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Aging process

A Project Submitted to the College of Dentistry, University of Baghdad, Department of Pediatric and Prevention in Partial Fulfillment for the Bachelor of Dental Surgery

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Certification of the Supervisor

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Date: 14/4/2022

Dedication

To the kindest hearts in my life my mother and my father… who give me all the support and care in my life…

To the closest person to me my brother and my sister…

Last but not least to all healthcare workers who fighting against covid -19 with great person risk…

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MSCs	mesenchymal stem cells
MSC	mesenchymal stem cell
DPSCs	Dental pulp stem cells
HA	hydroxyapatite
MMPs	matrix metalloproteinases
TNF α	tumor necrosis factor α

Introduction

Aging is the physiologic change that occurs in the body with time **(Morgan et al., 2001)**. Although changes occur in the tissues, organs and systems, not all changes are considered to be physiologic. Many factors contribute to changes that are not part of normal aging **(Lopez-Otin et al., 2013)**. Determining if these changes are part of the aging process, or if they occur independently of aging, can be challenging as aging increases the incidence of certain diseases and disorders **(Morgan et al., 2001)**.

Normal changes that occur as a result of the aging process can take place at different rates **(Cassel et al., 2006)**. Changes associated with age are affected by multiple factors, such as lifestyle, environment and genetics. The changes can be considered as diseases if they become severe enough to affect a person's ability to function or shorten their lifespan **(Stenholm et al., 2015)**. General changes that occur start with the ability to respond to alterations in normal function and the maintenance of homeostasis. Homeostasis is the ability to function at rest and under stress **(Morgan et al., 2001)**. As people age, the functional capacity to respond to external or internal stressors decreases. The body's functional reserve, which is used to maintain homeostasis, is reduced as people get older **(Cassel et al., 2006)**.

The world's population is ageing. By 2050 the number of people of 65 years of age and older will reach about 1.5 billion. The occurrence of general pain in the elderly is high, with the prevalence of chronic pain ranging from 27 % to 86 % **(Larsson et al., 2017)**. This might be due to longstanding persistent disease processes, such as impaired vascular function and age-specific autoimmune conditions **(Ungvari et al., 2018)**. The process of altered immune capability that accompanies ageing is known as immune senescence, which leads to increased susceptibility of older individuals to infections **(Preshaw et al., 2017)**. Also, in

dentistry, chronic pain in the elderly is frequently attributed to several factors, in particular neuropathy and dysregulation of immune responses **(Zakrzewska et al., 2013; Ástvaldsdóttir et al., 2018)**. Consequently, there is an increasing interest in studying ageing processes, with the aim of preventing age-related pathologies and developing cell-based therapies tailored for older people. Indeed, several novel medical disciplines such as regenerative and personalised medicine are evolving very rapidly in the attempt to meet these contingencies **(Partridge et al., 2018)**.

Chapter One: Review of Literature

1.1 Physiologic changes that occur with aging

Ageing is a natural process. Everyone must undergo this phase of life, Ageing reflects many physiologic changes taking place over the course of life some of the changes are listed below:

1.1.1 Vision

Changes that occur in vision include anatomical changes around the eye and the eye itself. The tissue around the eyes atrophies, which can cause changes in the eyelids **(Salvi et al., 2006)**. There is also decreased tear production as well as decreased drainage. Changes in the lens and iris can lead to changes in vision, such as presbyopia (i.e. loss of acuity). Distance and depth perception decrease, and there are changes in the ability to adjust to light. These changes become abnormal when they start to affect vision and thus compromise daily function. Examples of ophthalmic dysfunction include retinopathy (often associated with diabetes), macular degeneration, cataracts and glaucoma.

Hearing Hearing loss associated with age is known as presbycusis **(Cassel et al., 2006)**. This is a gradual loss of hearing as a result of the loss of hair cells in the organ of Corti and of cochlear neurons. The tympanic membrane becomes thicker and there are degenerative changes in the ossicles. However, some older individuals may not notice any change in hearing. Other types of hearing loss may be caused by persistent exposure to loud noises **(Kujawa and Liberman, 2006)**, chronic infection or the presence of a tumor.

