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Could periodontitis play a role in the pathogenesis of Alzheimer's disease?

Periodontitis and Alzheimer's disease cause totally different symptoms, but there are many similarities in their pathogenesis. Both are chronic, inflammatory, and degenerative conditions that have both familial and sporadic forms, and both are caused by a multifactorial interplay of wider genetic, environmental, and behavioural risk factors. *Tanya Cerajewska* and *Nicola West*, researchers at the University of Bristol, explore the links between the two conditions.

'I'm losing my sense of self, and that is more frightening than anything because that's all I have – that's all any of us have.'

This poignant insight, from the recent memoir *Somebody I used to know* by Wendy Mitchell, casts light on what it is like to live with Alzheimer's disease (AD), a severely debilitating, incurable, neurodegenerative condition.

AD commonly presents with worsening forgetfulness and eventually progresses to gravely affect every aspect of cognitive function. It is often a frightening condition, capable of terrorising those affected and their loved ones.

The most common cause of dementia, AD affects six per cent of the European population over 60 years of age. The chance of developing dementia increases exponentially beyond the age of 60: while fewer than two per cent of Europeans aged between 60 and 64 are living with dementia, the figure rises to nearly 40% of people aged over 90.

The vast majority of people living with AD have sporadic forms of the condition, with autosomal-dominant familial forms of AD accounting for only two or three per cent of all AD diagnoses.

The first case of AD was described in the early 1900s, but the pathogenesis of the condition remains elusive, despite vast amounts of scientific and clinical research. The key discoveries relating to AD, which are relevant to its possible association with periodontitis, are outlined in Figure 1.

The pathological hallmarks of AD are recognised as:

1. Neurofibrillary tangles (NFT) within neurons;
2. Amyloid plaques containing amyloid beta peptides (Aβ).

These hallmarks, along with the symptoms of clinical dementia, are required for a diagnosis of AD. Both NFT and amyloid plaques can predate the onset of dementia symptoms by 10 years or more. It is widely believed that the pathogenesis of AD is related to increased amounts and toxic forms of Aβ within the brain. This can occur as the result of genetic mutations known to play a causal role in the familial forms of the condition. The causation of sporadic AD is not fully understood, yet it seems likely that there is an interplay of factors leading to these same pathological hallmarks.

Aβ is known to disrupt synapse function and cause neuronal death, although the amount of Aβ does not correlate with AD symptoms. Reducing

Key –Type of discovery

- Pathology
- Theoretical
- Genetic
- Bacterial
- Host immuno-inflammatory response
- Other important findings

1906	Alois Alzheimer reported the case of Auguste Deter. 'Milliary foci' (later called amyloid plaques) were found in Auguste's brain post-mortem
1974	NFTs first isolated from human brain with AD
1984	Aβ identified as main component of amyloid plaques
1986	Hyperphosphorylated tau protein identified as the main component of NFTs
1987	Amyloid Precursor Protein (APP) gene mutations found to cause inherited AD
1990	Aβ found toxic to neurons in vitro
1991	Amyloid cascade hypothesis proposed
1993	Presenilin 1 & 2 genetic mutations found to cause inherited forms of AD via increased toxic forms of Aβ
	Apolipoprotein-e4 was the first gene variation found to increase the risk of developing AD, and remains the most significant risk factor for sporadic AD
1999	Pathology of Aβ plaques and NFTs shown to present more than a decade before AD symptoms
2002	Oral spirochaetes isolated from brainstem and cortex of those with AD more readily than controls
2005	Type-2 diabetes mellitus found to increase risk of developing AD
2010	Aβ peptides recognised as having anti-microbial function capable of killing bacteria & fungi
2013	Aβ recognised as capable of inducing inflammation via Inflammasome in AD
	LPS from periodontal pathogens is found in human AD brain
2015	Peripheral neutrophils found capable of crossing the blood-brain barrier to influence rate of cognitive decline
2016	Cognitive decline shown to be more rapid among those with periodontitis and AD compared to those with AD and no periodontitis
	Consortium of experts outline the evidence to support the infection hypothesis of AD
	Cultured spirochaetes shown to form Aβ. Bacterial and host derived Aβ are both found in amyloid plaques
2017	Cognitive decline and Aβ in the brains of AD mice were shown to increase after inducing periodontitis with oral P.gingivalis
	Neuroinflammation generally accepted to play a role in the development and progression of AD
	Bacterial DNA more readily sequenced from post-mortem AD brain than control brain tissue

Figure 1. Timeline of key AD discoveries relevant to the potential association with periodontitis

