GENGIGEL®
Hyaluronic Acid

ORAL HEALTH & ALZHEIMER DISEASES

FACT FILE

HOW CAN ALZHEIMER DISEASE AFFECT ORAL HEALTH?

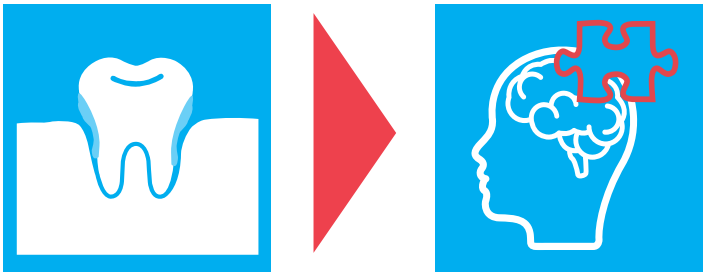
Periodontal diseases has long been linked with inflammatory diseases such as diabetes and heart disease, but a functional association between periodontal disease and Alzheimer Disease (AD) has been established only recently (Sandrameli et al. 2020).

50 mln people in the world live with dementia. Of these 2/3 are affected by AD

Alzheimer Disease is a progressive neurodegenerative disorder characterized by short- and long-term memory loss, impaired decision making, forgetfulness, and changes in mood. According to the World Alzheimer's Report of 2018, 50 million people in the world live with dementia. Of these, two-thirds are affected by AD. It appears more frequently in people over 65 years of age and is more prevalent in women than in men (Calsolaro et al. 2019). The two hallmarks of AD are aberrant accumulation of extracellular amyloid-beta (Aβ) in senile plaques and of hyperphosphorylated tau intracellular neurofibrillary tangles (NFT). The molecular and cellular mechanisms underlying neurodegeneration have not been defined; however, inflammation within the brain is thought to play a pivotal role.

There is a functional association between periodontal disease and Alzheimer disease

During the last decade, many studies have reported the relationship between periodontal disease and Alzheimer's dementia. For example, Ide et al. (2016) showed that the presence of periodontal disease in subjects with mild to moderate Alzheimer disease was associated with a marked increase in cognitive decline over a 6-month follow-up period, suggesting that periodontal disease is a risk factor for AD. Other studies have reported higher circulating antibodies to periodontal pathogens, including *Porphyomonas gingivalis* in AD patients or patients who later developed clinical AD when compared with patients without AD (Dominy et al. 2019; Osorio et al. 2019). Kamer et al. (2015) also found higher levels of amyloid beta deposits in the brains of patients with periodontal disease.



HOW DOES ALZHEIMER DISEASE FAVOUR PERIODONTITIS?

Two mechanisms have been proposed to explain the association of periodontitis and AD.

The first one involves proinflammatory cytokines - such as IL-1, IL-6, IL-8, TNF-α - produced in response of periodontal microorganisms. These inflammatory molecules are spurted out in the systemic circulation through which they may reach the brain. Trigeminal nerve in the oral cavity has also been proposed as alternative way for them to enter the cerebral regions (Sansores-España et al. 2021). The inflammatory molecules could enter even through areas of the brain that have a blood brain barrier (BBB) by various mechanisms: 1) diffusion through fenestrated capillaries of the BBB, 2) using specific cytokine transporters, 3) increasing the permeability of BBB or 4) activating brain endothelial cells to produce cytokines that induce signalling molecules such as nitrous oxide. Once in the brain, they activate microglial cells involved in neuronal damage, favouring AD progression (Sansores-España et al. 2021).

The second mechanism is thought to be due to the detection of several periodontopathic bacteria in the brain have led to the hypothesis that AD might also be caused by microorganisms of the dental plaque biofilm invading the brain. Indeed, *Treponema denticola* and *Treponema pallidum* have been detected in the trigeminal ganglion and cortex and *Porphyromonas gingivalis* in the fourth ventricle and cerebrospinal fluid of patients affected by AD (Singhrao et al. 2015; Dominy et al. 2019). These microorganisms can enter brain either through the blood stream or via the peripheral nerves and elicit an inflammatory mechanism within the central nervous system (CNS). *P. gingivalis* translocation to the brain has been found to promote inflammatory reactions and increase oxidative stress that occlude and damage the microvasculature to the brain, lead-