1.1.2 Thermoregulation

A decrease in lean muscle mass results in a reduction in the ability to produce and conserve heat. There is also a decrease in the vascular response to temperature changes. This can lead to greater susceptibility to fluctuations in

temperature, with increased risk of hyperthermia or hypothermia. Owing to these changes, tactile sensitivity also decreases **(Cassel et al., 2006)**.

1.1.3 Skin

The skin ages as a result of sun (actinic) damage and the influence of hormonal changes. There is a loss of hydration, which leads to drier skin, resulting in wrinkles. The loss of elasticity and thinning of the skin leads to easier bruising and abrasions **(Cassel et al., 2006)**. There is a decrease in nail growth and in the number of sebaceous glands. Thinning and graying of the hair occurs. Skin changes not associated specifically with aging include damage from excessive exposure to the sun and burns.

1.1.4 Cardiovascular system

The response of the heart to exertion becomes impaired with aging and a longer period of recovery is observed **(Dai et al., 2015; Cassel et al., 2006)**. The left ventricle increases in size, while the intrinsic activity of the heart decreases, which leads to the heart having to work harder. Both systolic and diastolic blood pressure increase as a result of changes in the arteries, including loss of compliance and elasticity of the vessels, and thickening of the arterial walls **(Dai et al., 2015)**.

1.1.5 Respiratory system

In general, age-related changes are caused by functional and anatomic alterations **(Dai et al., 2015; Cassel et al., 2006; Ramly et al., 2015)**. The loss of elasticity in the alveoli decreases the amount of surface area for gas exchange. Although total lung capacity does not change significantly, pulmonary function, such as forced vital capacity and forced expiratory volume, needed for effective respiration, are decreased.

1.1.6 Gastrointestinal system

There is a decrease in the production of gastric acid, but gastric motility is not altered **(O'Mahony et al., 2002)**. Changes in the small intestine cause decreased motility and reduce absorption of nutrients. The large intestine undergoes changes that lead to slowed motility and transit **(Dai et al., 2015; Cassel et al., 2006)**. These changes can result in constipation, but other factors also contribute to this condition, such as a sedentary lifestyle, previous surgery and medications.

1.1.7 Genitourinary system

The kidneys lose about a third of their size with age **(Dai et al., 2015; Cassel et al., 2006)**. With normal aging, this is accompanied by a slow decline in function, specifically the filtering of toxins and the metabolism and excretion of medications **(Baylis and Corman, 1998)**. There is a decrease in bladder capacity and changes in the urethra and muscles used in micturition; this leads to difficulty in the ability to urinate. Incontinence can result, which can also be associated with neurologic disease, stroke and infection. Changes in the female reproductive system lead to a decrease in estrogen and progesterone, a decrease in ovary size, and uterine and vaginal atrophy. Men do not lose the total ability to reproduce, but sperm production does decrease. Testosterone production is reduced.

1.1.8 Changes in nervous system

Ageing is associated with many neurological disorders, as the capacity of the brain to transmit signals and communicate reduces. Loss of brain function is the biggest fear among elderly which includes loss of the very persona from dementia (usually Alzheimer's disease) **(McKhann et al., 2011)**.

Alzheimer's is the most common type of pre-senile and senile dementia. This disease causes nerve cell death and tissue loss throughout the brain, affecting nearly all its functions. The cortex in the brain shrivels up and this damages the

areas involved in thinking, planning and remembering. The shrinkage in a nerve cell is especially severe in the hippocampus (an area of the cortex that plays a key role in the formation of new memories) as well as the ventricles (fluid-filled spaces within the brain) also grow larger. Alzheimer's disease causes an overall misbalance among the elderly by causing memory loss, changes in personality and behaviour-like depression, apathy, social withdrawal, mood swings, distrust in others, irritability and aggressiveness **(Das et al., 2012; Mayeux and Stern, 2012)**.

Nearly, 33 million Indians have neurological disorders, and these occur twice as often in rural areas **(Muthane et al., 2007)**. According to the World Health Organisation **(WHO, 2014)**, nearly 5% of men and 6% of women aged 60 years or above are affected with Alzheimer's-type dementia worldwide. In India, the total prevalence of dementia per 1000 elderly is 33.6%, of which vascular dementia constitutes approximately 39% and Alzheimer's disease constitutes approximately 54% **(Mishra and Palanivelu, 2008)**. Stroke is another common cause of mortality worldwide **(WHO, 2014)**. However, in India, the prevalence rate of stroke among elderly is reported to be very low compared to Western countries **(Das et al., 2007)**.