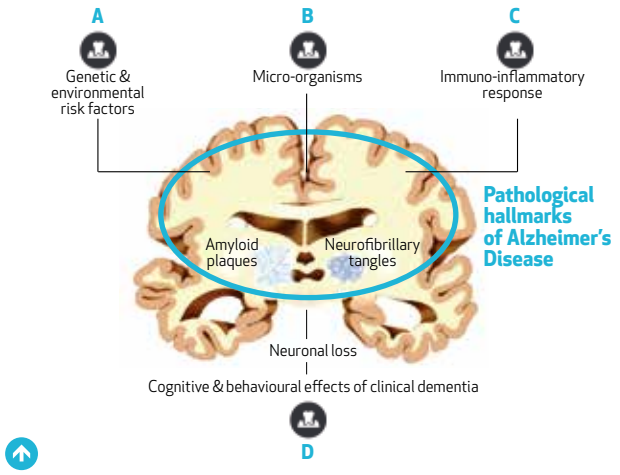

Figure 2. Possible mechanisms of periodontal influence on AD pathogenesis

cerebral Aβ does not cure or stop the progression of AD, as has been shown by numerous unsuccessful drug trials. Aβ has antimicrobial functions and may be responsive to bacteria, viruses, or fungi, initiating a chain of neuroinflammatory pathological events that, once begun, can continue independently of amyloid levels. Neuroinflammation is now widely recognised as being implicated in AD progression. Recent discoveries, including those related to periodontitis (Figure 1), add weight to the likelihood of an immuno-inflammatory aetiology of AD – which could potentially be influenced by peripheral diseases such as periodontitis.

Although periodontitis and AD cause entirely different symptoms, their pathogenesis shares many similarities. They are both chronic, inflammatory and degenerative conditions that have familial and sporadic forms, and which occur as a result of a multifactorial interplay of wider genetic, environmental and behavioural risk factors.

Epidemiologic evidence

Over the last decade, numerous epidemiological studies have investigated the co-existence of periodontitis and AD, providing evidence of an association between the two diseases.

A small study in cognitively normal healthy adults correlated cerebral Aβ with participants' clinical attachment loss, finding that increased Aβ in vulnerable brain regions correlated with greater periodontal attachment loss (after controlling for a comprehensive list of variables).

Another recent, well-designed study measured cognition in 585 elderly people and correlated it with alveolar bone loss and periodontal pocket depth. Prevalence of alveolar bone loss ≥4mm at ≥30% sites was associated with reduced cognitive score after adjustment for age, gender, and education (odds ratio 2.7, p=0.013). These and other studies appear to demonstrate an association between past periodontal destruction and cognition. However, as they are cross-sectional, they give no indication of causality.

Periodontitis has also been significantly associated with an increased rate of cognitive decline in people with mild to moderate AD. The cognitive decline of AD patients, with and without periodontitis, was measured for 52 participants over a six-month period. Those with periodontitis had a six-fold increase in the rate of cognitive decline, independent of the baseline cognitive state.

The principle genetic risk factor for late onset AD – *APOE4* status – was not statistically different between periodontitis and control groups. Larger studies are required to verify that the results obtained in these smaller studies did not occur by chance.

Three case-control studies – which analysed between 6,000 and 28,000 data sets – found that periodontitis may increase the risk of developing dementia. These studies identified those with chronic periodontitis as being 1.16 to 2.54 times more likely to develop dementia in the follow-up period of between one and 10 years. However, the results of these studies need to be interpreted with caution for various reasons.

Each of these studies retrospectively analysed the same cohort of patients using information from insurance healthcare records of a Taiwanese population, which may or may not be applicable to other cohorts with dissimilar genetic backgrounds. Little information was provided regarding the diagnostic criteria for periodontitis, while the diagnostic criteria used for dementia is known to select patients with more advanced symptoms. Thus, reverse causality cannot be excluded. In addition, shared risk factors – such as *APOE* risk – were not controlled for.

Potential mechanisms

The potential mechanisms through which periodontitis could affect the pathogenesis of AD are shown in Figure 2. An interplay between several mechanisms could account for the observed association between periodontitis and AD.

A plethora of evidence has come to light which refutes the traditional view of the brain as sterile and isolated from the rest of the body by the blood-brain barrier (BBB). Immune cells and inflammatory mediators involved in the periphery are now known to be capable of crossing the BBB. Many studies have identified microbes, their DNA, and components within brain tissue affected by AD. A variety of microbes, including periodontal pathogens (Figure 2, B), have been identified within the AD brain by numerous researchers using a range of molecular techniques. There are several potential means by which microbes could enter the parenchyma of the brain, shown in Figure 3.

