eating behaviors, such as refusing food, overeating, allotriophagy or interrupted meals. When severe, such impairments can lead directly to malnutrition, impacting the prognosis and increasing the burden on caregivers [67,68]. Also, factors such as declines in awareness and behaviors related to oral hygiene, difficulty in carrying out oral care and eating soft food due to declines in eating and swallowing functions clearly increase the risk of periodontal disease [69] (shown schematically in Fig. 1). Mice in which periodontal disease was induced experimentally, as mentioned earlier, showed reduced cognitive function and increased deposition of amyloid β-protein in the hippocampus and cerebral cortex [41]. Such findings suggest that the oral function and oral hygiene condition of elderly individuals may affect the status of dementia. However, clarification of causal relationships between dementia and oral function or oral hygiene will require comprehensive survey analysis not only of factors such as the knock-on effect of oral infection or chronic inflammation, but also factors strongly influenced by masticatory function, such as the effectiveness of periodontal disease treatment, nutrient intake, motor function, sphere of activity and intellectual activity. The emergence of clear causal relationships will mean that dental treatment can contribute in a substantial way to the prevention of dementia and the control of its progress. We hope that large-scale studies carried out not just by dental professionals, but also with the input of personnel from various different occupational categories will clarify the relationship between mastication and dementia.

4. Conclusion

Looking to the future of health, medicine and welfare, society will be confronted by the issue of how a healthy longevity

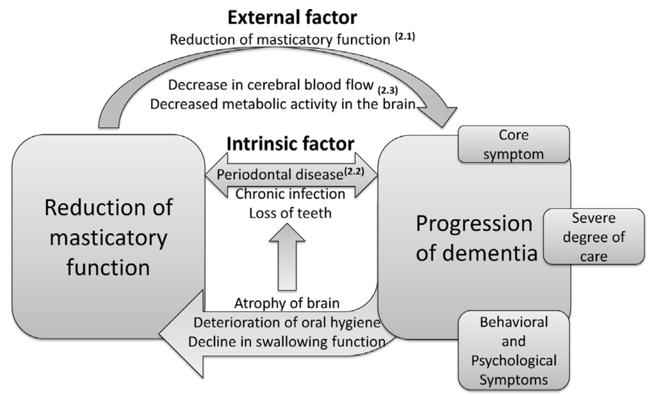

Figure 1 Relationship between dementia and masticatory function. Reduced cerebral metabolic and nervous activities and CBF due to a decrease in masticatory function are external factors for severe dementia. In addition, tooth loss and persistent infection caused by periodontal disease are internal factors for severe dementia. There are core symptoms and behavioral and psychological symptoms of dementia, these exacerbate the level of care for patients with dementia. In addition, the decline in cognitive function due to atrophy of the brain exacerbates poor oral hygiene and also impairs swallowing function. Further, the periodontal disease is exacerbated. Reduction of the masticatory function and the progression of dementia are associated with each other in this way. In this figure, (2.1) shows Section 2.1 of the text (Studies of masticatory function and dementia). (2.2) shows Section 2.2 of the text (Studies of periodontal disease and dementia). (2.3) shows Section 2.3 of the text (Neuroscientific studies of mastication).

that encompasses the quality of life and the purpose in life can be achieved. In this respect, the maintenance and recovery of masticatory function is of great importance, as shown by the various effects of mastication on the whole body. Dental science will therefore have considerable obligations and will have important roles to play in this respect [70]. For dental treatment to take on these challenging problems in the fields of health, medicine and welfare, an understanding will be crucial not just by other medical or healthcare professionals, but also by the general public. For this reason, it is important to promote research into the relationship between mastication and health with cooperation between oral biology and clinical dentistry, and with the collaboration of fields such as medicine, nutritional science, and science and engineering to disseminate necessary and accurate information to the general public.

Conflict of interest statement

The authors have no conflict of interest to declare.

