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Review Article

Hyperglycaemia Accelerates Local Cellular Inflammaging Senescence and Alters the Periodontal Tissues Environment During Periodontitis

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ABSTRACT

Diabetes mellitus is a group of metabolic diseases which have several aetiologies that involve millions of people around the world. Hyperglycaemia, the hallmark of diabetes mellitus, causes detrimental complications such as nephropathy, neuropathy, retinopathy, and cardiovascular disease in both Type 1 and 2 diabetic patients. Inflammaging is recently linked with the development of diabetic complications. Local cellular senescence and its senescence-associated secretory phenotype (SASP) are the main contributors to inflammaging which can be triggered and accelerated by high glucose level. Regarding the oral cavity, hyperglycaemia, provokes the severity of inflammation and destruction in the tooth supporting structures (periodontium) and increases the susceptibility to periodontitis and eventually tooth loss. This paper provides insights into the impact of hyperglycaemia in causing cellular senescence of teeth supporting tissues and escalating periodontal tissue deterioration.

Keywords: *Hyperglycaemia, periodontitis, cellular senescence.*

INTRODUCTION

Cellular senescence is a state of permanent and irreversible cell cycle arrest, in which the cells become insensitive to mitogens and apoptotic signals (Muñoz-Espín & Serrano, 2014; Sharpless & Sherr, 2015). The cells also undergo a series of morphological and functional alterations, which may further inhibit or affect the normal physiological activity of the tissue surrounding the senescent cells (Regulski, 2017; Tominaga, 2015).

Basically, Cellular senescence was described as a loss of proliferative capacity after multiple replications of human diploid fibroblasts (Chen, Li, & Tollefsbol, 2013; Kuilman, Michaloglou, Mooi, & Peeper, 2010). This form of replicative senescence was later shown to be due to telomere attrition. Telomere attrition can cause a temporary arrest of cell proliferation, permitting the cells to rebuild the damaged telomere. However, in case the DNA damage persists for a long term and surpasses a certain threshold, cells are fated to endure either irreversible cell cycle arrest or apoptosis (Cao et al., 2019).

Although cellular senescence is considered as a defensive mechanism against tumour formation, persistence or accumulation of a high number of senescent cells can escalate tumour progression (Myrianthopoulos et al., 2019). This is attributed to few deleterious factors such as chronic inflammation, disruption of tissue function, excessive free radicals' production, and senescence-associated secretory phenotype (SASP) growth factors (Ovadya et al., 2018; Prata, Ovsyannikova, Tchkonia, & Kirkland, 2018). Senescent cells also promote the spread of senescence to nearby cells by producing paracrine signals and mediators (Davalos, Coppe, Campisi, & Desprez, 2010; Krtolica, Parrinello, Lockett, Desprez, & Campisi, 2001). Cellular senescence can be triggered by various inducers, such as ionizing and non-ionizing radiation, genotoxic drugs, demethylating and acetylating agents, carcinogens, epigenetic changes, metabolic disturbances, oxidative stresses or hyperglycaemia (Hernandez-Segura, Brandenburg, & Demaria, 2018; Sidler, Kovalchuk, & Kovalchuk, 2017).

Previous studies reported that senescent cells are the cause and consequence of metabolic alterations and tissue damage, and hence, they might be part of a pathogenic loop in diabetes and other systemic diseases (McHugh & Gil, 2018; Palmer et al., 2015). Animals and in-vitro studies showed that vascular endothelial cells were susceptible to glucose-induced senescence which consequently triggers the microvascular complications of diabetes, such as retinopathy, and nephropathy (Garofolo et al., 2019; Liu et al., 2020; Shosha et al., 2018). Senescent cells may contribute further to accelerate tissue injury and ultimately exacerbate the underlying complications of diabetes in advanced cases (Spinelli et al., 2020; Yokoi et al., 2006).

HYPERGLYCAEMIA AND INDUCTION OF SENESCENCE

Diabetes mellitus is an inducer of premature and accelerated cellular senescence and has been correlated with aging-related kidney diseases and cardiovascular diseases mediated by high levels of glucose (Burton & Faragher, 2018; Guo et al., 2020; Kruszynska, 2004; Peterson & Jovanovic, 1986; Verzola et al., 2008).

Uncontrolled hyperglycaemic condition causes β-cell dysfunction, which consequently leads to accelerated cellular senescence and inadequate insulin secretion (Imai, 2020; Li et al., 2019).

Accumulated senescent cells, in turn, adversely affect pancreatic β-cell function, and induces SASP-mediated tissue damage (Docherty, O'Sullivan, Bonventre, & Ferenbach, 2019; He & Sharpless, 2017; McHugh & Gil, 2018). SASP factors have a detrimental role in the immune-mediated senescent β-cell damage that ultimately leads to Type 1 diabetes (Brawerman & Thompson, 2020; Roep, Thomaidou, van Tienhoven, & Zaldumbide, 2020). As such, eradication of senescent β-cells stops the damage of immune-mediated β-cell and is effective to counteract diabetes (Thompson et al., 2019).