It is well known that periodontal pathogens enter the blood vessels of the systemic circulation and viable periodontal pathogens have also been identified in atherosclerotic plaques. It is therefore possible that oral bacteria could reach the brain via systemic circulation. *Porphyromonas gingivalis* is capable of disrupting the host's barrier function, potentially affecting both the junctional epithelial attachment of the gingivae and the BBB.

Once within the circulatory system, pathogens may also penetrate the brain via structures not encapsulated by the BBB (e.g. circumventricular organs) or via meningeal channels. Another potential entry portal for peripheral pathogens to reach the brain is via the cranial nerve afferents, particularly as oral treponema have been identified in the trigeminal ganglia, and many of the first changes associated with AD pathology occur in the locus coeruleus within the brainstem, close to the cranial nerve nuclei.

In the 1990s, spirochaetes – including oral pathogens – were identified using microscopy from human post-mortem cerebrospinal fluid from people with AD, but without age-matched controls.

Treponema denticola and other spirochaetes were subsequently identified using molecular DNA analysis and immunological techniques. Spirochaetes were identified from more than 90% of AD brains analysed. Lipopolysaccharide (LPS) from *P. gingivalis* has also been detected in the human AD brain, but not in control samples.

Elevated plasma levels of antibodies to the periodontal pathogens *Aggregatibacter actinomycetemcomitans*, *Tanerella forsythia, T. denticola,* and *P. gingivalis* were found in more AD patients than in controls, demonstrating that these bacteria are capable of stimulating a cerebral immune response. Furthermore, a longitudinal study of cognitively unimpaired individuals found that higher baseline serum antibody levels to *Prevotella intermedia* and *Fusobacterium nucleatum* correlated with cognitive deficits a decade later.

Other bacteria – e.g. *Borrelia burgdorferi*, *Propionibacterium acnes*, and *Escherichia coli* – have also been identified more

frequently from AD brains than from controls. Recent microbiome analyses using multiplex DNA sequencing with reduced bias have provided noteworthy and similar differences in the proportion of bacterial families between AD and control samples. *Staphylococcaceae*, *Burkholderiaceae*, and *Propionibacteriaceae* appear to be present in increased proportions in the AD brain.

Recent findings indicate a direct mechanism whereby bacteria could initiate pathological changes associated with AD and potentially contribute to uncontrolled neuroinflammation. Aβ has antimicrobial functions and, because of this, it potentially increases in response to cerebral infection. LPS from *P. gingivalis* has been shown to induce Aβ production in neuronal cell cultures.

Spirochaetes were recently shown to form Aβ and amyloid plaques containing both bacterial and host-derived Aβ. Oral inoculation of *P. gingivalis* in an AD mouse model – which induced periodontitis (determined by alveolar bone loss) – resulted in increased levels of IL-1β, TNFα, and endotoxin in the brain. Cognitive function was significantly impaired in mice affected by periodontitis and they also had increased toxic forms of Aβ in the hippocampus and cortex.

Bacteria are not the only microbes implicated in AD. There are around 100 individual studies that indicate the herpes simplex virus 1 (HSV 1) as a major risk factor for AD. Circulating antibodies to cytomegalovirus (CMV) have also been associated with AD progression, and faster cognitive decline was seen in those infected over the following five years. These viruses have also been isolated from periodontal pockets with greater frequency than from healthy gingival crevices. Similarly, there is evidence that fungi (e.g. *Candida albicans*) are more commonly associated with brains with AD than with those in control groups.

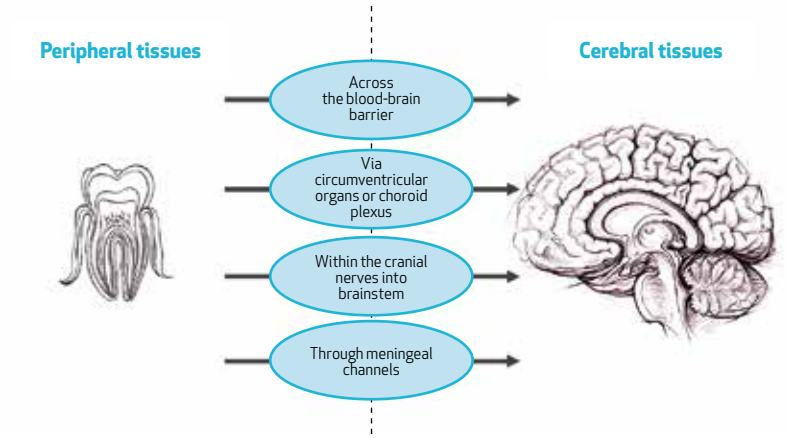

Figure 3. Potential routes for peripheral pathogens and inflammatory mediators to enter the brain

The immuno-inflammatory response typical of periodontitis may contribute to heightening the neuroinflammation in AD (Figure 2, C) and therefore contribute to AD progression.