Role of the funding source

This work was supported by Grants-in-Aid from the Research Committee of Comprehensive Research on Aging and Health, the Ministry of Health, Labour and Welfare of Japan (H25-Choju-Ippan-005).

Acknowledgements

We address special thanks to Makoto Hagiwara, Naoyuki Ishida, and Shiho Morishita, who are members of the Department of Oral Diseases Research National Center for Geriatrics and Gerontology, Japan.

References

[1] Moriya S, Miura H. Oral health and general health at the early stage of ageing: a review of contemporary studies. Jpn Dent Sci Rev 2014;50:15—20.
[2] The Survey of Dental Diseases in Japan 2012. http://www.mhlw.go.jp/toukei/list/62-23.html [accessed 03.03.14].
[3] Hashimoto M, Yamanaka K, Shimosato T, Ozawa A, Takigawa T, Hidaka S, et al. Oral condition and health status of elderly 8020 achievers in Aichi Prefecture. Bull Tokyo Dent Coll 2006;47:37—43.
[4] Hirano H, Ishiyama N, Watanabe I, Nasu I. Masticatory ability in relation to oral status and general health on aging. J Nutr Health Aging 1999;3:48—52.
[5] Squire LR, Bloom FE, Spizer NC. Fundamental neuroscience. 2nd ed. London: Academic Press; 2002. p. 753—66.
[6] Palmer JB, Rudin NJ, Lara G, Crompton AW. Coordination of mastication and swallowing. Dysphagia 1992;7:187—200.
[7] Matsuo K, Palmer JB. Coordination of Mastication, Swallowing and Breathing. Jpn Dent Sci Rev 2009;45:31—40.
[8] Kandel ER, Schwartz JH, Tm J. Principles of neural science. 4th ed. McGraw-Hill; 2000. p. 348—80, 982—96.
[9] Kamer AR, Morse DE, Holm-Pedersen P, Mortensen EL, Avlund K. Periodontal inflammation in relation to cognitive function in an older adult Danish population. J Alzheimer Dis 2012;28:613—24.
[10] Gulati M, Anand V, Jain N, Anand B, Bahuguna R, Govila V, et al. Essentials of periodontal medicine in preventive medicine. Int J Prevent Med 2013;4:988—94.
[11] Katz J, Wallet S, Cha S. Periodontal disease and the oral-systemic connection: is it all the RAGE? Quintessence Int 2010;41:229—37.
[12] Weijenberg RA, Scherder EJ, Visscher CM, Gorissen T, Yoshida E, Lobbezoo F. Two-colour chewing gum mixing ability: digitalisation and spatial heterogeneity analysis. J Oral Rehabil 2013;40:737—43.
[13] Yamamoto T, Kondo K, Hirai H, Nakade M, Aida J, Hirata Y. Association between self-reported dental health status and onset of dementia: a 4-year prospective cohort study of older Japanese adults from the Aichi Gerontological Evaluation Study (AGES) Project. Psychosom Med 2012;74:241—8.
[14] Miura H, Yamasaki K, Kariyasu M, Miura K, Sumi Y. Relationship between cognitive function and mastication in elderly females. J Oral Rehabil 2003;30:808—11.
[15] Kimura Y, Ogawa H, Yoshihara A, Yamaga T, Takiguchi T, Wada T, et al. Evaluation of chewing ability and its relationship with activities of daily living, depression, cognitive status and food intake in the community-dwelling elderly. Geriatr Gerontol Int 2013;13(3):718—25.
[16] Asada T. An introduction to geriatric psychiatry: recent topics. Psychiatr Neurol Japon 2013;115:84—9 [in Japanese].
[17] Iwamoto T. Dementia and lifestyle-related diseases in Japanese aging society. Nihon Rinsho Jpn J Clin Med 2011;69:953—63 [in Japanese].
[18] Takeda S. Two-year survival and changes in the level of care for the elderly patients recognized as in need of long-term care in the public nursing-care insurance scheme. Nihon koshu eisei zasshi 2004;51:157—67 [in Japanese].
[19] Kondo K, Niino M, Shido K. A case-control study of Alzheimer's disease in Japan — significance of life-styles. Dementia 1994;5:314—26.