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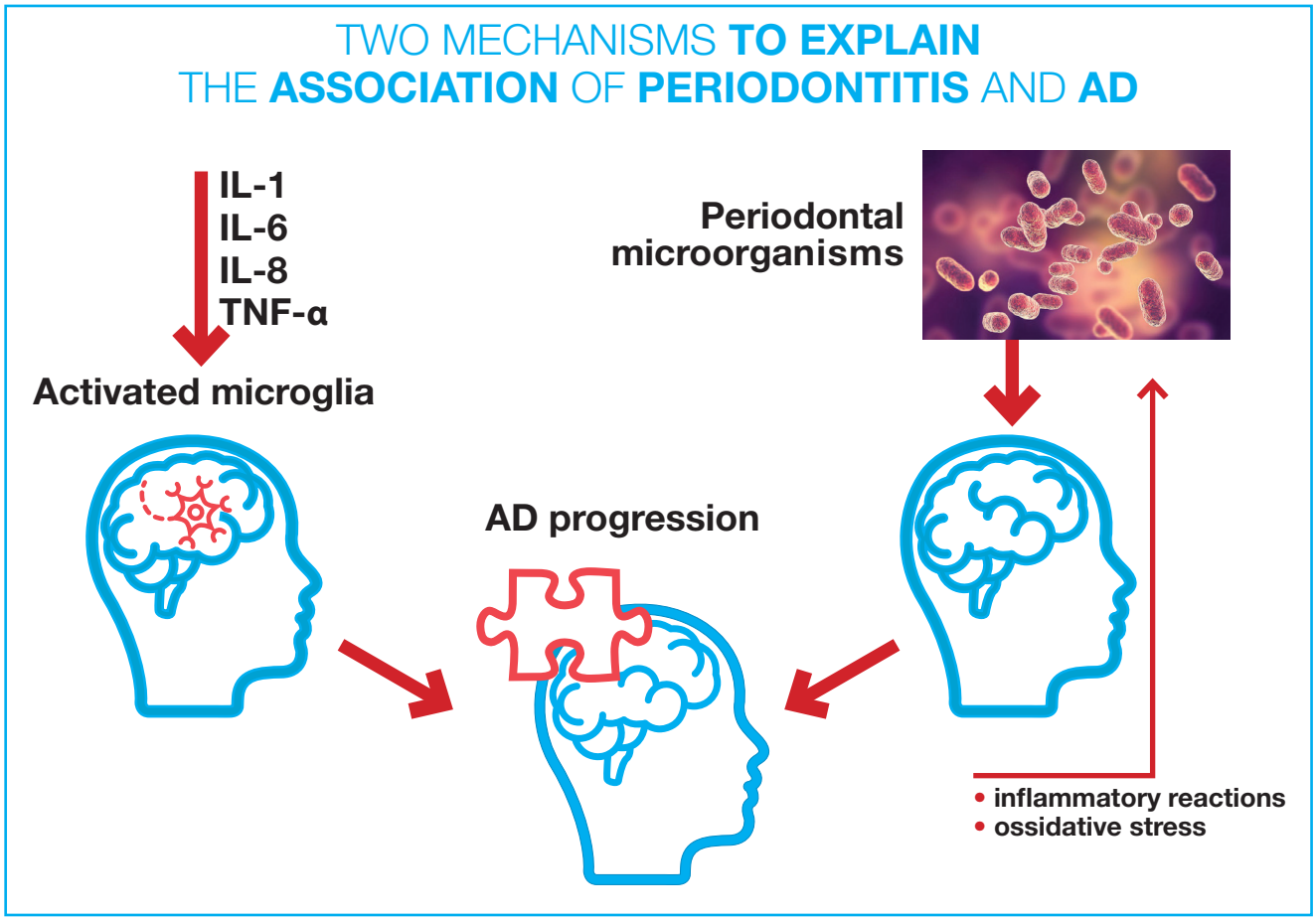
>>> HOW DOES ALZHEIMER DISEASE FAVOUR PERIODONTITIS?

ing to microstrokes and loss of cognitive function (Rokad et al. 2017). Additionally, it may inhibit the adaptive immune responses, resulting in impaired clearance of amyloid beta (Czesnikiewicz-Guzik et al. 2019). Also, bacterial molecules – particularly lipopolysaccharides and the gingipain proteolytic enzymes produced by *P. gingivalis* – seem to be involved in neurodegeneration as they can spread from periodontal tissues to the brain inducing neuroinflammation (Ryder and Xenoudi, 2021). With the potential connection of periodontal disease and AD, the reduction of the intraoral microbiota load, as well as of the inflammatory reactions, is not only critical for the treatment of periodontitis but may also have benefits on reducing the incidence, severity, and/or rate of cognitive decline itself.