The central nervous system (CNS) has a specialist immune system that includes numerous glial cells. Microglia, the predominant immune cell within the brain, can change from a benign supporting cell to a pro-inflammatory state when stimulated. Periodontitis is an example of peripheral inflammation that could cause microglia to be primed into a pro-inflammatory phenotype, capable of causing further neurodegeneration. The pro-inflammatory phenotype of peripheral macrophages is also associated with tissue destruction in periodontitis. Primed peripheral macrophages and inflammatory mediators involved in periodontitis may be implicated in priming microglia. Other glial cells have also been shown to have similar pro-inflammatory responses, which ultimately result in heightened cognitive decline.

Neutrophils, the most prevalent leukocyte in inflamed periodontal tissues, can enter the human brain. Once there, they can contribute towards the pathogenesis of AD to affect the rate of cognitive decline. There is evidence of neutrophils surrounding Aβ plaques with extracellular traps (NETs), which can cause breakdown of the BBB and – once within the brain – could cause pro-inflammatory glial cell activation, with further potential for neuronal damage.

The additional load placed on the CNS as the result of peripheral infection and inflammation (e.g. periodontitis) could lead to an overload of the clearance mechanisms for Aβ, resulting in the build-up of this neurotoxic peptide within the brain. Astrocytes contribute to the clearance of Aβ by direct phagocytosis and control of water channels involved in venous clearance. These mechanisms are efficient when also required to phagocytose other inflammatory mediators or pathogens. Microglia also become less efficient at clearing Aβ when chronically stimulated, thus chronic microglial activation in mice following repeated LPS results in increased Aβ deposition. In animal studies, cytokines (IL-1β, IL-6, and TNFα) have been shown to cross the BBB and influence efflux transporters, leading to the overall increase of cerebral Aβ and cytokines that further drive the neurodegenerative processes.

Periodontitis and AD share several risk factors (Figure 2, A). Genome-wide association studies, which search the genome for small genetic differences associated with particular traits, have identified genes that have single-nucleotide polymorphisms (SNPs) implicated both in periodontitis and AD. At least 25 genes share SNPs associated with AD and periodontitis.

These encode for proteins involved in a wide range of cellular functions, membrane transport, and immuno-inflammatory functions.

In addition to this, shared environmental and behavioural risk factors – including diabetes mellitus, atherosclerosis, tobacco smoking, and previous educational attainment – increase the likelihood of developing both periodontitis and AD.

The impact of reverse causation is also an important probable mechanism to explain part of the association between periodontitis and AD (Figure 2, D). As cognitive function deteriorates, so does the patient's ability to perform effective oral hygiene. For most patients, impaired plaque control increases periodontitis risk. For the patient with AD and periodontitis, this could result in a negative feedback loop, where peripheral pathogens and/or inflammation impact negatively on further neurodegeneration.

Conclusion

Recent epidemiologic studies indicate there is an association between AD and periodontitis, but further work is required to describe the nature of this association. Mounting scientific evidence strongly suggests that cerebral microbial infection and neuroinflammation are implicated in the pathogenesis of AD. Oral bacteria and periodontal pathogens are some of the microbes identified from post-mortem AD brains.

Despite growing evidence for the potential role of periodontal pathogens and inflammation in the pathogenesis of AD, further research is required across several research spheres to determine whether there is a causal association between periodontitis and AD. These are likely to include clinical, epidemiological, and scientific studies using genomic and proteomic techniques to understand more about the human microbiome interactome.

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Prof Nicola West is Professor of Periodontology and Head of Restorative Dentistry and the Clinical Trials Unit at the University of Bristol in the United Kingdom. Nicola has been the Secretary of the British Society of Periodontology since 2012 and EFP representative for the UK since 2015. She is due to become secretary general of the EFP in March 2019.

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What impact will new classification have on research?

Mia Rakic

The new classification of periodontal and peri-implant diseases and conditions, presented formally at EuroPerio9 in June 2018, will have a big impact on clinical research. *Mia Rakic*, EFP delegate from the Serbian Society of Periodontology, offers an overview of the research implications, highlighting how correct classification of periodontal conditions "is fundamental to successful disease resolution", while clinicians from across Europe explain what replacing "chronic" and "aggressive" periodontitis with a system based on four "stages" and three "grades" will mean for researchers and clinicians.