[20] Kusaga M, Mkouyama N, Tatemich Y, Uemura T. Mastication as indicator of brain function in the elderly people II. J Kyushu Univ Nurs Soc Welf 2002;4:179—83 [in Japanese].
[21] Watanabe M, Tsuboi A, Ohi T. Dental treatment and oral care for patients with dementia. Dementia Japan 2008;22:269—78 [in Japanese].
[22] Taguchi A, Miki M, Muto A, Kubokawa K, Migita K, Higashi Y, et al. Association between oral health and the risk of lacunar infarction in Japanese adults. Gerontology 2013;59:499—506.
[23] Miranda Lde P, Silveira MF, Oliveira TL, Alves SF, Junior HM, Batista AU, et al. Cognitive impairment, the Mini-Mental State Examination and socio-demographic and dental variables in the elderly in Brazil. Gerodontology 2012;29:e34—40.
[24] Shigetomi T, Asano T, Katou T, Usami T, Ueda M, Kawano K. A study on oral function and aging — an epidemiological risk factor for dementia. J Jpn Stomatol Soc 1998;47:403—7 [in Japanese].
[25] Kim JM, Stewart R, Prince M, Kim SW, Yang SJ, Shin IS, et al. Dental health, nutritional status and recent-onset dementia in a Korean community population. Int J Geriatr Psychiatry 2007;22:850—5.
[26] Hansson P, Sunnegardh-Gronberg K, Bergdahl J, Bergdahl M, Nyberg L, Nilsson LG. Relationship between natural teeth and memory in a healthy elderly population. Eur J Oral Sci 2013;121:333—40.
[27] Endo Y, Mizuno T, Fujita K, Funabashi T, Kimura F. Soft-diet feeding during development enhances later learning abilities in female rats. Physiol Behav 1994;56:629—33.
[28] Aoki H, Kimoto K, Hori N, Toyoda M. Cell proliferation in the dentate gyrus of rat hippocampus is inhibited by soft diet feeding. Gerontology 2005;51:369—74.
[29] Kato T, Usami T, Noda Y, Hasegawa M, Ueda M, Nabeshima T. The effect of the loss of molar teeth on spatial memory and acetylcholine release from the parietal cortex in aged rats. Behav Brain Res 1997;83:239—42.
[30] Kawahata M, Ono Y, Ohno A, Kawamoto S, Kimoto K, Onozuka M. Loss of molars early in life develops behavioral lateralization and impairs hippocampus-dependent recognition memory. BMC Neurosci 2014;15:4.
[31] Kushida S, Kimoto K, Hori N, Toyoda M, Karasawa N, Yamamoto T, et al. Soft-diet feeding decreases dopamine release and impairs aversion learning in Alzheimer model rats. Neurosci Lett 2008;439:208—11.
[32] Kawanishi K, Koshino H, Toyoshita Y, Tanaka M, Hirai T. Effect of mastication on functional recoveries after permanent middle cerebral artery occlusion in rats. J Stroke Cerebrovasc Dis 2010;19:398—403.
[33] Noble JM, Borrell LN, Papapanou PN, Elkind MS, Scarmeas N, Wright CB. Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III. J Neurol Neurosurg Psychiatry 2009;80:1206—11.
[34] Sparks Stein P, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E, et al. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. Alzheimer Dementia 2012;8:196—203.
[35] Kamer AR, Craig RG, Pirraglia E, Dasanayake AP, Norman RG, Boylan RJ, et al. TNF-alpha and antibodies to periodontal bacteria discriminate between Alzheimer's disease patients and normal subjects. J Neuroimmunol 2009;216:92—7.
[36] Kamer AR, Dasanayake AP, Craig RG, Glodzik-Sobanska L, Bry M, de Leon MJ. Alzheimer's disease and peripheral infections: the possible contribution from periodontal infections, model and hypothesis. J Alzheimer Dis 2008;13:437—49.
[37] Kamer AR, Craig RG, Dasanayake AP, Brys M, Glodzik-Sobanska L, de Leon MJ. Inflammation and Alzheimer's disease:

