Causality: periodontology's Holy Grail

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reports
on new
research

from Birmingham which goes further than any other in identifying the causal link between oral and systemic disease.

Alcohol is bad for you. Eggs are bad for you. Burnt toast is bad for you. Alcohol is **not** bad for you. Eggs are **not** bad for you. Burnt toast is...

You understand where I am going with this. Week in, week out there are excited and conflicting headlines around the *associations* between diet, lifestyle and health.

These media stories can be exaggerated by making an association appear causal. The same is true for the association between oral and systemic health conditions. If, however, associations could be upgraded, via high quality research, to a causal link between oral and systemic health conditions, excited headlines would be well and truly justified.

The health of our mouths and how this impacts on our physical wellbeing is a topic that has been a matter of keen interest to everyone in dentistry for decades. The quest to establish causality between oral and systemic health has assumed Holy Grail-like proportions.

We know the mouth is the window to the body. We know that dental professionals can identify a range of conditions just from looking in the mouth. We know there is a link between oral health and diabetes and we know it's bi-directional. We know periodontitis is triggered by an abnormal inflammatory-immune response to bacteria in plaque biofilm. But we still don't know exactly how and why.

More than 700 papers have examined the oral health and systemic disease connection from countless perspectives over the last few decades. Huge advances have been made, in part driven by the international periodontal community which, through workshops and consensus documents, has set out the importance of periodontal health and prevention of disease.

Some of the most significant advances have been the result of dental and medical

collaborations. An early example was a study at University College Hospital in 2007¹ involving dentists and cardiologists interested in identifying whether the inflammation observed in the pathogenesis of atherosclerosis could be linked to periodontal inflammation (PI); a trial was structured involving a group of 120 volunteers with severe generalised periodontitis, but otherwise healthy, who were provided with periodontal therapy to test the impact on endothelial function. This resulted in short-term acute systemic inflammation and endothelial dysfunction but, within six months of the treatment there was an improvement in endothelial function.

published in 2020 in *Frontiers in Immunology*. 'Despite significant advances made in both periodontal microbiology and periodontal pathology, the issue of which comes first the inflammatory response or the change to a dysbiotic subgingival microbiota, is still debated'.

Now, however, we might be within reach of enlightenment thanks to a new study⁵ led by Dr Praveen Sharma, of the Periodontal Research Group at the University of Birmingham School of Dentistry. With colleagues, he undertook a cross-sectional study examining periodontal inflammation and renal function among a cohort of more than 700 patients with chronic kidney disease (CKD). Their aim was to ascertain factors,

inflammation, as previously thought.

'The magnitude of the effect was such that a 10% increase in periodontal inflammation resulted in a 3% decrease in renal function and 10% decrease in renal function resulted in a 25% increase in periodontal inflammation. Inflammation plays an important role but, in this cohort, it's the oxidative stress spilling over which has more of an impact.'

So, can we finally say we have found the Holy Grail? Do we fully understand how oral and systemic health are linked? Dr Sharma thinks not. Proof positive would require the kind of randomised controlled trial (RCT) that no-one would want to undertake: predicated on depriving a cohort of patients of treatment that they are entitled to. His own study was able to gain ethical approval because he provided 50% of the patients in the study with periodontal therapy that they would not have had otherwise.

More research is needed, Dr Sharma says, to determine whether periodontal therapy can slow down the progression of chronic kidney disease long-term. In the meantime, there should be no mistaking the importance of both the study and the approach, which can now be tested in other areas of oral-systemic disease links. Finally, the pursuit of good oral health is a worthy goal, in and of itself and any benefits beyond the mouth, for now, can be thought of as a bonus!

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Lead author Professor Maurizio Tonetti, now chair professor and chief scientist at the clinical research centre of Shanghai Jiao Tong University school of Medicine, China, recalls the significance of the results: 'We were able to establish the cause and effect mediated between the local inflammation and the systemic inflammatory burden: the whole body senses what happens in our mouth'.

Another collaboration which has proved significant took place in 2017 when the International Diabetes Federation (IDF) and European Federation of Periodontology (EFP) produced joint guidelines for patients with diabetes.² Now that the co-morbid relationship between periodontal disease and type 2 diabetes is more established, a roadmap for the joined up management of the two conditions has been made the basis for an important new NHS commissioning document.

The *Commissioning Standard: Dental Care for People with Diabetes*,³ published by NHS England in 2019, means that theoretically, local commissioners of dental services are procuring contracts which ensure that people with diabetes can access dental care.

This is a major step but there are still unanswered questions. For instance, if oral inflammation is the driver for the spread of microbiota from the mouth into the bloodstream, how exactly does this happen? The conundrum was eloquently set out in a paper⁴

including periodontal inflammation, which predict decline in renal function.

Once again, collaboration was critical, both with colleagues in this country and the USA as well as with the renal medicine team at the University of Birmingham Hospital. 'Without both detailed dental and biomedical data,' said Dr Sharma, 'you can't make sound inferences.'

The analysis employed Structural Equation Modelling (SEM), an approach by which many causal (cause and effect) hypotheses can be tested simultaneously to determine which hypotheses hold.

Their focus was on oxidative stress which Dr Sharma describes as an imbalance between the production of reactive oxygen species (ROS) and their elimination by protective mechanisms. 'So, much depends on our ability to neutralise ROS through antioxidant mechanisms. If this is not the case, ROS can themselves cause chronic inflammation.'

By using their knowledge of biological processes and data, they developed and tested hypotheses to see what inferences could be drawn. 'The mouth is an ideal place for bacteria to breed. It's a no-brainer that a substantial area of oral inflammation, present for decades, will have a systemic effect. The question is, of what magnitude?

'We found that periodontal disease and renal function have a bi-directional relationship and this is mediated by oxidative stress and not

References

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