The appropriate classification of periodontal conditions is fundamental to successful disease resolution in both clinical and research settings. From the clinical perspective, the diagnosis of periodontal conditions directly impacts appropriate treatment planning and prognosis because the treatment plan is built against pathological conditions and risk factors identified during diagnosis. In the scientific setting, the new classification stimulates future research to address appropriate solutions for clinical concerns and enables researchers to make an accurate case selection, which will ensure the quality of research outcomes.

In developing a new classification, the experts are required to turn state-of-the-art scientific and clinical knowledge into a clinical concept and simplify it so that it is easy for any clinician or researcher to interpret and apply. The main tendency in the evolution of classifications in periodontology has been a constant improvement in the precision of defining periodontal conditions.

Given the multifactorial aetiology of periodontitis and an ever-increasing number of discovered contributing factors, the task of updating the definitions was particularly challenging for the World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions in November 2017. The new classification introduces the use of biomarkers as the grading criteria. However, the question marks in the table on grading periodontitis (Figure 1) show that we still lack the necessary standardised biomarkers – as a footnote to the table notes, "Question marks in the last row indicate that specific biomarkers and their thresholds may be incorporated in the table as evidence becomes available". So, action is needed to identify new biomarkers and standardise them for diagnostic use in the clinical setting. Research is strongly encouraged to identify critical biomarkers and then develop personalised predictive models.

Aggressive periodontitis

The most controversial innovation in the new classification system is the removal of aggressive periodontitis as an independent form of the disease. The concept of aggressive periodontitis was introduced in the 1999 classification as a specific biological form of periodontal disease affecting the younger population, characterised by progressive periodontal destruction often located in the incisor-molar group. Such fulminant destruction was considered to result from an excessive host reaction to a low amount of bacterial biofilm associated with specific periopathogens, led by *Aggregatibacter actinomycetemcomitans*.

However, thanks to the progress of microbiological research and the development of more sensitive microbiological techniques, this specific pathogen-centred hypothesis has been abandoned. It was demonstrated that periodontal microflora is far more diverse than previously thought with a high rate of variability, and it is now considered that the key role in periodontal destruction is played by local dysbiosis rather than by individual periopathogens. In relation to *Aggregatibacter actinomycetemcomitans* as a hallmark pathogen, recent microbiological research reveals its presence in fewer than 50% of aggressive-periodontitis cases, in a low concentration before disease onset decreasing to undetectable levels following disease occurrence, and this periopathogen is detectable in healthy and diseased sites in almost the same ratio.

In addition, repeated research studies have failed to profile the specific immunophenotype in patients suffering aggressive periodontitis, so the immunological characteristics of the disease are still not established. Thus, despite the evident clinical characteristics of "aggressive periodontitis", the lack of intrinsic biological indicators meant that experts had to suspend this category until there is a better biotypology of the disease.

By highlighting the lack of accurate indicators of the aggressive periodontitis – which suggests that the previous diagnostic criteria were unreliable – the new classification system raises awareness among researchers and clinicians of the need to resolve this problem.

Periodontitis grade			Grade A: Slow rate of progression	Grade B: Moderate rate of progression	Grade C: Rapid rate of progression
Primary criteria	Direct evidence of progression	Longitudinal data (radiographic bone loss or CAL)	Evidence of no loss over 5 years	<2 mm over 5 years	≥2 mm over 5 years
	Indirect evidence of progression	% bone loss/age	<0.25	0.25 to 1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease (e.g., molar/incisor pattern; lack of expected response to standard bacterial control therapies)
Grade modifiers	Risk factors	Smoking	Non-smoker	Smoker <10 cigarettes/day	Smoker ≥10 cigarettes/day
		Diabetes	Normoglycemic / no diagnosis of diabetes	HbA1c <7.0% in patients with diabetes	HbA1c ≥7.0% in patients with diabetes
Risk of systemic impact of periodontitis[a]	Inflammatory burden	High sensitivity CRP (hsCRP)	<1 mg/L	1 to 3 mg/L	>3 mg/L
Biomarkers	Indicators of CAL/bone loss	Saliva, gingival crevicular fluid, serum	?	?	?