WHY RESORTING TO NON-DRUG TREATMENTS?

In recent years, it has become clear that oral health has a major impact on overall health.

Initial treatment of oral disease includes non-pharmacological measures such as effective daily oral hygiene with mouth rinses, fluoride toothpastes, and even removal of plaque biofilm and tartar deposits by scaling and root planing (Wilder and Bray 2016).

Topical treatment of non-keratinized sulcular epithelium has been found to deliver high concentrations of pharmacological agents to periodontal tissue, gingiva, periodontal ligament, alveolar bone, and cementum (Casale et al. 2016). Recently, Sánchez-Fernández et al. showed that topical application of high molecular weight hyaluronic acid (HMW-HA) in patients with peri-implantitis reduced inflammation and levels of proinflammatory cytokine IL-1β in the peri-implant crevicular fluid, suggesting that HMW-HA could be an effective therapeutic option to control the progression of this disease (Sánchez-Fernández et al. 2021). Therefore, resorting to non-drug treatments could also be a first line of protection for oral damage and consequently for AD.

WHY HIGH MOLECULAR WEIGHT HYALURONIC ACID?

HA is a natural and unbranched polymer belonging to a group of heteropolysaccharides called glycosaminoglycans (GAGs) diffused in the epithelial, connective and nervous tissues of vertebrates (Fraser et al. 1997). HA is major component of the ECM, particularly abundant during embryogenesis, in tissues undergoing rapid growth and development, during repair and regeneration, and in association with aggressive malignancies (Erickson and Stern 2012). HA has many different functions, including maintenance of tissue homeostasis and cell surface protection, but it is also involved in many physiological processes, such as cell attachment, migration and proliferation, wound healing, and regulation of immune response and inflammation (Kavasi et al. 2017). High molecular weight hyaluronic acid is deposited in normal tissues and interacts with other components of the ECM to control its structural organization and signaling. In addition, endogenous HMWHA possesses enhanced anti-angiogenic, anti-inflammatory and immunosuppressive properties (Kavasi et al. 2017). The amphophilic nature of HMWHA allows this molecule to trap large amounts of water while binding to hydrophobic molecules such as cell membrane lipids. This property is relevant to the control of hydration and helps to delay the passage of viruses and bacteria through the hyaluronan-rich pericellular zone, as well as during inflammatory processes (Chen and Abatangelo 1999). Clinical studies have shown that HA accelerates the healing of various types of wounds, including burns, epithelial surgical wounds, and chronic wounds (Shaharudin and Aziz 2016).

Why Gengigel®?

Gengigel® is a specific and innovative treatment for gingivitis and periodontitis. It is based on the action of its main ingredient HMWHA, which makes the product strongly bioadhesive, an action that can be enhanced by using a calibrated mixture of additional glycopolymers. Due to its adhesive properties, Gengigel® attaches to the oral mucosa long enough to promote the activation of physiological tissue repair processes that improve the healing response and reduce healing time. In addition, the presence of high molecular weight hyaluronic acid helps Gengigel® maintain the balance of extracellular fluids and promotes the resorption of oedema in inflammatory conditions, rapidly reducing the associated pain. Last but not least, Gengigel® protects the oral mucosa by preserving the micro-environment of the mucosal surface and by regulating the growth of bacterial flora. The evidence on Gengigel® includes clinical data from high-quality prospective comparative studies (Polepalle et al. 2015; Gupta 2017; Al-Shammari et al. 2018). The studies covered various Gengigel® indications, including the treatment of clinical signs associated with periodontal disease or gingivitis following surgical periodontal therapy. In all cases, patients were treated with the gel formulation, either with a single application at the time of surgery, or with multiple applications following periodontal surgery/treatment. Gengigel® proved to be an effective treatment for controlling the inflammatory process and gingival bleeding at various stages of periodontal disease.

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RICERFARMA S.R.L

www.ricerfarma.com

Via Egadi, 7 - 20144 Milano – Italy
info@ricerfarma.com