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Review article

Update and review of the gerodontology prospective for 2020's: Linking the interactions of oral (hypo)-functions to health vs. systemic diseases

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Abstract New lines of evidence suggest that the oral-systemic medical links and oral hypo-function are progressively transcending beyond the traditional clinical signs and symptoms

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of oral diseases. Research into the dysbiotic microbiome, host immune/inflammatory regulations and patho-physiologic changes and subsequent adaptations through the oral-systemic measures under ageism points to pathways leading to mastication deficiency, dysphagia, signature brain activities for (neuro)-cognition circuitries, dementia and certain cancers of the digestive system as well. Therefore, the coming era of oral health-linked systemic disorders will likely reshape the future of diagnostics in oral geriatrics, treatment modalities and professional therapies in clinical disciplines. In parallel to these highlights, a recent international symposium was jointly held by the International Association of Gerontology and Geriatrics (IAGG), Japanese Society of Gerodontology (JSG), the representative of USA and Taiwan Academy of Geriatric Dentistry (TAGD) on Oct 25th, 2019. Herein, specific notes are briefly addressed and updated for a summative prospective from this symposium and the recent literature.

Introduction

Recent studies in oral health and geriatric medicine have suggested a new dimension for linking critical associations between the reduced oral functions (i.e., oral dysbiosis, occlusal/mastication, dysphagia/chewing difficulty, tongue pressure, *etc*.) to certain systemic disorders, such as: pneumonia, gastrointestinal (GI) and pancreatic cancers, cognitive brain functions, Alzheimer's disease (AD), dementia, *etc*. The consensus gathered at the Joint Symposium of "International Association of Gerontology and Geriatrics (IAGG), Japanese Society of Gerodontology (JSG), the representative of USA and Taiwan Academy of Geriatric Dentistry (TAGD)" held on October 25, 2019, at Taipei, Taiwan, entitled: "New Horizon of the Gerodontology for the 2020's: Interactions of oral (hypo)-functions and the underlying links to systemic illnesses vs. health", which was part of the themed scientific programs of the 11th IAGG Asia/Oceania Regional Congress 2019, jointly organized by IAGG and CTGG (Chinese Taipei Association of Gerontology and Geriatrics). Collectively, a brief update and review of the new evidence on the gerodontologic prospective for the coming 2020's have been synthesized, based on the topics presented and materials discussed, which are scientifically collected for a narrative with summative illustration (see Fig. 2) and for the general readers with broader interests, as presented herein below.

Shifting the focal infection paradigm to systemic health vs. disease via oral-medical links in the elderly

The foci of infection theory returned 30-yrs ago, where Mallita et al. and Offenbacher et al. both pioneered that dental caries and periodontal infections were associated with acute or fatal vs. chronic cardiovascular diseases, thereby termed: oral-periodontal medicine.[1,2] Till now, studies have recently suggested that oral microbiome can be found in other parts of our body, including: atherosclerotic vessels, lungs, enteric tracts, pancreas, CNS via blood—brain-barriers (BBB), *etc*., where each compartment may employ the oral-systemic access for underlying interactions towards health or/and illnesses.[3]

Researchers have sought to clarify the plausible relationships between periodontal disease and certain oral-systemic illnesses. The commensal and dysbiotic microbiomes that colonize the mucosal surfaces of our body are capable of generating small peptides or/and metabolites exerting both local and/or systemic effectors (e.g., microbial toxins, pro-inflammatory cytokines, cross-reactive and crippled immunity as well).[4–7] These agents may trigger distant or systemic disorders with undesirable outcomes; i.e., ischemic cardiovascular events & strokes, premature births and/or low birth-weight infants, rheumatoid arthritis, diabetes and overt obesity, pulmonary infections, meningitis (brain abscesses), neurologic disorders (i.e., Alzheimer's disease, AD), colorectal and pancreatic cancers as well, *etc*.[8–18] These devastating diseases derived from local dysbiosis have inevitably resulted in the subsequent losses of teeth and oral functions or dysfunctional sequels; esp., in the frail elderly, and in-turns accompanied by the physical deficits, malnutrition, geriatric syndrome (GS) and poly-comorbidities over time.[19,20]

For example, Hajishengallis et al., have proposed the keystone pathogen hypothesis,[21] suggesting that oral *Porphyromonas gingivalis* (*P. gingivalis: Pg*) may be an important key pathobiont for periodontal infection, enabling to regulate the behavior patterns of oral biome in a low degree. Thus, selective removal of other target probiotic species (i.e., target peptides of *Pg*) could open the possibility of manipulating symbiotic species, so that the host may be beneficial to have removed the harmful ones, leading to a healthier microbiome. Conceivably, the interaction of known risk factors with oral microbiome may lead to an increasing local dysbiosis and pathogenic communities. Meanwhile, the relationships between oral microbiome and systemic effectors have been investigated in animal & human studies, where detection of *Pg* may alter the composition of intestinal microbiome, thereby triggering inflammation in different tissues and organs.[22–25] In

addition, LPS of G(−) Pg initiates an innate immune response involving Toll-like receptor-4 (TLR-4) signaling, resulting in stimulation of MyD88-dependent vs. MyD88-independent pathway, which in turn activates the nuclear factor-κB- pathways and releases the pro-inflammatory cytokines associated with dysbiotic pathologies.[8,9,26–28]

Further, it has been suggested that long-term microbial infections promote direct cell—cell interactions where specific TLRs are linked to pre-cancerous oral epithelium development, thereby leading to OSCC. Later, Ochi et al. reported that TLR-4 was specifically found to be highly expressed in human pancreatic cancers, rather than the normal ones, through blocking MyD88-independent pathway exerting a protective effect on developing pancreatic cancers.[29–32] The above dynamics proposed have been shown rather relevant, since un-notifiable chronic inflammatory disorders (i.e., cardiovascular diseases, various cancers, chronic obstructive lung diseases and DM) are the leading cause of disability and death and linked to deaths more than other diseases combined in the developed world recently.[8–18] In essence, disrupted oral microbiome or dysbiosis can lead to an eco-imbalance of local biofilms, emerging pathobionts and subsequent risks for regional or/and distant diseases.[26–32] Some exemplified recent progresses have been explored for the underlined interactions, briefly outlined as follows:

Periodontal infection and rheumatoid arthritis (RA)

New evidence has provided a correlation between RA and periodontal infections, where the DNA sequence of highly conserved structural motifs of RA antigens manifest a significantly homologous to oral and intestinal microbiome, via a proposed "molecular mimicry model".[33–35] Potential microbes that could trigger inappropriate inflammation in the host may include: EBV, CMV, Proteus & *E. coli* (i.e., microbial vs. human HSP spp.) are involved in the RA pathogenesis.[33–37] To date, dysbiotic *Pg* is the only oral microbiome known to produce peptidyl deiminase (enzyme involved in elimination of arginine residues, called: citrulline) and participating the cellular apoptosis, internalization of the chain-reactions for chromatin remodeling vs. inflammation, and stress responses to certain microbial infections.[34–37] While immunity against *Pg* infection may occur before the onset of RA, the concentration of autoantibodies to citrullinated protein (ACPA) was shown much higher in severe periodontitis subjects.[38] Patients with RA and active periodontitis were likely ACPA positive,[39] as the evidence from genetically modified sterile vs. reproductive mouse studies suggested that defining the probable characteristics of *Trofferyma whipplei*, a gut microbe, may have tip-toed the host susceptibility via (counter)-balancing the periodontal dysbiosis and symbiotic communities. Thus, these results suggest that the specific immunity to pathobiont may be modulated via the oral vs. intestinal microbiomes to the highly homologous self-associated motifs of RA antigens in the host.[40]