possible role of periodontal diseases. Alzheimer Dementia 2008;4:242—50.
[38] Miklossy J. Emerging roles of pathogens in Alzheimer disease. Expert Rev Mol Med 2011;13:e30.
[39] Miklossy J. Alzheimer's disease — a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. J Neuroinflamm 2011;8:90.
[40] Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S. Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. J Alzheimer Dis 2013;36:665—77.
[41] Ishida N, Ishihara Y, Ishida k, Tada H, Kato Y, Isoda R, et al. Periodontitis induced by bacterial infection exacerbates features of Alzheimer's disease in transgenic mice. Alzheimer Dementia 2013;9:P851 [Supplement].
[42] Shaik MM, Ahmad S, Gan SH, Abuzenadah AM, Ahmad EA, Tabrez S, et al. How do periodontal infections affect the progression of type 2 diabetes and Alzheimer's disease? CNS Neurol Disord Drug Targets 2013.
[43] Lexomboon D, Trulsson M, Wardh I, Parker MG. Chewing ability and tooth loss: association with cognitive impairment in an elderly population study. J Am Geriatr Soc 2012;60:1951—6.
[44] Savikko N, Saarela RK, Soini H, Muurinen S, Suominen MH, Pitkala KH. Chewing ability and dementia. J Am Geriatr Soc 2013;61:849—51.
[45] Batty GD, Li Q, Huxley R, Zoungas S, Taylor BA, Neal B, et al. Oral disease in relation to future risk of dementia and cognitive decline: prospective cohort study based on the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial. Eur Psychiatry 2013;28:49—52.
[46] Miyake S, Wada-Takahashi S, Honda H, Takahashi SS, Sasaguri K, Sato S, et al. Stress and chewing affect blood flow and oxygen levels in the rat brain. Arch Oral Biol 2012;57:1491—7.
[47] Takeda S, Matsuzawa T, Matsui H. Age-related changes in regional cerebral blood flow and brain volume in healthy subjects. J Am Geriatr Soc 1988;36:293—7.
[48] Sekimoto H, Matsumoto M, Goriya Y, Nakano T, Matsumoto M, Lin K, et al. Evaluation of common carotid blood flow volume in elders studied with a two-dimensional echographically guided ultrasonic blood flow-meter. Jpn J Geriatr 1988;25:38—43 [in Japanese].
[49] Matsubayashi K, Matsumoto M, Kawamoto A, Shimada K, Saito N, Ozawa T. Evaluation of the cerebral lesion and perfusion as risk factors in vascular dementia. Jpn J Geriatr 1988;25:569—75 [in Japanese].
[50] Momose T, Nishikawa J, Watanabe T, Sasaki Y, Senda M, Kubota K, et al. Effect of mastication on regional cerebral blood flow in humans examined by positron-emission tomography with (1)(5)O-labelled water and magnetic resonance imaging. Arch Oral Biol 1997;42:57—61.
[51] Farella M, Bakke M, Michelotti A, Marotta G, Martina R. Cardiovascular responses in humans to experimental chewing of gums of different consistencies. Arch Oral Biol 1999;44:835—42.
[52] Miyamoto I, Yoshida K, Tsuboi Y, Iizuka T. Rehabilitation with dental prosthesis can increase cerebral regional blood volume. Clin Oral Implants Res 2005;16:723—7.
[53] Onozuka M, Fujita M, Watanabe K, Hirano Y, Niwa M, Nishiyama K, et al. Mapping brain region activity during chewing: a functional magnetic resonance imaging study. J Dent Res 2002;81:743—6.