Figure 1. Grading periodontitis according to the new classification


Darko Božić


Hady Haririan


Dominik Hofer


Paula Matesanz


Peter Eickholz


Kristin Kolltveit


Werner Lill


Virginie Monnet-Corti

'It will take time for the new classification to sink in'

While **Darko Božić (Croatia)** admits to being "emotionally tied to the old classification," he adds that in many cases he could " never really understand when we could call a case 'aggressive' or 'chronic'. You would see people aged 45 to 50 who suddenly developed periodontitis and, by examining their older x-rays, you would see that in the course of a few years they suffered significant bone loss. But, if you looked at their age, they were not 'aggressive' cases.

"This perplexed me, and I would always ask myself: what's the difference between these people suffering from severe attachment and bone loss and the younger one? Furthermore, microbiological testing could not distinguish the two entities and gene-arrays. So, there must be something more to it!"

His initial reaction to the new classification was that "it had more logic and was pretty clear" and that it created new opportunities to understand the behaviour of the disease at the same stage and grade in younger patients and older ones. "For example, is there a different response to the same regenerative surgical treatment in younger and older patients with the same attachment loss?" In these cases, he thinks it likely that there will be a difference between the age groups in term of attachment gain and that there will be more data on the treatment possibilities in advanced periodontitis cases (stages III and IV).

"It will take time for the new classification to sink in," he concludes, "but it gives us new avenues in periodontal research and will give us more information on retaining of extracting 'hopeless' teeth."

For **Hady Haririan (Austria)**, there is a risk that the new classification "might bring some confusion" because "aggressive periodontitis was also linked to a typical distribution of attachment loss in the dentition, which I cannot find in the new system." However, if what was previously called aggressive periodontitis were linked to "Grade C" in the new classification (defined as "rapid rate of progression"), "ongoing research should not be affected very much." Nonetheless, "most difficulties will now arise for new research in terms of comparability with previous data based on the old classification."

This point was echoed by **Dominik Hofer (Switzerland)**, who says "I hope that all the older studies are not automatically made 'worthless' by the new classification. Comparison would certainly be very tricky and complex. This will be a huge challenge for scientists."

Paula Matesanz (Spain) suggests that for research already under way, "I think nothing can be done, because there is no way to adapt the followed inclusion and exclusion criteria once the study has been approved. The results obtained will need to be published based on the later classification, although this may cause a loss of impact of the publication."

Picking up this point, **Peter Eickholz (Germany)** says "there will be a transient time while chronic and aggressive periodontitis will still appear in publications. But authors will increasingly have to refer to the new classification even if they started projects with the former system."

'Clear definition of stages'

Kristin Kolltveit (Norway) is enthusiastic about the benefits to research from the new classification. "It can be hard to differentiate between aggressive and chronic periodontitis – whereas a stage 2 and 3 periodontitis is clearly defined," she says. "For future research, the new classification system will facilitate uniform study groups whether in epidemiological or clinical studies. A clear definition of the different stages of periodontitis is making it easier to design study groups, interpret results, perform multicentre studies, and compare studies."

However, for work already started, depending on how advanced it is, "it might be an idea to redefine the study population in accordance with the new classification."

Werner Lill (Austria) welcomes the implications of the new classification for research, saying that "the more precise definition and differentiation will additionally increase the sensitivity and specificity of scientific work."

Virginie Monnet-Corti (France) raises three questions about the implications of the shift from aggressive/chronic periodontitis to a model of the disease based on stages and grades: "Can we extrapolate the results of the studies based on aggressive/chronic periodontitis? Do we have to redo all the clinical and epidemiological trials in the long term? Can we use the former studies for the new meta-analysis?"

She adds that, in terms of research, the new classification may offer two important benefits. "Perhaps it will help us put forward (to highlight) new associated factors to manage and to improve our future patient outcomes."

The EFP is preparing a toolkit for periodontists and other dental professionals to help them implement the new classification of periodontal and peri-implant diseases. The toolkit will be launched at the next EFP general assembly in Bern (Switzerland) on March 30, 2019. The full reports and proceedings of the World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions have been published as an open-access supplement of the Journal of Clinical Periodontology (available at: https://www.onlinelibrary.wiley.com/toc/1600051x/2018/45/S20).

Latest research from the EFP's Journal of Clinical Periodontology

Journal of Clinical Periodontology

The *Journal of Clinical Periodontology (JCP)* is the official scientific publication of the European Federation of Periodontology. Edited by Maurizio Tonetti, the *JCP* aims to convey scientific progress in periodontology to those concerned with applying this knowledge for the benefit of the dental health of the community.

The journal is aimed primarily at clinicians, general practitioners, periodontists, as well as teachers and administrators involved in the organisation of prevention and treatment of periodontal disease. The *JCP* is published monthly and has an impact factor of 4.046. The six articles summarised below were published in the *JCP* in September, October, and November 2018.