Periodontal infection and Alzheimer's disease (AD)

AD is a chronic neurodegenerative disease accompanied by progressive cognitive deterioration, a leading cause of dementia in the older adults over age 65. A large amount of research has provided significant evidence for an infectious nature, including the HSV-1 and microbes (i.e., *Helicobacter pylori*, *Chlamydia pneumonia*, *Borrelia burgdorferi*, *etc.*), which can trigger to amplify self-antibodies with resultant effects in or around the CNS.[16,17,41–44] These findings have been proposed as a potential mechanism by which periodontal infection may contribute to initiation or progression of AD. In the susceptible host, *Pg* may cross the BBB to involve the activated complement-C3 pathway with bystander damages;[16,36,45] whereas, orally dysbiotic microbiome, *Treponema denticola*, was also identified in the cerebrospinal fluid and neuronal ganglion cells.[16,17]

Intriguingly, Dominy SS. et al., have recently reported that Pg-derived cysteine proteases, called: gingipains, were identified in AD patients' brain tissues, which were correlated with the Tau and Ubiquitin pathology known previously[45] and oral infection with *Pg* in experimental mice resulted in its brain colonization and increased $A_{\beta 1-42}$ production, a hallmark of pathologic amyloid plaques found in AD. Later, a synthesized small-molecule chemical inhibitor targeted against gingipains, termed: Azeliragron (COR388), has been shown to reduce the microbial load of *Pg* in brains, $A_{\beta 1-42}$ production and neural inflammation in CNS, and manifest rescued neurons in the affected hippocampus. Though the above findings have suggested the potential application of gingipain inhibitors (COR388) for treating *Pg*-associated brain infection or neuro-degeneration markedly characterized in AD, it remains to be seen whether there is a substantiated and real cause of *Pg*-mediated periodontal infection as to the explored mechanism of developing into AD.[45–47] Thus, overall evidence linking oral microbiome to systemic conditions may involve *Pg*-mediated development of AD, as briefly outlined below (please refer to the illustrative collectives in Fig. 2):

i) Pg DNA is present in the CSF of diagnosed AD patients;
ii) Tau molecules can be fragmented by *Pg* gingipains;
iii) Small-molecule gingipain's inhibitors are neuroprotective;
iv) Oral infection of mice with *P* results in brain infection and induction of $A\beta_{1-42}$;
v) $A\beta_{1-42}$ has anti-bacterial effects against *Pg* resolving to *Pg*-associated brain infection mediated by inhibitors and preventive loss of Citrullination as a plausible link to chronic periodontitis, RA, atherosclerosis and AD;
vi) Periodontal keystone pathogen *Pg* and its secreted enzyme-peptidyl arginine deiminase (PPAD) can be found in the area of hippocampal inter-neurons.

Periodontal infection and gastro-intestinal (G-I) cancers

Studies have suggested that certain microbial species can migrate during oral swallowing or circulations, resulting in spreading throughout our body. Other than being a tumorigenic microbe with impact on G-I cancers; *H. pylori* (*Hp*) is often found in periodontal pockets. Further, oral pathogens [i.e.,*Pg, Fusobacterium nucleus (Fn), Streptococcus, Peptococcus & Przewia*] have been suggested to have some roles in developing colorectal and pancreatic cancers, where *Pg* may co-exist with dysbiotic species [i.e., *Fn, Prevotella intermedia (Pi) & melaninogenica (Pm), Streptococcus mitis (Sm)*] associated with G-I vs. oral cancers and poorer prognosis.[18,48–50] Notably, *Fn* and *Pg* are reported to have

association with pancreatic cancer,[48–50] in addition to Clostridium, certain Actinomycetes strains and streptococci;[4,6,7,51–53] whereas the abundant Fn at the colon cancer sites may be associated with regional metastasis (i.e., rectal ~2%, caecum ~11%).[4,6,7,18,48–53] The framework of cancer-associated *Pg* (co)-infection proposed may suggest that oral microbiome, effectors of dysbiotic activity from inflammatory cells and/or mediators that translocate from the primary sites could interact to produce wider systemic consequences. Thus, such pathogenic community (microbiome) may develop tumorigenic aggression with profound effects on human cells via chronic inflammation, anti-apoptosis and/or direct carcinogenesis,[4,6,7,18,49–53] as proposed.

Moreover, Swidsinski et al. have reported that the presence of complex microbiome in the pancreatic ducts was accompanied by different oral species,[54] while some of them were also found in brain tissues of AD patients, distal vascular tissues, atherosclerotic plaques and fetal-placenta.[4,6,7,18,32,51,52,54] In addition, serum Abs from *Pg* may be applicable to improving cancer diagnosis and prognosis, as the elevated serum anti-*Pg* IgG levels have been related to cancers of the G-I systems. Therefore, a direct relationship between Pg (or other microbiome) and G-I cancer is possible, whose contributions to tumorigenesis may be duly associated with oral microbiome or/and subsequent invasion outside the oral cavity. In this regard, Abs specific to Pg may be useful to improving certain cancers' diagnosis and the prognoses.[4,7,45,53] After all, whether oral microbiome migrates and colonizes distant parts during disease development, after having been colonized by the original microbiome *in-situ*,[1–7,55] require more research to definitively elucidate the causal role of specific oral microbiome with proposed carcinogenic potencies, based on the critical oral microbiome or/and certain biomarkers targeted.

What evidence have been acquired on the aging for oral functions vs. systemic health in geriatrics

The global population has aged at an unprecedented rate in recent decades. This ageing that has increased the life expectancy in the population has become significant, especially in some Asia countries (i.e., Japan, Korea, Taiwan *etc.*). As it is often accompanied by the geriatric syndrome (GS), which gradually progress into chronic or/and systemic disorders; i.e., memory & cognitive impairment (MI & CI) and dementia, a quasi-natural degradation along with comorbidities.[19,20,56] Certain specific general concerns have modified the oral health-care outlooks and outcomes in recent years, as outlined below:

Linking the critical oral conditions and ageing processes: evidence from tooth number vs. dental deafferentation (DD)

It is clear that tooth loss has been suggested positively linked to developing MI, CI and dementia; esp., in the elderly carrying Lipo-E alleles, and those' mental health is significantly influenced by having a sub-optimal number of teeth.[57] It has been shown that the elderly with <20 teeth may be associated with a high(er) risk of developing declines to CI and dementia.[19,20,56] The number of natural or/and functional tooth-units with dental prosthesis may compromise the food selection upon chewing and in-take nutrients required for our body's needs daily. Shimazaki et al. suggested *that* about 50% of the completely edentulous and ~35% of the partial edentulous who did not use dentures developed at a significant risk of physical disability and mortality over time.[19,20] Further, it has been shown that significant reduction of the jaw muscles may come with ageism, where it affects muscles' sensorimotor regulation vs. control;[19,58] thereby, leading to impaired forces of mastication. Thus, maintaining as many teeth or using well-fit dentures appropriately may become an important measure for the oral and physical health of the elderly, especially in the frailer ones.