Previous reports concluded that shared mechanisms between the cellular senescence and insulin resistance implies that by targeting and clearing the senescent cells, it is possible to alleviate both the metabolic dysfunction and complications of diabetes (Palmer et al., 2015; Palmer et al., 2019).

Hyperglycaemia Induced Oxidative stress and SASP

Hyperglycaemia alter the local environment of the whole body tissues (including the tooth supporting tissues) by inducing damaging agents and disrupting the natural tissue homeostasis (Giri et al., 2018). High level of oxidative stress was found to have a pivotal role in the pathogenesis of systemic and oral disease (Dos Santos, Tewari, & Mendes, 2019; Valko et al., 2007). It enhances the development of diabetes complications whereas the metabolic disorder of diabetes exacerbates the production of mitochondrial superoxide in endothelial cells of both large and small vessels, and even in the myocardium (Folli et al., 2011; Giacco & Brownlee, 2010).

Free radicals, , known as reactive oxygen species (ROS), are reactive chemical elements that are short lived species containing one or more unpaired electrons (Asmat, Abad, & Ismail, 2016). The production of these free radicals can be contemplated as a 'two-edged' sword because in periodontal health, ROS not only play an essential role in antimicrobial activity, but also in cell signalling and gene regulation (Wang, 2015). The balance between free radicals and antioxidants is essential for proper metabolic and physiological function (Lobo, Patil, Phatak, & Chandra, 2010). They are considered as essential evil messengers for signalling involved in the physiological control of cells differentiation and migration (Dröge, 2002; Winrow, Winyard, Morris, & Blake, 1993). The free radicals alter the normal redox status by passing the unpaired electron to the cells resulting in oxidation of nucleic acids, lipids, and proteins that consequently cause transient or sustained oxidative tissue damage (Pacifici & Davies, 1991; Phaniendra, Jestadi, & Periyasamy, 2015; Sung, Hsu, Chen, Lin, & Wu, 2013).

Hyperglycaemia elevates the local burden of senescent cells in gingival tissue by increasing the release of SASP factors *in vivo* (Zhang et al., 2019). Previous studies showed that high glucose level induces senescence of macrophage and secretion of SASP factors through activation of NLRC4 inflammasome, a mechanism that ultimately provokes gingival cells senescence (Yuan et al., 2016; Zhang et al., 2019). Hyperglycaemia aggravates the creation of advanced glycation end products (AGEs), triggers protein kinase C and polyol pathway, which increase the level of oxidative stress (Nowotny, Jung, Höhn, Weber, & Grune, 2015; Singh, Bali, Singh, & Jaggi, 2014). The production of irreversible AGEs induces a flawed constitution of the extracellular matrix (ECM) components and therefore adversely affects the physiologic and mechanical functions of the tissues involved. Subjects with DM would have their periodontal tissues ECM targeted by AGEs which contribute to the production of ROS and initiation and progression of periodontal disease (Gurav, 2013; Schmidt et al., 1996).

High glucose level and the accompanied oxidative stress facilitate the anaerobic bacterial invasion of periodontal structure that further activate NLRC4 (Hanes & Krishna, 2010; Harijith, Ebenezer, & Natarajan, 2014; Velsko et al., 2015). NLRC4 activation is mostly related to components of Gram-negative bacteria (Olsen & Yilmaz, 2016) that subsequently lead to the activation of caspase-1 (CASP1) which induces a rapid and inflammatory form of cell death by pyroptosis (Rocha et al., 2020; Vladimer, Marty-Roix, Ghosh, Weng, & Lien, 2013).

Unlike apoptosis (classic programmed cell death), pyroptosis (a program of cellular self-destruction that is intrinsically inflammatory) result in rapid release of cytosolic contents (Fink & Cookson, 2006) and spillage of proinflammatory mediators that further drive immune responses and promote inflammation in nearby host cells which consequently undergo senescence (Aquino-Martinez, Khosla, Farr, & Monroe, 2020). In addition to triggering inflammatory host immune responses, activation of CASP1 and pyroptosis contributes to host defence by restricting the intracellular multiplication of invading pathogens that activate NLRC4 (Jorgensen, Zhang, Krantz, & Miao, 2016; Mariathasan & Monack, 2007).

Chronic periodontal disease, in turn, may have an impact on systemic health (Jeffcoat, Jeffcoat, Gladowski, Bramson, & Blum, 2014; Winning & Linden, 2015). In patients with periodontal disease, chronic low-level systemic exposure to periodontal microorganisms may result in low-grade chronic inflammation leading to significant long term increase in levels of inflammatory cytokines and hormones in plasma (Kim & Amar, 2006). This condition is conducive to initiate or aggravate the existing systemic pathological condition such as insulin resistance (Santos Tunes, Foss-Freitas, & Nogueira-Filho Gda, 2010) .