1.1.9 Musculoskeletal system

Normal ageing is characterised by a decrease in bone and muscle mass and an increase in adiposity **(Villa-Forte, 2014)**. A decline in muscle mass and a reduction in muscle strength lead to risk of fractures, frailty, reduction in the quality of life and loss of independence **(Faulkner et al., 2007)**. These changes in musculoskeletal system reflect the ageing process as well as consequences of a reduced physical activity. The muscle wasting in frail older persons is termed 'sarcopaenia'. This disorder leads to a higher incidence of falls and fractures and a functional decline. Functional sarcopaenia or age-related musculoskeletal

changes affect 7% of elderly above the age of 70 years, and the rate of deterioration increases with time, affecting over 20% of the elderly by the age of 80 **(McGowen et al., 2004)**. Strength declines at 1.5% per year, and this accelerates to as much as 3% per year after 60 years of age. These rates were considered high in sedentary individuals and twice as high in men as compared with those in women **(Van Kan et al., 2008)**. However, studies show that on an average, men have larger amounts of muscle mass and a shorter survival than women. This makes sarcopaenia potentially a greater public health concern among women than among men **(Van Kan et al., 2008)**.

With ageing, toxins and chemicals build up within the body and tissues. As a whole, this damages the integrity of muscle cells. Physical activity also decreases with age, due to a change in lifestyle. Somehow, the physiological changes of the muscles are aggravated by age-related neurological changes **(Fell and Williams, 2008)**. Most of the muscular activities become less efficient and less responsive with ageing as a result of a decrease in the nervous activity and nerve conduction.

1.2 Body composition changes in old age

The human body is made up of fat, lean tissue (muscles and organs), bones and water. After the age of 40, people start losing their lean tissue. Body organs like liver, kidneys and other organs start losing some of their cells. This decline in muscle mass is associated with weakness, disability and morbidity **(Duren et al., 2008)**.

The tendency to become shorter occurs among the different gender groups and in all races. Height loss is associated with ageing changes in the bones, muscles and joints. Studies show that people typically lose almost one-half inch (about 1 cm) every 10 years after age 40 **(Jiang et al., 2015)**. Height loss is even more rapid after age 70. These changes can be prevented by following a healthy

diet, staying physically active and preventing and treating bone loss **(Ferraro et al., 2008)**.

Changes in the total body weight vary for men and woman, as men often gain weight until about age 55 and then begin to lose weight later in life. This may be related to a drop in the male sex hormone testosterone. Women usually gain weight until age 67–69 and then begin to lose weight. Weight loss later in life occurs partly because fat replaces lean muscle tissue and fat weighs less than muscle **(Ferraro et al., 2008)**. Studies have also shown that older people may have almost one-third more fat compared to when they were younger. Fat tissue builds up towards the center of the body, including around the internal organs **(Ferraro et al., 2008)**.

1.3 The aging mouth

Aging is a normal process, but individuals in a population age at different rates. Although this is also true for the oral cavity, disorders of the dentition are cumulative. The dentition, its supporting structures and associated skeletal and muscular components, including the mandible and the maxilla, the temporomandibular joints and the muscles of mastication, form a remarkably effective and reliable system. The stomatognathic system is responsible for biting, mastication and initial digestion of food, and as such usually functions actively at least three times per day from the time of tooth eruption. In addition, unintended usage, such as that associated with clenching, bruxism and other oral habits, would mean that the dentition is actively in use for 2–3 h per day, and teeth may be in intermittent contact at many other times. However, with regular care this system can function effectively throughout the lifetime of the individual **(Lamster et al., 2016)**.