Subsequently, the impaired mastication/chewing ability and related conditions (i.e., chewing difficulty or dysphagia) found in the institutionalized elderly are likely to develop greater risk of mortality. Shimazaki et al. had showed that the folks who were toothless without wearing dentures may present a significant risk for death, independent of physical & mental status from the baselines, where the physical disability is known to lead to higher rate of mortality.[20] More functional tooth units on dental occlusion may potentially develop into a longer life expectancy, due to resultant increased chewing capacity for functions; likewise, a feedback selection of foods' repertoire in daily meals is like the intellectual & social activities for functional quality of life.[59] On the same token, chewing deficiency may directly or indirectly affect the subsequent mortality as a result of masticatory reduction or dysphagia. Conceivably, changes in dietary intake may be adversely associated with increased potential risk(s) of developing systemic diseases, such as: cardiovascular disorders and cancers.[60]

Neurocognitive vs. oral functions via ageing: evidence from the mechano-transduction

Recent studies have suggested that significant DD and ageing on the brain activity and functions will minimize the functional apparatuses on mastication, resulting in cross-modal disturbances, including the gustatory, auditory and olfactory deficits.[61] The results of animal studies where applying texturally-hard food as the diet may ameliorate such functional declines, thereby further substantiate the links between DD interactions and neurocognitive vs. neurogenic brain axes.[62,63] Thus, there has been a growing trend of plausible association between DD and ageing brain, which may lead to prospects in treating the cognitive decline and neurodegenerative diseases in the elderly. Human and animal studies have suggested that deterioration of the brain and masticatory functions are associated with the decline of hippocampal brain-derived neurotrophic factor (BDNF) levels. In parallel, the molar-less mice housed in an enriched supporting environment have shown an attenuated reduction in the hippocampal BDNF levels and neuronal differentiation, partial improvement of the proliferation and survival of new progenitors, as well as the spatial memory restoration via a Morris water maze test. This may be explained by suppressed neuronal differentiation of progenitors or declined dendritic spines in the hippocampal CA1 basal cells in an age-dependent

manner.[64] In parallel, the number of dendritic spines in molar-less mice mounting lower differentiation of newly neuronal generated cells is suppressed, as the hippocampus-dependent spatial memory is being impaired,[65,66] which may be associated with a decline in the proliferation and survival of new-born cells in the dentate gyrus (DG), an increase of hippocampal amyloid-beta (Aβ), degeneration of norepinephrine neurons in the locus coeruleus and degeneration of dopamine neurons in the substantia nigra as well.[67,68]

Though our brain is in a constant dynamic state, the new connections are being made, including learning new skills or adaptation to an altered oral environment. The hypothesis of "neuroplasticity" has yet to be supported by more studies.[68] Moreover, studies have also shown the specific and reversible neuroplasticity of cortico-motor excitability related to the control of peri-oral tongue muscles in motions. The plastic changes have been shown to return to baseline levels two weeks after the tongue training.[68,69] Similarly to that of fMRI study, Kumar et al. reported a return to baseline levels of cortical activity in brain three months after insertion of new dentures in the denture users' study group. This return to the baseline after the training became ceased might give an impression of cortical changes having been more "elastic" (i.e., reversible) than plastic (i.e., irreversible).

Further to the above, how chewing decline or lack of mastication forces invariably can result from a molar-less operation side (i.e., unilateral molar loss), ipsilateral always with lower EMG and smaller pupil. After amelioration of the above conditions with implant-supported prostheses, such dental therapy may improve trigeminal unbalance, cognitive impairment and then be responsible for the pupil's asymmetry. Yet, despite dental prostheses may improve the masticatory performances, the natural tooth offers the best outcomes, when compared in parallel. Moreover, there are sensational differences between implant prostheses and natural teeth measured by passive tactile test, where the ranking orders of magnitude are typically ~0.3 N (N) for vital tooth, 0.3 N for non-vital tooth and 15 N for Implant-supported prosthesis,[70] whereas the measures of high-density surface electromyography (sEMG) on the superficial layer of masseter muscle are ranked by natural dentate > implant-supported prostheses > removable prostheses, at the end.[69,70]

Next frontier of brain signatures on oral & cognitive functions for the elderly in 2020's

It has been shown that aging is associated with declined oral function, which may be measured by functional assessments, including: mastication, salivary flow rate, missing tooth numbers and muscle volumes.[19,20] Evidence from animal studies has unraveled the underlying mechanisms regarding oral sensorimotor activity, such as: brain's plasticity vs. adaptation of specific oral behaviors.[71] Further reports from recent neuroimaging analyses also highlighted the complex relationships between brain and its stomatognathic functions,[72] which may be highly associated with timely declines of cognitive ability.[73] It is thus urgently needed to translate these critical determinants onto clinical managements for the frailer elders with cognitive impairments.[74]

Further to the above, we have proposed to exploring the brain-stomatognathic axis for the specifics of brain signatures, which could contribute to individual differences in their oral functions in the elderly,[75] as the primarily structural vs. functional MRI be valuable tools for quantifying the potential signatures. Recently, our neuroimaging studies have identified the roles of primary sensorimotor cortices during the mastication and swallowing activities, consistent with those from the animal counterparts.[58,72,75] Meanwhile, the neuroimaging analyses have also revealed the age-related changes in the cerebellum and pre-frontal cortex. As a result, it is clear that declined oral functions may be associated with a reduced capacity of motor functions regarding the learning & cognitive controls, which are essential for adaptations of the feeding behaviors. It is thus speculated that in elderly dental patients, the underlying associations between cognitive decline and the functional adaptions will require further investigations. **Collectively**: Based on our studies of the elderly patients, we have shown that signature changes in feeding behaviors (i.e., chewing & swallowing, *etc.*) are closely linked to the dynamics of cognitive functions. The age-related dynamic changes detected to have become the brain signatures may underlie both the oral and cognitive activities on functions. From a clinical prospective, dentists will likely be facing more challenges in the elderly patients with CI. It is hoped that an evidence-based assessment for evaluating their cognitive abilities on functions may become part of the standard protocols for the risk profiling of their oral sensorimotor functions over time.

Ever-changing prospective in a juxta-posed super-aged society, like Taiwan, in 2020s'

Taiwan has faced in close proximity to a juxtaposed super-aged (the >65-yr elderly ≥20% population, by year 2025) and children-less society in recent decades. Since February 2020, her gross birth-rate has been lowered than gross death-rate, with a surplus of the disabled ~1.2 million folks; therefore, the socio-economic burden has been increasingly dampened by this reversed labor-growth trend (i.e., ageing index >120%) to date.[76] Thus, how to maintain and keep up with the constant challenge of health-care system for the good quality and dignity of the elderly in daily life is an urgent national concern in the juxta-posed super-aged country, likely the next-second forerunner, other than Japan, in the world.