Hyperglycaemia-induced telomer shortening

Telomeres are normally shortened as a result of cell division that ultimately leads to replicative cellular senescence (van Deursen, 2014; Victorelli & Passos, 2017). Although mitotic division of cell is the main cause of telomere length reduction, this process can be influenced or accelerated when cells are exposed to oxidative stress or genotoxic agents, (Blazkova et al., 2010; Coluzzi et al., 2014; Trusina, 2014; Venkatachalam, Surana, & Clément, 2017).

Various studies have reported that oxidative stress and exposure to ROS accelerate telomere shortening in human cells in-vitro (Ahmed & Lingner, 2018). The ROS high-level induced by hyperglycaemia detrimentally causes telomere erosion and dysfunction (Barnes, Fouquerel, & Opresko, 2019; Davalli, Mitic, Caporali, Lauriola, & D'Arca, 2016). The accelerated telomere shortening may disrupt the process of DNA repair that ultimately result in DNA damage response and senescence (Victorelli & Passos, 2017). Other factors, among others, which accelerate telomer shortening and senescence are hydrogen peroxide and gram-negative bacterial products (Gölz et al., 2014; Huang et al., 2020).

Effects of Hyperglycaemia on Chemokine Gradient and pH Level of Periodontal Pocket

Periodontitis is a destructive inflammatory response of the periodontal tissues to the commensal bacteria and opportunistic pathogens which inhabit the gingival crevice (Bostanci & Belibasakis, 2018). As the disease progresses, gingival crevice becomes the part of battle zone which converts to a periodontal pocket. The gingival crevice or the periodontal pocket is bathed continuously with gingival crevicular fluid, a transepithelial transudate in healthy status of gingival crevice, or inflammatory exudate which floods into the periodontal pocket (Barros, Williams, Offenbacher, & Morelli, 2016).

In the healthy periodontium, the gingival tissue interstitial fluid (transudate) is produced and passed through the sulcular epithelium by an osmotic gradient. However, PMNs can always be found in the sulcus, though the flow of GCF is relatively low (Saito et al., 1987). The exudate flows due to the increased permeability of the vessels underlying the junctional epithelium. It carries inflammatory mediators and immune cells to the periodontal pocket and contains bacterial antigens, and enzymes of both host and bacterial origin (Krasse, 1996).

Bacterial pathogenicity is enhanced by modifying factors made by hyperglycaemia altering the host immune response (Berbudi, Rahmadika, Tjahjadi, & Ruslami, 2020; Hodgson et al., 2015). In diabetic patient, the pH of GCF is increased as a consequence of hyperglycaemia, together with bacterial invasion, oxidative stress accompanied by cellular senescence (Hanes & Krishna, 2010; Koidou, Hagi-Pavli, Cross, Nibali, & Donos, 2022). The increased pH in subgingival area, in turn, enhances the growth of anaerobic bacteria and plays a role in the exacerbation of host tissue destruction due to the constant microbial proteolytic activity at alkaline pH (Takahashi & Schachtele, 1990). In addition, as the pH of the pocket rises, the activity of the trypsin-like enzyme increases, which may enable the microbes to inactivate key components of the host defences such as immunoglobulins and complement (Jie Bao, Kari, Tervahartiala, Sorsa, & Meurman, 2008). Evading the host immune defence help in the progression of bacterial invasion. Further rise in pH in the gingival sulcus is thought to occur when subgingival bacteria extensively utilise proteins as primary nutrients. Degradation of host tissues proteins by protease released by bacteria and host immune cells ends in the production of ammonia; which promotes the proliferation of acid-sensitive pathogenic bacteria (Dahlen, Basic, & Bylund, 2019; Niederman, Brunkhorst, Smith, Weinreb, & Ryder, 1990) and facilitate the precipitation of GCF minerals contents in the subgingival plaque to form calculus (Eley & Cox, 2003; Ramadan, Hariyani, Indrawati, Ridwan, & Diyatri, 2020; Takahashi, 2015).

It was reported that expression of cytokines such as IL-6 and 8 was reduced at low pH of 5.5–6.0 (Hackett, Trinick, Rose, Flanagan, & McNamara, 2016). This may explain why the increased alkalinization of GCF is a conducive factor to accelerate the inevitable destruction of periodontal tissues in diabetic patients. Furthermore, diabetic patient has an inadequate local response by PMN, partially explained by an altered chemokine gradient, which may contribute to periodontal disease initiation and progression (Engebretson, Vossughi, Hey-Hadavi, Emingil, & Grbic, 2006).

CONFLICT OF INTEREST

The authors would like to declare that there is no conflict of interest.

CONCLUSION

Hyperglycaemia s is one of the major risk factors for periodontitis. Uncontrolled or poorly controlled individuals with diabetes are more likely to have periodontitis. If there are effective measures to alleviate prediabetes and cure early diabetes, then the progression of hyperglycaemia could be prevented or delayed, which may eventually lead to reduced progression of periodontitis. Aging and altered immune response due to aging are associated both with a progressive decline in glucose tolerance and inadvertently with increasing prevalence and severity of periodontal diseases.

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