However, the stomatognathic system is vulnerable. Enamel covers the teeth, and while it is the hardest natural substance in the human body, its

maximum thickness in the permanent adult dentition in humans is 2.5 mm. Enamel is comprised of dense mineral (hydroxyapatite) but is susceptible to acid dissolution. Oral-hygiene procedures are intended to limit the accumulation of dental plaque/ biofilm, specifically the bacteria that metabolize and ferment carbohydrates (producing acid by-products), leading to tooth demineralization. However, oralhygiene procedures, primarily a toothbrush used with toothpaste, whilst beneficial, can also cause minor trauma to the soft tissues (buccal gingiva) and the tooth surface (primarily affecting the tooth roots), especially if a brush with hard bristles is used. The texture of food and the acidity of different beverages also can, over time, have an adverse effect on the teeth **(Kunin et al., 2015)**.

It is important to emphasize that the line between aging and disease is not always clear (Table 1). Making this distinction is dependent upon many factors, including the individual's physiologic status and reserve, which will be determined by their overall health status **(Abrams and Thompson, 2014)**.

Table (1): The continuum of change between normal oral aging and disease, in which the decision to provide treatment is modified by intrinsic and extrinsic factors (Lamster et al., 2016).

		EXAMPLES OF POTENTIAL MODIFIERS • GENERAL HEALTH STATUS • ORAL HEALTH STATUS • ORAL HEALTH LITERACY • FINANCIAL RESORCES	
	NO TREATMENT		TREATMENT
	Normal aging		Disease
Dentition	Fracture lines; incisal edges are chipped; teeth are darker in color;		Caries; loss of significant tooth structure
Periodontium	Limited attachment loss, observed as recession on buccal surfaces		Extensive alveolar bone loss; tooth mobility
Oral mucosa	Adequate barrier function; wound healing slightly delayed;		Thinning mucosa; dysplastic change
Salivary flow	May be reduced compared with that found in younger individuals; but considered adequate		Altered by medications and certain diseases
Temporomandibular joints	No discomfort		Pain; inability to properly masticate the full range of food
Masticatory function	Reduced but adequate efficiency		Inability to properly masticate the full range of food

1.4 Changes to the dentition with aging

1.4.1 Appearance

There are a number of changes that occur to the dentition, which are considered to be part of normal aging and not disease. These changes include wearing of the enamel; chipping and appearance of fracture lines, with staining of the chipped areas and fracture lines; exposure of the dentin, which will wear more quickly than enamel; and deposition of secondary dentin, reducing the size of the pulp chamber and canals (which is often observed radiographically). As part of normal aging, the teeth are generally darker in color, a result of the combination of the deposition of secondary dentin, thinning of the enamel and the accumulation of surface stain. A study of more than 700 older individuals (defined here as 40–50 years of age) **(Liu et al., 2014)** revealed that tooth wear was very common, affecting more than 85% of all tooth groups (molars, premolars, caries and incisors) in both the mandible and maxilla. More wear was observed for the incisors and canines compared with the posterior teeth. Risk factors for wear included food characteristics (hard and acidic), nighttime bruxism and reported temporomandibular joint noise (‘clicking’). Although the authors did not comment on whether the individuals in their study were at risk for tooth loss as a result of tooth wear, wear is a consequence of aging and use, which is modified by extrinsic factors (diet) as well as intrinsic factors (bruxism). With the effects of wear and tear, the appearance of teeth changes as a person-ages **(Hartmann and Muller, 2004)**.

1.4.2 Dental caries

Dental caries is a pathologic change, and treatment can vary depending on a variety of factors, including the physical and cognitive status of the affected individual, the extent and severity of the carious lesions, and individual wants and desires. Of greater significance is the need to prevent the development of carious

lesions in older adults, which should begin well before a person reaches their older adult years. A review of the burden of dental caries across the globe used available epidemiological evidence and identified an apparent shift of untreated caries away from children to adults **(Kassebaum et al., 2015)**.

There were three peaks of caries activity, which occurred at ages 6, 25 and 70. The peak at age 70 was related to the presence of root caries/cementum caries, representing the effect of increased tooth retention in older adults, with root surfaces exposed as a result of loss of periodontal support. With the trend for increased retention of teeth over the lifetime, in the future the prevalence of root caries can be expected to increase **(Rapp et al., 2019)**.