Into the super-aged society (by 2025): core-issues to the oral health-care system

In the past two decades, there has been a lack of oral health-related geriatric research based on the outcome measures that have impacted systemic health issues in Taiwan. Institutions and clinicians have likely been providing medical & dental services through empirical clinical judgments or unjust test results, thereby facing the cliff-hanging dilemma or even in darkness, for being not-so-effective vs. no-efficacy regarding the subjects' overall long-term medical benefits.[76,77] Their oral and systemic manifests have been shown to include the frail elderly with significant high rates of: renal dialysis with diabetic

complications, certain cancers (i.e., oral, colon & breast, *etc*.), three systemic peak-measures (e.g., blood sugar, blood pressure & cholesterols), institutionalized patients with medical tubing devices for life supports, patients on psychiatric medications and poly-pharmacy, *etc*.[78–81] In addition, i) dementia in the frailer patients provides another dimension of the oral-medical challenge over the tops of so-called "holistic" health-care, raising a significant public health attention,[82–84] and ii) the highest rate/prevalence of oral cancers has outranked all other countries' measures.[80,83] Subsequently, the resulting oral and medical health-care for the frailer elderly survivors are further complicated by the functional, behavioral/familial or/and psycho-social constrains involved, as the overall health situations may have become worsened.[77–80]

Therefore, for the health-care professional, it is quite urgent to understand the disease-associated oral changes caused by aging-vs. GS-associated comorbidity & poly-pharmacy on the overall health impact and learn how to implement critical oral-systemic health assessments, clinical measures and effective protocols for older adults and their treatment needs. These functional measures may include the GS vs. aging-associated mucosal changes, decreased (neuro)-tactile sensations, muscle weakness (i.e., sarcopenia & frailty) accompanied by difficult denture-wearing and/or dysphagia, less nutrient intakes and weakening oral and bone functions vs. oral hygiene regiments, *etc*.[85] Further issues may also additionally involve that: **i)** there is a dual deficiency in bridging the dental and medical services on the outcomes and the available budgets allocated to the local vs. regional long-term health-care stations/centers in the country, which drive the above situations more difficult, and sometimes be-crippled; **ii)** there has been a lack of consensus vs. standards on the evaluations and outcome measures, due to significantly heterogeneous and intertwined opinions amongst the medical & dental professionals, which may impede the patients' benefits on outcomes over time; **iii)** moreover, a huge demand on training the gerodontology specialists/dentists and qualified practitioners competent in the clinical care of oral geriatrics for the frailer elders.[76–78]

To date, it is evidently clear that the role and function of the traditional dentally disabled in "special care" categories (i.e., pregnant women, physically disabled folks or under-served children with developmental concerns, etc.) cannot support the real challenges and critical needs of modern dental and medical connotations in today's super-aged population of Taiwan, where recent prime report [76,77] has shown that it is only in the well-designed and equipped institutions or university settings featured by the competent specialists or experienced senior practitioners in academic programs to provide proficient and sufficient calibers and expertise in caring for the frail-(er) and functionally dependent elderly. Without these, most dental graduates and dentists are found unlikely to care for the high-risk patients in the geriatric settings. Thus, to overcome the above issues, it is essential to allocate: **i)** sufficient instructions and practices in the overcrowded undergraduate curriculum for the courses of gerodontology discipline, and **ii)** different levels of post-graduate and graduate training blocks adequately designed to deal with the frailer or dependent elderly due to their complex comprehensive and total health-care treatments required in dental-&-medical health-care services so that the trainees or juniors do not feel overwhelmed uncomfortably (i.e., medical emergency) or overly challenged (i.e., disputes) upon engagements. In this way, oral and general health of the super-aged "frail" elderly will be protected and ensured to achieving and enjoying a long and dignified life in high quality health-care society.[77,84–87]

Prospective of oral disease(s) and dementia: an update from 2020 big-data of USA

Recent surveys evaluating the oral health of older adults with dementia have revealed higher plaque scores and greater incidence of periodontal disease and tooth loss, relative to their peers without dementia.[88] Researchers have sought to identify the pathways linking dementia with poor oral health and have implicated the following potential causations: poorer oral hygiene practices by those with dementia, decreased capacity of their caregivers to assist with oral health care,[89] and reduced access to dental services due to barriers including the costs and transportations.[90] Researchers have also considered the ways that poor oral health may render vulnerable ones to developing dementia. Investigators have identified periodontal disease, both pathogens and resultant inflammation, as potential causative agents in developing dementia. Herein, the key theories and critical findings regarding the complex associations between Alzheimer's disease (AD) and poor oral health are summarized and reviewed. It is helpful to include the main themes of AD etiologies in order to exploring the underlying links of current research on the oral health connections. They are outlined briefly as follows:

i) ***Amyloid cascade hypothesis:*** This is among the oldest theories and has been supported by the human biopsies and mice studies. The A_{β} peptides generated from amyloid precursor aggregates to form amyloid plaque.[91] They both serve as barriers which prevent neurons from connecting with each other and thus producing new or retrieving memories. Unfortunately, no intervention targeting these mechanisms have been shown effective to date.[92] Emerging research suggests that amyloid is likely the result of the disease, not its cause, and may hold promise for early detection of the disease using specific antibodies.[93]

ii) ***Tau hypothesis:*** Hyper-phosphorylation of tau, a microtubule-associated protein, turns normal adult tau into PHF-tau (i.e., paired helical filaments) and intracellular neurofibrillary tangles (NFT). These molecules interfere with axonal transport and can lead to neuronal death over time.[94]

iii) ***Oxidative stress theory:*** The reactive oxygen species produce free radicals and (super)-peroxides, which can damage cellular components and then lead to neuron degeneration.[94]

iv) ***Inflammation theory or microbial/peripheral infection theory:*** Viruses, such as: herpes simplex

and hepatitis, microbes including certain spirochetes and periodontal pathogens such as: *P. gingivalis* and *Treponema denticol*a have all been proposed to act as potential causes of tissue inflammation which leads to neuron death.[94]

Research into the causes of neural death is ongoing, as well as the role of the blood—brain barrier (BBB), where vascular integrity reduces the risks of substances passing through the BBB.[95] Factors associated with poor vascular health, such as fatty diet and sedentary lifestyle, have been associated with increased risks of developing to AD. As with several other systemic conditions found to be associated with poor oral health, it is tempting to draw strong conclusions regarding causation. The pathophysiology of dementia and AD continues to influx with a key factor now considered the health of BBB. Factors such as certain diets and physical exercises have been associated with reduced risks of developing AD and those associated with cardiovascular health in general.

Recent studies exploring the linkage of periodontal disease and AD have looked at the periodontal pathogens, its epidemiology, and the impact of treatments. Aligning with the Inflammation theory, both *Pg* and associated proteases, called: gingipains, have been reported by multiple groups who have found these in higher quantities in human brains with AD.[45,96] Overall, they are not unique to the brains of AD, as the gingipains were found in 96% of the specimen employed. How these microbiome(s) or microbial products may have reached the brain is a key subject of high research interest; it is not clear if the higher quantity detected in AD is attributable to more leaky BBB or degree of periodontal infection.[46] Animal study found that application of *Pg* gingipains orally had resulted in increased amyloid production.[47] Further investigations aimed at the potential impact of systemic inflammation on the integrity of BBB as a risk factor of developing AD has been suggested.[97]

The association between AD and chronic periodontitis (CP) has also been explored through epidemiologic research. In one study, retrospective data of a cohort diagnosed with CP was compared with a control and found a 10-year CP exposure was associated with a 1.707-fold increase in the risk of developing AD. This research results relied on a large insurance database[98] and was an important opportunity because in most other countries, dental diagnoses and treatments are not quite available to be associated with medical diagnoses for such analyses. A longitudinal cohort study followed a population of over 8000 adults for 18 years, and after controlling for social-demographic variables found periodontal disease to be associated with modestly increased risk for incident dementia and mild cognitive impairment.[98]

Further, research exploring plausible linkages between oral health and dementia is equivocal; yet, answers to these questions will help researchers and dental professionals to understand whether periodontal and dental care is a reasonable strategy for delaying its onset, preventing or reversing cognitive declines. Though obtaining underlying answers to this question is rather challenging and difficult, as traditionally diagnoses of AD are made only after significant cognitive changes have identifiably occurred, due to the ability of affected individuals to mask the disease. As the blood tests for early detection become available, in-depth analytical research modeling will arise. While the link between periodontal conditions and AD holds certain promises for greater utilization of dental services which has overall benefits, one must be cautious with the risk of both placing unsought weights behind the theory with likely significant confounders or/and efforts, which may reduce motivation to a holistic approach for disease prevention or/and managements. There is high likelihood that the disease is multifactorial by facts and its natures. Individuals with excellent periodontal health will continue to suffer from AD just as those with significant microbial presence and/or loads may live to later years of life with full cognition. Cross-disciplinary research teams, bringing together oral health, neurology, and even epidemiologic experts would be essential in carrying out significantly rigorous designs for appropriate analyses that can delineate the mechanistic pathways linking dementia and poor oral health, and potential interventions to weaken or even reverse such physiological linkages on their outcomes.