PERIODONTAL DISEASES

Periodontal disease and susceptibility to breast cancer: a meta-analysis of observational studies

This meta-analysis was conducted because, while individual studies have suggested an association between periodontal disease and breast cancer, there had not been a formal meta-analysis of this evidence.

Relevant studies published until April 2018 were retrieved and screened according to established inclusion criteria. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to assess the association between periodontal disease and the risk of breast cancer and fixed-effect models were used according to the results of the heterogeneity test.

Eight studies, involving 168,111 individuals, were identified as having explored the association between periodontal disease and breast cancer. Summary estimates in view of adjusted data showed that periodontal disease increased susceptibility to breast cancer (RR = 1.18, 95% CI: 1.11-1.26, I^2 = 17.6%), with robust results confirmed by sensitivity analysis.

The results provided evidence of a modest positive association between periodontal disease and breast cancer and the researchers recommended further studies to explore this topic in more detail.

Authors: Tingting Shi, Min Min, Chenyu Sun, Yun Zhang, Mingming Liang, Yehuan Sun.

Published in *Journal of Clinical Periodontology* Volume 45, Number 9 (September 2018).

Full article: https://www.onlinelibrary.wiley.com/doi/abs/10.1111/jcpe.12982

PERIODONTAL DISEASES

The effects of periodontal treatment on diabetic patients: the DIAPERIO randomised controlled trial

This study sought to assess whether periodontal treatment can lead to improvements in clinical glycaemic control and quality of life in metabolically unbalanced diabetic patients (type 1 or type 2) diagnosed with periodontitis.

In this open-labelled, randomised controlled trial, diabetic subjects (n = 91) were given "immediate" or "delayed" periodontal treatment (full-mouth, non-surgical scaling and root planing, systemic antibiotics, and oral-health instructions). The main outcome was the effect on glycated haemoglobin (HbA1c) and fructosamine levels. The General Oral Health Assessment Index and the SF-36 index were used to assess quality of life.

Periodontal health significantly improved after periodontal treatment ($p < 0.001$), but the treatment had no significant effects on glycaemic control based on HbA1c. However, there was significant improvement in oral-health-related quality of life.

Authors: Jean-Noel Vergnes, Thibault Canceill, Alexia Vinel, Sara Laurencin-Dalicieux, Françoise Maupas-Schwalm, Vincent Blasco-Baqué, Hélène Hanaire, Elise Arrivé, Vincent Rigalleau, Cathy Nabet, Michel Sixou, Pierre Gourdy, Paul Monsarrat, the DIAPERIO Group.

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Full article: https://www.onlinelibrary.wiley.com/doi/abs/10.1111/jcpe.13003

PERIODONTAL DISEASES

Effect of two periodontal treatment modalities in patients with uncontrolled type-2 diabetes mellitus: a randomised clinical trial

This randomised controlled clinical trial evaluated the impact of two non-surgical periodontal treatment modalities on metabolic and periodontal clinical parameters in subjects with type-2 diabetes mellitus (T2DM) with poor glycaemic control and chronic periodontitis.

Ninety-three T2DM subjects with glycosylated haemoglobin (HbA1c) >7% were randomly assigned to one of two groups receiving scaling with root planing in multiple sessions, quadrant by quadrant (Q by Q), or within 24 hours (one stage). Periodontal parameters, HbA1c, glycaemia blood levels, and C-reactive protein values were assessed at baseline and at three and six months after therapy.

At six months, HbA1c had decreased by 0.48% in the Q-by-Q group and by 0.18% in the one-stage group (p = 0.455). After therapy, subjects with an initial HbA1c <9% showed an increase of 0.31% (p = 0.145), compared with a decrease of 0.88% (p = 0.006) in those with an initial HbA1c ≥9%. Periodontal parameters improved significantly ($p < 0.0001$) post-therapy, with similar results for both treatment modalities.

Improved HbA1c levels were more apparent among patients who were more severely uncontrolled at baseline.

Authors: Antonio J. Quintero, Alejandra Chaparro, Marc Quirynen, Valeria Ramirez, Diego Prieto, Helia Morales, Pamela Prada, Macarena Hernández, Antonio Sanz.

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Full article: https://www.onlinelibrary.wiley.com/doi/abs/10.1111/jcpe.12991

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PERIODONTAL THERAPY

Predictor factors for long-term outcomes stability of coronally advanced flap, with or without connective tissue graft, in the treatment of single maxillary gingival recessions: nine-year results of a randomised controlled clinical trial

This randomised controlled clinical trial assessed the clinical outcomes nine years after the surgical treatment of single maxillary gingival recessions and identified predictors for long-term gingival-margin stability.