1.5 Changes to the periodontium with aging

A modest reduction in periodontal support accompanies aging. This most often manifests as attachment loss, generally observed as gingival recession of ≤ 3 mm on the buccal surfaces. However, the amount of attachment loss can be > 3 mm and still be considered physiologic if the tooth is functional and without mobility, and the person does not have discomfort. There is disagreement as to whether this is part of a disease process or a consequence of repeated use and low-level insult over decades. In the absence of any symptoms such as tooth sensitivity or structural changes to the teeth, treatment generally is not required **(Hunter et al., 2009)**.

Periodontal disease is cumulative, and recent data from the National Health and Nutrition Examination Survey in the USA illustrate that the prevalence of periodontitis increases steadily from 30 to 80 years of age **(Eke et al., 2015)**. A review indicates that the global prevalence of severe periodontitis ranges from 10.5% to 12.0% **(Kassebaum et al., 2014)**. Of interest, the prevalence of severe periodontitis demonstrates a sharp increase in subjects between 20 and 40 years of age, and then plateaus. The peak incidence occurs at 38 years of age. These

data may suggest that the active phases of periodontitis peak in early to midadulthood and that disease progression slows as a person reaches their sixth or seventh decade of life. Furthermore, in a study of a population with access to oral health-care services, there was a high proportion of tooth surfaces that were unaffected by periodontitis. This indicates that periodontal destruction per se is not specifically associated with aging **(Papapanou et al., 2011)**.

In older adults, the risk factors for periodontitis are the same as for younger individuals. However, these risk factors may be more prominent in older individuals, who may be less able to remove plaque deposits as a result of reduced dexterity, have diminished visual acuity or an increased risk of developing contributing conditions such as diabetes mellitus. With healthy aging, the periodontal tissues are reduced but functional, there is some increase in the crown-to-root ratio, the teeth have only physiologic mobility, probing depths are ≤ 4 mm and gingival inflammation can occur in many areas of the mouth, but is not pronounced **(Wu et al., 2016)**. Deviations from this standard can be considered as pathologic. Treatment may be needed but should be viewed from a broad perspective. Treatment may involve modification of general health-risk factors (i.e. improved metabolic control if diabetes mellitus is present and smoking cessation) and oral health-specific risk factors (i.e. modification of the toothbrush handle to aid persons with arthritic changes in the hands, and increased frequency of professional prophylaxis visits). Mechanical therapy should be aimed at removal of biofilm, and surgical procedures should be aimed at improving the environment to allow plaque removal and not solely toward reduction in probing depth **(Darby, 2015)**.

1.6 Changes to the oral mucosa with aging

Compared with the skin of younger individuals, the skin of an older person is notable for flattening of the junction between the epidermis and dermis. The

dermis is thinner, with reduced vascularity and fewer constituent cells, reduced ground substance, disorganized collagen and fewer number of elastic fibers. The result is that the skin is more susceptible to injury and delayed repair (**Farage et al, 2013)**.

Although aging of the skin and aging of the oral mucosa have been compared, this comparison is only partly valid as exposed skin is subject to the effects of daylight (ultraviolet light), air quality (pollution) and the cumulative effect of its role as the integument, experiencing insults related to cuts, abrasions and wear. The oral mucosa is generally unaffected by ultraviolet light, existing in a dark and moist environment, but is subject to trauma related to mastication and the presence of the dentition. Furthermore, whilst the skin has a resident microflora, the oral mucosa is challenged by a far greater infectious burden. This results in greater influx of inflammatory and immune cells, with production of proinflammatory mediators in the gingival aspect of the oral mucosa. These inflammatory mediators are also found in the saliva that bathes the oral mucosa **(Hill, 2004)**.

With aging, the oral mucosa in humans demonstrates a loss of elastic fibers and thickening and disorganization of collagen bundles in the connective tissue **(Klein, 2003)**. The mucosa becomes less resilient, and this, accompanied by a reduction in the microvasculature, leads to impaired wound healing **(Kassebaum et al., 2014)**. A comparison of the oral epithelium at different ages revealed that with aging (> 50 years) the epithelial cells enlarge but flatten **(Abu et al., 2012)**. No changes were observed in the architecture of the epithelial tissue– connective tissue boundary. Furthermore, a study of the clinical appearance of the oral mucosa in healthy adults ranging from 20 to 95 years of age did not detect changes attributable to aging **(Wolff et al., 2002)**.