The Japanese recent update of the dementia and frailty on oral health in 2020's

At present, there are 4.6 million people diagnosed with dementia and 3.8 million with mild cognitive impairment (CI) in Japan, whose rates of progression detected have been unprecedented.[99] Based on these facts, in 2015, the Ministry of Health, Labor and Welfare of Japan adopted a "Comprehensive Strategy to Accelerate Dementia Measures" [called: the New Orange Plan, NOP;[100] at http://japanhpn.org/en/dementia2-1-2/] as an innovative strategy to bolster measures against dementia. One key mission of NOP has been collaboratively to realize into a society where people with dementia can live with dignity in pleasant familiar environments as they hope and desire to as long as possible in life. The NOP consists of seven pillars as briefly described below:

i) raising awareness and promoting the understanding of dementia;
ii) providing healthcare and long-term care services in a timely and appropriate manner as the dementia stages progress;
iii) strengthening countermeasures for the early onset dementia;
iv) supporting those who look after people with dementia;
v) creating an elderly- & dementia-friendly community;
vi) promoting research and development, and disseminating the results of prevention, diagnosis, managements & rehabilitations, and the support & care models for people with dementia;
vii) prioritizing the perspectives for those with dementia and their families;

A 2015 positional statement of the oral health management for the elderly with dementia

Previously, one of the important strategic acts on oral health promotion for the elderly was the national 8020

campaign: to keep the elderly at least ≥20 natural teeth till aged 80, which was launched in 1989 (which was nationally <10%). Then, by 2017, >50% population has achieved the campaign goal successfully. Meanwhile, there has been a serious health issue amongst all that aged >80 was the dementia. In general, the elderly with dementia likely practice good oral hygiene insufficiently with greater difficulties for health, thereby suffering higher rates of caries, periodontal disease and other oral illnesses.[99–104] In addition, they develop further problems from the dietary intake, chewing & swallowing issues, and dysphagia as well.[74,85,105] Further to these, Japanese Society of Gerodontorogy (JSG) has worked proactively to launching research in order for revealing the links between dementia and oral care in the elderly. Based on the results of 2080 campaign & NOP, JSG had published "a positional statement of dental care for the elderly with dementia" in 2015, as listed. Later, JSG has published the dental treatment guidelines for the elderly with dementia,[102] primarily focused on the second pillar of the NOP.

The guideline for dental treatment of older adults with dementia

A summary of this guide-line (GL) was established in collaboration with JSG and Japanese Dental Association, post-reviewing 593 clinical questions (CQ) and professional opinions. Then, the aggregated data was placed into five CQ categories: (1) Treatment plans and management methods for patients with dementia uncooperative with dental treatment, (2) Standards of performing extractions & oral surgery treatments for patients with dementia, (3) Preparation of dentures for patients with dementia, (4) Providing the dental interventions, assessing swallowing function and nutritional counseling for patients with dementia, and (5) Effects of dental treatment for the patients with progressive dementia. The final GL is consisted of essential 38 CQs gathered via recruitments of public comments prior to its publication for documentation.[104–108] Nevertheless, new information and knowledge produced from CQs of the GL has enabled the development of Dentists' Response to the Training for Dementia Improvement in patients, as advocated in NOP. Further implementation for training at the workplaces regarding oral & nutritional care and managements has become possible later as to promotion and corporation with dental care and appropriate orally nutritional support for the elderly with dementia.[109] Importantly, it is expected that a supportive environment in which sufficient medical care to the elderly with dementia is physically available, thereby enabling its extension to the field of oral health promotion and nutritional care management, including the dental treatments and care for the elderly who require nursing care.

The genesis and dawn of oral frailty

The oral frailty is a new concept, being utilized as one of the preventive strategies to maintain or improve eating/chewing ability of the elderly.[85,99,110–112] The diagrammatic steps of its diagnosis consist of four phases, and each phase depicts different level of declining oral functions. Patients in the first and second phases are usually assisted by the population approach services. Specifically, patients in the fourth phase diagnosed with "oral dysfunction/dysphasia", then are covered by the National Health Insurance of Japan.[85] However, the third phase, called "Oral hypo-function", was originally excluded from the coverage, but has become an important geriatric health topic recently.[85] After tedious researches and efforts from the dental-medical experts & government officials, NHI policy was updated later in April, 2018 to recognize the "Oral hypo-function", now categorized under the national coverage. The clinical concern of "oral frailty" cannot be unique but limited to Japan; whereas other Asian countries like Korea and Taiwan share very similar social structures, medical systems and the epidemics of oral dysfunction in the elderly.

Currently the Japanese has the longest life expectancy in the world, where "health care, frailty prevention & integrated multi-disciplinary care" have become an indispensable medical strategy for the rapid aging/super-aged society to serve and care for the elderly, in general.[85] Further, oral health is a vital topic in both calls stated above; conceivably, oral health is integral to the general health and social well-being of the common people, esp., for the elderly. Oral health does not merely refer to the number of teeth present (i.e., functioning tooth-units) and levels of oral hygiene, but also to the overall oral functions, including: masticatory forces, tongue and lip motor skills, and salivary secretions, swallowing efficiency, *etc*.

In light of the renewed focus on "eating/chewing ability and oral function" for the elderly, we have pioneered a new functional term, called "oral frailty", where it highlights a biologic issue about a decline of oral functions can easily lead to a sarcopenia-related physical state of frailty and a further decline in oral functions even detectable at earlier stages. This novel concept has been supported and evidently echoed by the recent large-scale, cross-sectional and longitudinal health surveys.[99,101,109–113] The resulting findings from these studies strongly supported that assessment of oral frailty can have sufficient and significant impact on the host's general health, as it may reduce the risks of physical frailty or/and mortality in the community-dwelling elderly as depicted previously.

In conclusion, our recent findings suggest that in order to maintaining and improving the eating/chewing ability for the elderly, effective collaborations among the dental, medical and nutritional specialists are furthermore required. Our findings also suggest that early detection and prompt management of dementia vs. oral frailty are critically important that we need to raise the awareness among all health-care providers. In addition, we also have to educate our general population for recognizing the importance of their early dual detections and managements. Hopefully, more comprehensive policy or/and new protocols to empowering the management & prevention strategy on oral frailty will go forward, in which the status-quote & strategy of concerns on oral dysfunction vs. oral frailty matters among the community-dwelling elderly using the Japanese examples were elaborately discussed at this TAGD-JSG symposium, as briefly reported above.