[54] Zhang M, Hasegawa Y, Sakagami J, Ono T, Hori K, Maeda Y, et al. Effects of unilateral jaw clenching on cerebral/systemic circulation and related autonomic nerve activity. Physiol Behav 2012;105:292—7.
[55] Sakagami J, Ono T, Hasegawa Y, Hori K, Zhang M, Maeda Y. Transfer function analysis of cerebral autoregulation dynamics during jaw movements. J Dent Res 2011;90:71—6.
[56] Hasegawa Y, Ono T, Sakagami J, Hori K, Maeda Y, Hamasaki T, et al. Influence of voluntary control of masticatory side and rhythm on cerebral hemodynamics. Clin Oral Investig 2011;15:113—8.
[57] Ono T, Hasegawa Y, Hori K, Nokubi T, Hamasaki T. Task-induced activation and hemispheric dominance in cerebral circulation during gum chewing. J Neurol 2007;254:1427—32.
[58] Hasegawa Y, Ono T, Hori K, Nokubi T. Influence of human jaw movement on cerebral blood flow. J Dent Res 2007;86:64—8.
[59] Narita N, Kamiya K, Yamamura K, Kawasaki S, Matsumoto T, Tanaka N. Chewing-related prefrontal cortex activation while wearing partial denture prosthesis: pilot study. J Prosthodont Res 2009;53:126—35.
[60] Jiang J, Yamato E, Miyazaki J. Long-term control of food intake and body weight by hydrodynamics-based delivery of plasmid DNA encoding leptin or CNTF. J Gene Med 2003;5:977—83.
[61] Finklestein SP, Caday CG, Kano M, Berlove DJ, Hsu CY, Moskowitz M, et al. Growth factor expression after stroke. Stroke 1990;21(11 Suppl.):III122—4.
[62] Balduini W, Mazzoni E, Carloni S, De Simoni MG, Perego C, Sironi L, et al. Prophylactic but not delayed administration of simvastatin protects against long-lasting cognitive and morphological consequences of neonatal hypoxic—ischemic brain injury, reduces interleukin-1beta and tumor necrosis factor-alpha mRNA induction, and does not affect endothelial nitric oxide synthase expression. Stroke 2003;34:2007—12.
[63] Stephens R, Tunney RJ. Role of glucose in chewing gum-related facilitation of cognitive function. Appetite 2004;43:211—3.
[64] Hirano Y, Obata T, Kashikura K, Nonaka H, Tachibana A, Ikehira H, et al. Effects of chewing in working memory processing. Neurosci Lett 2008;436:189—92.
[65] Ono Y, Dowaki K, Ishiyama A, Onozuka M. Gum chewing maintains working memory acquisition. Int J Bioelectromagnet 2009:2009.
[66] Kinoshita T, Hanabusa H. Issues facing home-based medical support services. Psychogeriatrics 2010;10:90—4.
[67] Edahiro A, Hirano H, Yamada R, Chiba Y, Watanabe Y, Tonogi M, et al. Factors affecting independence in eating among elderly with Alzheimer's disease. Geriatr Gerontol Int 2012;12:481—90.
[68] Edahiro A, Hirano H, Yamada R, Chiba Y, Watanabe Y. Comparative study of eating behavior in elderly patients with Alzheimer's disease and vascular dementia: a first report-Comparison of disturbed eating behavior. Jpn J Geriatr 2013;50:651—60 [in Japanese].
[69] Arrive E, Letenneur L, Matharan F, Laporte C, Helmer C, Barberger-Gateau P, et al. Oral health condition of French elderly and risk of dementia: a longitudinal cohort study. Community Dent Oral Epidemiol 2012;40:230—8.
[70] Kobayashi Y. A long life built by mastication and occlusion. Ann Jpn Prosthodont Soc 2011;3:189—219 [in Japanese].