Oral sensation, defined as discrimination of touch points, does not change appreciably with age. Only a slight diminution was observed in individuals who were more than 80 years old **(Calhoun et al., 2012)**. However, in the presence of defined risk factors, such as smoking, premalignant and malignant changes in the oral mucosa may occur **(Shckorbatov et al., 2005)**.

1.7 Changes in salivary gland function with age

Reports have also identified changes in the composition of saliva as a person-ages. The concentration of IgA has been reported to increase in saliva **(Eliasson et al., 2006)**. Furthermore, total protein concentration in saliva is reduced.. Anatomical changes occur in the major and minor salivary glands with aging. Both human and animal studies have indicated that aging is accompanied by atrophy of the acinar cells and replacement of the normal gland parenchyma with fibrous and/or adipose tissue **(Azevedo et al., 2005)**. Xerostomia is a patient-reported condition of dry mouth and when it occurs in older adults it is not considered a normal aspect of aging. It is estimated that between 25% and 50% of older adults have a complaint of xerostomia **(Nagler, 2004)**. Approximately onethird of those older adults who complain of xerostomia do not demonstrate a measurable reduction in salivary flow. This suggests an emotional or psychiatric component. The major cause of xerostomia is believed to be a side effect of medications, and a much smaller percentage of patients have a clearly identifiable underlying cause, such as diabetes mellitus or Sjogren € 's syndrome **(Vissink et al., 2010)**.

More than 400 medications have a side effect of reduced salivary flow. Salivary flow can also be reduced in patients with certain disorders, including poorly controlled diabetes mellitus, Sjogren € 's syndrome, AIDS and Parkinson's disease **(Hjertstedt et al., 2014)**. The reduction in salivary flow associated with use of a large number of medications is of particular importance

(Wu and Ship, 2013). This can be a significant complication of medication use, and occurs more frequently when a patient is using multiple medications. An analysis of unstimulated and stimulated salivary flow rates indicated that, in particular, drugs associated with treatment of cardiovascular disease reduced salivary flow **(Scelza et al., 2010)**. Medications associated with xerostomia also include anticholinergic drugs, psychotropic drugs, antihistamines and diuretics **(Astor et al., 1999)**.

1.8 Function of the temporomandibular joints in the elderly

Temporomandibular joint disorders are generally subjective, yet potentially debilitating. There is a general agreement that the highest prevalence of temporomandibular joint disorders occurs in middle age, but the data are conflicting with regard to the effect of aging on temporomandibular joint disorders. The consensus is that the prevalence of temporomandibular joint dysfunction does not increase with age **(Lundeen et al., 2006)**; however, an increase in temporomandibular joint symptoms with age has been reported **(Dibbets and van der Weele, 2009)**. With awareness of this controversy, The prevalence of temporomandibular joint disorders and bruxism in 65- and 75-year-old individuals in two counties in Sweden. Their findings indicate a low percentage of individuals who report 'rather great' or 'severe' problems. Only 5% or fewer reported these symptoms, regardless of age (65 or 75 years) or sex **(Unell et al, 2012)**.

1.9 Age-related changes in the dental pulp tissue

Ageing affects all tissues and organs of the human body **(Lopéz-Otín et al., 2013; Kubben and Misteli, 2017)**. The dental pulp also undergoes age-related changes and several studies have focused on its ageing. The dental pulp is a highly specialised, cranial neural-crest-derived mesenchymal tissue that hosts many cell types and is responsible for the production of dentine (i.e. odontoblasts)

and the perception of pain (i.e. nerve fibres) **(d'Aquino et al., 2009)** (Fig. 1). Upon tooth damage by external insults, odontoblasts respond by increasing their secretory activity to produce reparative dentine, and the pulp cells activate inflammatory responses in the case of bacterial invasion **(Farges et al., 2011; Mitsiadis et al., 2015)**. The dental pulp is also characterised by high collagen content and the presence of few scattered fibroblasts. Pulp fibroblasts are responsible for the formation and turnover of extracellular matrix and play an important role during tooth damage **(Shimabukuro et al., 2009)**. The core of the pulp region contains a vast mesodermderived vascular network plexus as well as nerves, which contribute to the establishment of dental pulp stem cells (DPSC) niches **(Pagella et al., 2015)**.