The links of swallowing and tongue pressures to dysphagia for the elderly in 2020's

Swallowing involves the coordination of multiple oro-pharyngeal structures; whereas, dysphagia reflects a functional disorder of the oral feeding mechanisms, having become an increasing concern as a result of ageing in recent years. The tongue plays a critical role in swallowing dynamics to propelling bolus onto the pharynx. In patients with dysphagia, dis-coordination of tongue-jaw movements and weakened tongue motor strengths, including incomplete forming or impaired holding of bolus with distancing residues apart, often prevail before or during the swallowing. These may be seen in patients with disuse, neuro/-muscular atrophy or/and cerebrovascular illnesses. Typically, accessing the quantitative measures for tongue's motor kinetics via videofluorography[114] or ultrasonic device[115] is difficult unless at bedside or chair-side, comparing to the easier food test.[114–116]

Other ways of measuring tongue pressure include Iowa oral performance instrument (IOPI) and tongue handy probe (JMS), which are used to quantify its voluntary isometric contractions[117] and may be a predictor for frailty[118] as the function of ageing over time. However, these devices do not allow the occlusion of teeth, thereby not suitable for its motion dynamics during swallowing phases.[119] In addition, some pressure sensors can be allocated to measure tongue pressure kinetics under motion/swallowing, whose palate-anchored device (see Fig. 1A & B below) as a simple sensing sheet was originally developed by us.[120] In general, its profile and kinetics transcend via a geographically anterior, circumferential, to mid-posterior ended fashion, which has been shown associated with hyoid-bone elevation till the most up-forward position thereby producing the maximum tongue pressure in a video-fluorography study.[121] It has been sought that tongue pressure evidently measured in the elderly is rather different from that in the young (see Fig. 1C & D),[122] besides its duration estimated in a water-swallowing test in acts. Further, there is likely motion-specific change of the tongue-swallowing activities between the young and the elderly; as referred to Fig. 1C–D, depicting the much higher pressure detected from lateral-posterior located sensors close to Ch.4 & 5 nearing the circumferential motion, as to that from the lighter one of Ch.1, accordingly.[122]

Conceivably further to the above, the complete denture (CD) employed in the edentulous elderly not only reestablishes the occlusion for chewing and stabilizes the mandible in motions, but also restores the proper tongue-palate contacts for the subsequent swallowing function. This notion is supported by Kondoh et al., whose parallel study of CD users vs. non-users showed that the maximum pressure detected was from Ch. 1, Ch. 2 & Chs. 4 and 5 in the CD users, despite their durations of tongue pressure were almost the same.[123] Similar test values and results can be extended to those using the Repetitive Saliva Swallowing Test, confirming this critical tongue-palate contact during the swallowing processes. Moreover, our lab have also recently cross-examined the elderly patients manifest pathologies related to tongue cancer, stroke, Parkinson disease and muscular dystrophy,[124–127] and have suggested that tongue pressure measured presents different dynamics, thereby maybe considered useful in the diagnosis of early phases of dysphagia in the coming era.[127]

New challenges of oral (hypo)-functions in gerodontology for the Japanese super-aged society in 2020's

In Japan, it is estimated that the population of 75-yr old will increase to ~21,670,000 by 2025, an extreme phenomenon of the super-aged society where the medical/dental and nursing-care support is essentially required. Since 2000, medical & dental treatments including the nursing-care for the elderly have been covered and implemented as part of the national long-term health care insurance plan, to achieve a healthy longevity for our super-aged society. It has been generally thought that oral vs. systemic health and oral frailty vs. physical/mental frailty are interactively and evidently linked,[128,129] all of which exercise as the function of time. The Japanese Society of

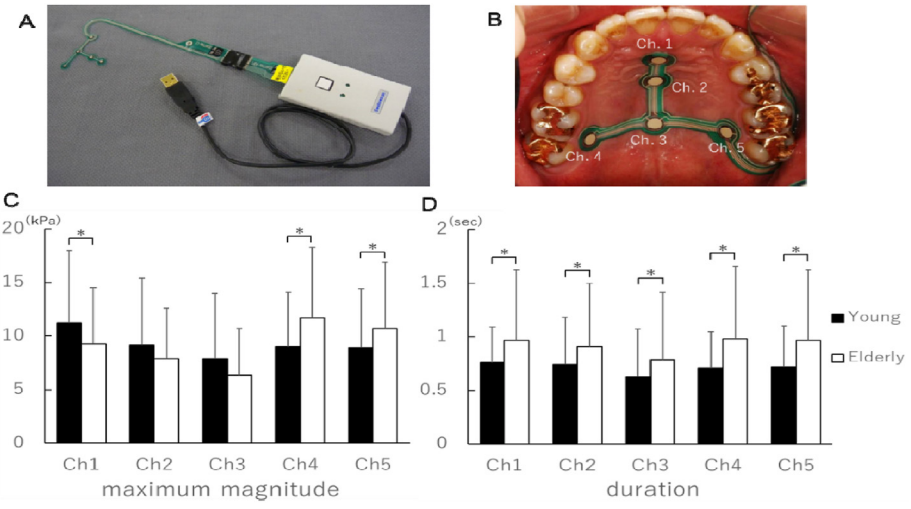

Figure 1 Sensor sheet system (A, B) and comparison of tongue pressure between younger and elderly subjects (C, D).

Gerodontology (JSG) has introduced the concept of "oral hypo-function", as the clinical stages and its recovery may be incorporated via prior dental treatments before functional declines or disorders occur.[85] Thus, their progress declines may be followed by the stepwise systemic frailty or/and illnesses.[85,120]

To date, JSG has focused on the function, which is divided into four stages: near-healthy, oral frailty, hypo-function and functional disorders in the diagram below,[85] illustrating how the conditions by levels are remedied; as to through education and awareness for oral frailty, the programs for prevention to reach a state requiring nursing-care, those identified at risk with manifests of oral hypo-function in need of visiting dental clinic. Meanwhile, seven oral conditions are assigned (i.e., levels of hygiene, dryness, occlusal forces, tongue-lip motor function, tongue pressure, masticatory function & swallowing function), together for making the diagnosis of oral hypo-function with initial thresholds as the diagnostics established for the conditions described (see Table 1 below[85]).

JSG has further suggested that oral hypo-function is clinically defined as the state when three out of these seven diagnostic criteria are met.[130] It is empirically reinstated that clinical intervention or/and training may bring back oral hypo-function and restore it to oral frailty state. If dental professionals provide appropriate intervention for the patients with oral hypo-function, it will likely help them avoid functional disorders, thereby preventing the frailty and/or requiring subsequent need for long-term care. Thereafter, since 2018, Japanese government has adopted the concept of oral frailty as part of important criteria on "oral hypo-function" for the glossary of the disease diagnoses in our national dental insurance program.

The conceptual signs and symptoms for "oral hypo-function"

1 "***poor oral hygiene***" means that the number of microorganisms in the mouth of the older adult has abnormally increased. This leads to an increase of microorganisms in saliva and may cause aspiration pneumonia, postoperative pneumonia, postoperative infection, intraoral infection and so on; in parallel, the microbial counts measured on the dorsum of tongue is correlated with that in saliva.[131]

2 "***oral dryness***" refers to an abnormal dryness in oral cavity or a subjective sign/symptom manifest a dry feeling intra-orally. As the pathophysiological condition involves lacking the moistures from saliva, the contribution to functional homeostasis of a living organism are lost, inducing various disorders.