Twenty-five gingival recessions (Miller Class I and II) were randomly treated with Coronally Advanced Flap (CAF) plus Connective Tissue Graft (CTG) or CAF alone. Outcomes included complete root coverage, recession reduction, keratinised-tissue gain, and dentin hypersensitivity, and were evaluated at six months, one year, and nine years. Multilevel analysis was performed to identify predictors for long-term gingival-margin stability.

Baseline gingival recession was 2.4 ± 0.8 mm and 2.4 ± 1.0 mm in the CAF + CTG and in the CAF-treated sites, respectively ($p = 0.693$).

The chance of gaining and preserving complete root coverage over time is equal to 70% in the CAF + CTG group, while with CTG an increase in keratinised tissue was recorded nine years after the surgery ($p = 0.019$).

Both treatment modalities demonstrated stability over time, the additional use of CTG provided a greater increase in keratinised tissue, and the presence of non-carious cervical lesions affected both complete root coverage and recession reduction.

Authors: Giulio Rasperini, Raffaele Acunzo, Gaia Pellegrini, Giorgio Pagni, Maurizio Tonetti, Giovan Paolo Pini Prato, Pierpaolo Cortellini.

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Full article: https://www.onlinelibrary.wiley.com/doi/abs/10.1111/jcpe.12932

IMPLANT THERAPY

Morbidity following transcrestal and lateral sinus floor elevation: a randomised trial

This study sought to make a comparative evaluation of the morbidity following maxillary sinus-floor elevation, according to either the transcrestal (tSFE) or the lateral (lSFE) approach, with concomitant implant placement.

Patients with ≥1 edentulous maxillary posterior site with residual bone height of 3-6mm were enrolled. While tSFE was performed in association with a xenograft and a collagen matrix, with lSFE the sinus was grafted with the xenograft and the antrostomy was covered with a membrane. Implants were inserted concomitantly. The postoperative course was assessed through questionnaires and pain level was recorded using a 100-mm visual analogue scale (VAS_{pain}).

Twenty-nine and 28 patients were respectively included in the tSFE and lSFE groups. On the day of surgery, VAS_{pain} was significantly higher for tSFE compared to lSFE, and a similar result was reported over the following two weeks. There was significantly less swelling, bruising, and nasal discharge/bleeding in the tSFE group. Significantly less severe limitation in swallowing, continuing daily activities, eating, speaking, opening the mouth, and going to school/work was found for tSFE only at specific post-surgery intervals.

The research concluded that while lSFE was associated with lower pain on the day of surgery, tSFE revealed lower postoperative morbidity and had a more tolerable postoperative course.

Authors: Roberto Farina, Giovanni Franceschetti, Domenico Travaglini, Ugo Consolo, Luigi Minenna, Gian Pietro Schincaglia, Orio Riccardi, Alberto Bandieri, Elisa Maietti, Leonardo Trombelli.

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Full article: https://www.onlinelibrary.wiley.com/doi/abs/10.1111/jcpe.12985

IMPLANT THERAPY

A randomised controlled study comparing guided bone regeneration with connective tissue graft to re-establish convexity at the buccal aspect of single implants: a one-year CBCT analysis

In a study to compare guided bone regeneration (GBR) with connective tissue graft (CTG) to re-establish convexity at the buccal aspect of single implants, patients with a single tooth gap in the anterior maxilla and horizontal alveolar defect were enrolled in a single-blind, randomised controlled trial.

Sites had to demonstrate buccopalatal bone dimension of at least 6mm before surgery to ensure complete embedding of an implant without the need for bone augmentation. All received a single implant and were randomly allocated to the control group (GBR) or the test group (CTG). Cross-sectional CBCT images before surgery, two weeks after surgery, and one year after surgery were used to evaluate the buccal soft-tissue profile. Secondary outcome variables were buccal bone thickness, buccal soft-tissue thickness, vertical bone loss (VBL), and clinical parameters.

Twenty-one patients were included in each group. After one year, a significant increase in the buccal soft-tissue profile of between 0.7mm and 1.5mm was observed in both groups ($p \leq 0.010$). Vertical bone loss did not differ significantly between the groups ($p \geq 0.644$) and implants demonstrated healthy clinical conditions with no significant differences between the groups for any of the parameters ($p \geq 0.095$).

Authors: Thomas De Bruyckere, Célien Eeckhout, Aryan Eghbali, Faris Younes, Paulien Vandekerckhove, Roberto Cleymaet, Jan Cosyn.

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