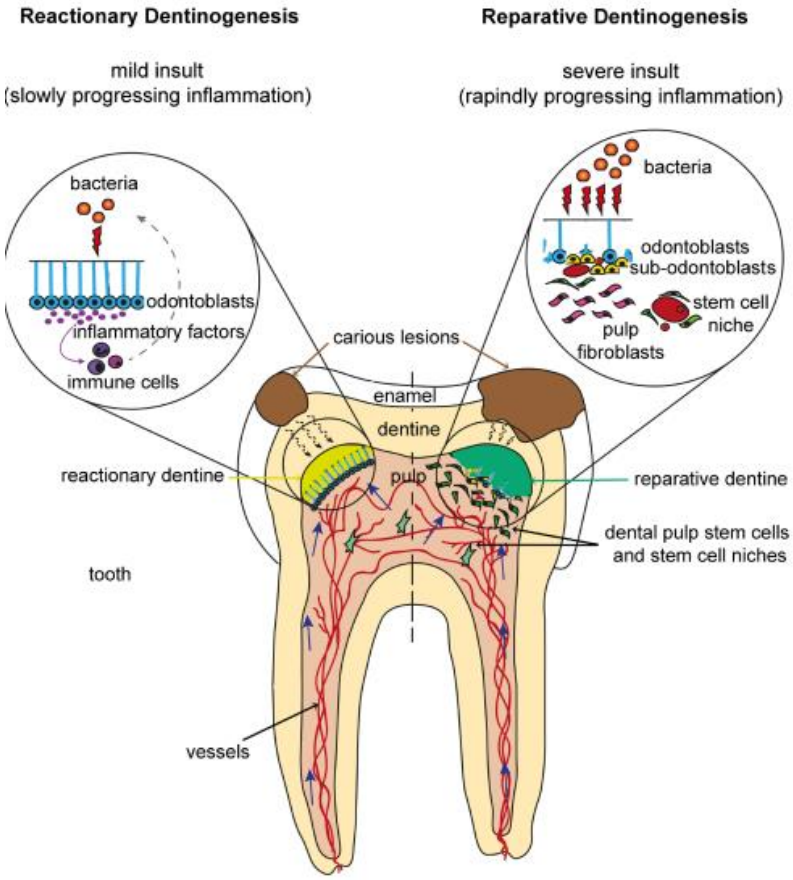

Fig. 1: Schematic representation of a tooth indicating the regenerative capacity of the dentine-pulp complex upon a carious lesion (Iezzi et al., 2019).

All of these dental pulp cell populations undergo age-related modifications, which include the reduction of the pulp chamber caused by continuous formation of dentine **(Burke and Samarawickrama, 2005)**, a reduced vascular supply, the formation of fibrous bundles, and the reduction of fibroblast density. Extensive calcification of the pulp is also a particular condition occurring with ageing. Calcifications in the coronal region are known as pulp stones, whereas those in the radicular pulp are diffuse and may lead to a complete calcific degeneration, a process termed pulpal obliteration **(Goldberg, 2014; Montoya et al., 2015)**. All these events take place approximately in the same period (20-39 years of age), and they are often followed by a decrease in odontoblast cellularity (40-59 years of age). Moreover, with increasing age, pulp cells modify their morphology and acquire a flattened and spindle-like shape **(Daud et al., 2016)**. Similarly, odontoblasts from older individuals show clear signs of decrease of autophagic activity, which results in the accumulation of intracellular lipids and a subsequent loss of functionality **(Couve and Schmachtenberg, 2011)**.

1.9.1 Impact of ageing on dental pulp stem cells

Organs possess an astonishing capacity for extensive and continuous tissue renewal throughout the individual's lifetime, which is maintained by reservoirs of various stem cell populations **(Mitsiadis et al., 2007)**. As physiological functions of all organs decay with age, stem cells have gained increasing consideration in age-associated regenerative processes. It is indeed essential to preserve a sufficient number of stem cell populations in order to maintain organ functionality with advancing age. It has long been recognised that the function and proliferative potential of mesenchymal stem cells (MSCs) declines with age and this might influence the effect of autologous MSC transplantation in the elderly **(Zhang et al., 2005)**. Recent studies showed that age-related dysfunctions also occurred in Dental pulp stem cells (DPSCs) **(Yi et al., 2017)**. Ageing affects

DPSCs, which exhibit typical senescence features such as enlarged cell shape, decreased proliferation and decreased differentiation potential.