3 "***reduced occlusal force***" is a clinical condition where the occlusal forces with natural teeth or artificial dentures are reduced. While it is strongly correlated with the host's mastication and occlusal support, it is also heavily affected by peri-oral muscular strength or weakness.[132]

4 "***decreased tongue-lip motor function***" refers to a clinical condition, whose speed and dexterity of the tongue and lips are reduced as a result of a physical decline in brain and perioral muscle functions, associated with ageing or/and systemic diseases. Comprehensive measurements of such speed and dexterity are defined as oral diadocho-kinesis. A typical diagnosis of reduced tongue-lip motor function is given when any of sounding for/pa/,/ta/, or/ka/produced is less than 6 times/sec.[133]

5 "***decreased tongue pressure***" refers to a condition where the physical pressure produced between the tongue and palate upon chowing food is reduced owing to persistent decline in the strength of masticatory muscles that move the tongue.[134] As this condition progresses, subsequent mastication, bolus formation and dynamic phases of swallowing are impaired or compromised, leading to insufficient food processing required to meet the nutritional needs or called dysphagia.[85]

6 "***decreased masticatory function***" refers to a decline of the occlusal forces and tongue's motor strength, resulting in a physical state leading to reduced metabolic rate and subsequent mal-nutrition. As the health status and intraoral functions are compromised from aging and/or disease, food spillage upon eating and/or choking during swallowing occur more frequently where the amount of un-chewable foods increases, leading to loss of appetite and progressive lesser foods that can be eaten.

7 "***deterioration of swallowing function***" refers to a condition where a decline in eating/swallowing function owing to aging has occurred; whereas its dysfunction represents a manifest of significant disorder. Deterioration of swallowing function can be assessed by a self-administered questionnaire (i.e., 10-item Eating Assessment Tool, EAT-10),[134] where sufficient criterion from EAT-10 screening is a score of totally three or higher.

The diagnostic criteria for oral hypo-function

Oral hypo-function does not reflect any morphological lesion or changes like missing teeth or caries, but a functionally pathophysiological condition, consisting of deterioration of oral functions and/or risk factors for mal-nutrition. Our recent study of hospitalized patients showed that oral hypo-function and mal-nutrition are closely related.[78,79,85,87,99,105,109] Oral hypo-function can be regarded as the precursor of oral dys-function; hence a score of 3 points or higher is likely to be an appropriate diagnostic criterion for oral hypo-function, and the score with 4 points carries a tendency towards mal-nutrition.[130] Thus, it is proposed that oral hypo-function be defined as the clinical state when $\geq$3 out of 7 oral functional measures (Diagram & Table above) to meet the criteria.

Future challenges regarding oral hypo-function

At present, Japan has one of the world's most rapidly aging populations; yet, the diagnostic criteria for oral hypo-function are met and made based on a broad range of findings described scientifically.[85] In the future, the outcome measures using oral hypo-function analyses or the efficacies from interventions based on oral hypo-function will be further rectified and justified by further in-depth studies.

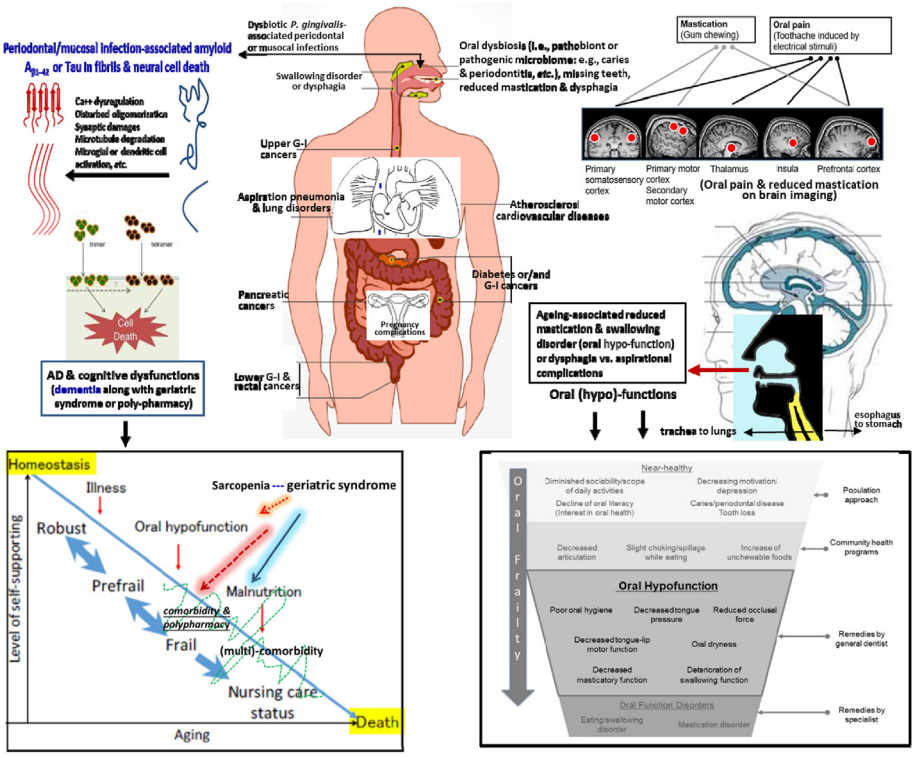

Figure 2 A summative depiction of the oral-medical systemic links. **The oral-medical systemic links are collectively illustrated**, where oral diseases (i.e., caries, periodontitis, mucosal illnesses, chewing difficulty, *etc.*) and associated oral (hypo)-function (i.e., sarcopenia, frailty, *etc.*[85]) transcending beyond the traditional clinical signs and symptoms, via the dysbiotic microbiome, host immune & inflammatory regulations, patho-physiologic changes (i.e., multi-comorbidity & poly-pharmacy, *etc.*) and underlying interactions with ageing through the oral-systemic routes onto developing the mastication deficiency, dysphagia, specific brain activities for (neuro)-cognition circuitries, Alzheimer's disease (AD), dementia and certain cancers of the digestive system as well. Therefore, the oral systemic links will likely affect and reshape the future of diagnoses and prognoses in gerodontology and its professional therapies.