Ageing also affects the ability of DPSCs to contribute to mineralisation processes. In fact, a decreased osteogenic potential was observed in aged human DPSCs **(Yi et al., 2017; Iezzi et al., 2019)**.

Adult DPSCs also display lower neurogenic differentiation potential. Various studies have shown that markers of neurogenic differentiation decreased with age **(Feng et al., 2013)**, and that this is associated with impaired localisation of β-tubulin III **(Martens et al., 2012)** and β-catenin expression upon neural induction **(Feng et al., 2013)**.

Age-related features of DPSCs can possibly be reverted by providing appropriate extracellular cues and substrates. DPSCs from older individuals display similar regenerative properties to DPSCs isolated from younger patients, when cultured on nanostructured hydroxy apatite scaffolds and used in vivo to repair calvaria defects in rats **(Bressan et al., 2012)**.

1.9.2 Ageing and the role of secretory factors in dental pulp inflammation

Ageing is characterised by the accumulation of senescent cells and correlates with changes in proinflammatory events **(Campisi et al., 2011; Freund et al., 2011; Lopez-Otin et al., 2013)**. "Inflammaging" refers to the chronic, low-grade inflammation that characterises ageing **(Franceschi et al., 2018)**. In this context, chronic inflammations, along with the loss of the normal immune response capability during ageing, could alter immunocompetence and promote age-related diseases **(Franceschi and Campisi, 2014)**. The extent of caries increases progressively with age and might lead to pulpitis, a pathological condition of the dental pulp characterised by tissue inflammation **(Lee et al., 2013; Bernabé and Sheiham, 2014)**.

Ageing affects the secretion of some senescence-associated factors, including matrix metalloproteinases (MMPs) **(Coppè et al., 2010)**. Several studies have shown that the concentration of specific MMPs increased significantly in inflamed pulp compared to the normal pulp **(Hannas et al., 2007)**. In pulp tissue from patients suffering from acute pulpitis, the levels of MMP-2 and MMP-3 were significantly higher than in pulp from healthy individuals, suggesting that MMPs may play a role in the progression of pulp inflammation and/or damage. Indeed, MMP-3 may activate the expression of other MMPs, such as MMP-1, -7 and -9, which is crucial for triggering the collagen degradation that will eventually lead to changes in the extracellular matrix. These events have been observed in tooth tissues pathologies such as acute and chronic pulpitis and periapical lesions **(Goda et al., 2015)**.

The progression of dental caries into the dental tissues leads to the accumulation of inflammatory cells within the dental pulp. These cells release inflammatory cytokines such as tumor necrosis factor α (TNFα) that promote mineralisation **(Liu et al., 2005)**. This could explain the generation of nucleation points, which drive pulp stone formation in teeth of aged individuals **(Lee et al., 2013)**.

Conclusion

Older teeth have unique characteristics in appearance. The thickening and sclerosing of dentin creates a yellowish less translucent appearance of teeth. In addition, the increasing amount of crack lines that appear in enamel become more apparent as they stain with age. Gingival recession can exaggerate the appearance of a “long tooth.” However, the wear along the biting surfaces of teeth can counteract the “long tooth” appearance. The chemical and mechanical wear along the cementum and roots creates grooves along the gingival line that can readily stain and form root caries. Teeth can also worsen in crowding, especially in the lower anterior incisors.

The properties responsible for sensation in the teeth change with age. Generally, older adults feel less pain and thermal stimulus to their teeth. Teeth become less likely to recover from insult such as dental restorative work, trauma, and infection. Unfortunately, older adults are less likely to sense problems until they become much more serious.

A growing number of older adults are keeping their teeth longer. The future holds a growing need for dental services to keep people’s mouths healthy and functional. The mounting body of scientific evidence suggests the importance of oral health in contributing to general health. Therefore, oral health and maintaining healthy teeth should be a priority throughout life.

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