A silent epidemic of oral-medical links to the systemic health: the Taiwan status

The health statistics of ~2016–2018 reported that the prevalence of chronic diseases in Taiwan has shown significant up-rise in recent years,[55,76,77] where on average at least one person out of four has developed the signs of three systemic peak-measures (e.g., high blood pressure, cholesterols and sugars). The 2013 pharmaceutical surveys on Medicine and 2016 Health Surveys showed: i) 72.2% of adults over age-50 suffered from ≥1 chronic disease, and only 12% of ≥65 years old were completely healthy and free of systemic illnesses; ii) 93.8% > 75 years old elderly had suffered from >1, to 30% had >2 and 55–60% > 3 chronic diseases, respectively; iii) on average for the ≥65 years old elderly, they had 2.9 ± 1.8 chronic diseases, of which ~37% suffered from 3 to 4 kinds, 19.6% > 5 kinds chronic diseases; and 85% of all elderly in the long-term care facilities had taken ≥5 medications; iv) many chronic diseases manifested much earlier than expected in the younger adults (≤55 years old) recently, coupled with the impacts in already-aged population (by ~2018.04). This indicated that the multi-comorbidity and poly-pharmacy derived from systemic disorders have progressed timely far more worsening than ever before.[76,77] Further, a recent independent

Table 1 Measurements of clinical signs/symptoms of oral hypo-function.[91]

Clinical signs	Measurements
Poor oral hygiene	The total number of microorganisms (CFU/mL) is $10^{6.5}$ or more.
Oral dryness	The measured value obtained by a recommended moisture checker is less than 27.0.
Reduced occlusal force	The occlusal force is less than 200 N.
Decreased tongue-lip motor function	The number of any counts of /pa/,/ta/or/ka/produces per second is less than 6
Decreased tongue pressure	The maximum tongue pressure is less than 30 kPa.
Decreased masticatory function	The glucose concentration obtained by chewing gelatin gummies is less than 100 mg/dL.
Deterioration of swallowing function	The total score of EAT-10 is 3 or higher

analysis of the global quality of medical care assessed between 1990 and 2015, Taiwan was ranked 45th by comparisons,[76,80] where a number of chronic diseases only reached the passing margins: for instance, 50% on the chronic kidney disease, 58% on the diabetes and 60% on the hypertensive heart disease, *etc*. And, these results clearly reflected that there are significant needs to strengthen the clinical education and research to searching the effective therapies for the chronic diseases, as well as the outcomes for the clinical care and evolving concepts of critical multi-comorbidity involved.[76–82] These results in turns have shown that there are significant needs to promoting the clinical education and parallel research to searching and realizing effective managements for the frail(er) elderly suffering from chronic illnesses, as well as the clinical measures for the health-care professionals to evolving innovative vs. new protocols, thereby proactively reversing the downward trend of the multi-comorbidity concerns already developed.[76–82]

According to the latest 2016 Taiwan survey,[77,135] the prevalence of adult caries was as high as 98.6% (100.0% for >75-yrs, 99.8% for 65–74-yr) and that of the untreated caries was ~42.8%; whereas the tooth-loss rate accounted for 86.0%, with the highest up to 99.6% for >75-yrs, as to the total edentulism accounted for 4.4% in 65–74-yr and 9.9%, the highest, for those in >75-yrs. Significantly noted, that 1/4–1/3 vs. 30–40% of the "frailer" elderly manifested higher rates of total edentulism vs. untreated oral diseases, respectively, regardless their socio-economic status.[76,135,136] In light of the prevalence of periodontal disease in ≥65-yr elderly, their CPI index was 80.48% and 54.93% of them carried the periodontal attachment loss ≥5–6 mm; yet, most of which, those seniors sensed no periodontal-oral symptoms of such diseases at all.[77,135] In addition, the prevalence of oral cancer in Taiwan has been at the world's top (e.g., 42.4/100,000 people), though the less degree of Papua New Guinea, ~32.3/100,000, as officially published by WHO, that is the highest on the global list. In addition, the prevalence of abnormal oral mucosa (i.e., pre-malignancy) was ~6.1% in the Taiwanese elderly. Moreover, several types of cancers (i.e., oral, colon, breast, *etc*.) have frequently championed the world peaks of high prevalence or/and incidences globally.[77,135,136] Further onto this issue, our recent study reported that upon assessing the outcomes in Prolia/Xgeva-holidayed cancer survivors diagnosed with MRONJ, their un-attended prognoses (i.e., lesser progression & clinical staging, *etc*.) were found similarly up-graded for improvements, comparing to those treated with oral bisphosphonates (BP), rather than to those treated with IV-routed BP found progressively worse.[55,137] This may suggest that selecting the types of anti-resorptive drugs (ARDs) employed, the followed-up dosing interval, the overall ARD doses employed and the therapy lengths, *etc*., are critical to the treatments of diagnosed MRONJ, especially in the frailer elderly.[55,137–141]

These above matters must be taken into accounts before any definitive management or therapies choreographed for the measurable or anticipated outcomes for their overall cancer status vs. prognoses.[142–146] Nevertheless, these complex disorders can escalate to worsening physical vs. functional losses later, leading to severe sarcopenia vs. frailty and spreading deficits onto vital organs,[55,77] followed by declining adverse outcomes. At present, our researchers and clinicians have been confronted by these complicated oral manifestations interacting with the underlined multi-comorbidity, indicatively reflective of a silent epidemic for the frailer geriatric seeking the safe and comprehensive treatments. Thus, developing effective general health education and oral cancers prevention programs continues to have considerably critical needs required for improvements on the outcomes, thereby reducing further threats and damages caused by negative impacts stemmed from multi-comorbidity, poly-pharmacy & severe oral diseases, *etc*.

To date, the general and local medico-dental and long-term health-care facilities and institutes have rarely considered the critical importance of integrating and managing supportive therapies with proven clinical efficacies for the urgent needs of the Taiwanese frail elderly, based on their outcomes, as the complications arise, such as: aspiration pneumonia, physiological & pathological chewing disorders (i.e., dysphagia), advanced deteriorations from diabetes, renal dialysis & dysfunctional syndromes, poly-pharmacy, cancers-associated MRONJ, *etc*.[146–150] After all, deterioration and declines of oral functions detected amongst frail elders in the upcoming super-aged society will depend on whether the country and health-care authorities adopt prevention measures with achievable policies for evidence-based protocols, holistic health-care services can help dignify senior lives to achieve the nation's ultimate goals in medical health care; health maintenance and long-term care in an insured and well-versed super-aged geriatric society.[76,149–151]

In summary

Based on the topics and contents addressed above, it is foreseeable that the new development on relationships between oral microbial communities and its systematic effects in the era of post-focal infection theory has been further extended; while oral and gut microbiome can twitter the specific interplays between oral hypo-function/dysfunction and systemic and special diseases, including: the links to RA, pancreatic & colorectal cancers, neuro-cognitive or memory impairments & dementia, AD, dysphagia, respiratory tract & lung infections or pneumonias, *etc*. The key is oral-enteric microbial dynamics in the microbiome that provides critical signals to balance the tissue integrity, thereby regulating the subsequent host's immune responses. In other cases, disorders of the oral ecosystem could lead to eco-microbiome imbalances and loss of balances in the primary biofilms, dominate single or a few pathogenic communities and increase the risk of pathobionet-related diseases and spread outbound. Subsequently, the functional loses of natural teeth, mucosal changes during ageing, masticatory vs. neuronal declines and resultant deficits in squeals, *etc*., will likely interact with the systemic effectors at the regional or/and distant parts or organs, leading to dysfunctional state, comorbidity or even fetal instances, esp., in the frail elderly.

Though the dawn of gerodontology was about 40 years ago; firstly, in the United States, followed by Japan, Australia and then some European countries. The reported

recent new developments related to the health care dilemma depicted at IAGG-2019 herein (entitled:"New Horizon of the Gerodontology for the 2020's: interactions of oral (hypo)-functions and the underlying links to systemic illnesses vs. health") has clearly indicated that there are significant needs to strengthen the clinical education and research to realize the effective therapies of the oral (dys)-functional changes vs. illnesses, chronic systemic disorders, as well as the outcome measures for oral-medical systemic links in the clinical care to evolving innovative concepts in modern dentistry & medicine.[151] Importantly, we must continue to work with health-care professionals and research scholars not only to promote the well-beings of frail elders, but also to effectively progress to the next front edge of a geriatric healthy society.

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