Could periodontitis represent a risk for contamination of transfused blood units?

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Periodontitis is a chronic disease associated with a dysbiotic oral microbiota that, in predisposed hosts, causes the perseverance, for years and years, of a local inflammation of periodontal tissues, promoting the progressive destruction of the supporting structures of the teeth[1]. Recent evidence supports the potential deleterious impacts of periodontitis, not only topically, but also on systemic health and mortality[2,3]. Periodontitis has been related with increased risk of developing or manifesting diseases, such as diabetes, obesity, cardiovascular disorders, hypertension, cancer, chronic renal disease, pneumonia, rheumatoid arthritis, adverse pregnancy outcomes, and obstructive lung diseases[4-7]. Moreover, the presence of oral pathogens in the circulation has been associated with atheroma formation and dyslipidaemia[4].

Considering that periodontitis is the sixth most frequent disease in the world, with its severe form affecting 10% of the population, all the possible implications on global health should be analysed and investigated[8]. Oral pathogens can spread in the bloodstream, and patients with periodontitis can have raised levels of markers of systemic inflammation, such as C-reactive proteins; in contrast, a decrease in systemic inflammation was documented in subjects who underwent periodontal therapy[9-12]. There is robust evidence of the presence of oral bacteria in extra-oral sites of disease and inflammation, with some sub-types and strains seeming to exhibit greater systemic virulence[13]. Among these, *Fusobacterium nucleatum* is able to invade different types of cells, including epithelial and endothelial cells, by means of surface adhesins, which promote intracellular colonisation and other processes that loosen cell-cell junctions, thereby also facilitating extra-oral colonisation by other bacteria[13]. Another periodontal pathogen that is characterised by high virulence, *Porphyromonas gingivalis*, in the circulation is able to trigger autoimmune inflammation, which can lead to the development of chronic arthritis in susceptible hosts[13]. *Fusobacterium nucleatum* and *Porphyromonas gingivalis* have been implicated in cardiovascular disorders, adverse pregnancy outcome, inflammatory bowel disease, appendicitis and brain, lung, liver and splenic abscesses. In addition, although no specific virulence factors have been identified, oral infection by *Campylobacter rectus* is able to induce foetal growth restriction and placental inflammation[13]. The ability of oral pathogens to disseminate in extraoral sites and to cause bacteraemia has also been demonstrated by the presence, adherence to, and invasion of coronary endothelial cells by *Streptococcus mutans*, a cariogenic bacterium that increases the risk of endocarditis[13]. The impact of oral diseases on global health has been evidenced by Romandini *et al.*, who showed that periodontitis and its final sequalae, edentulism, are associated with increased risks of all-cause mortality and chronic diseases

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with respect to the risks in the healthy population without periodontitis[3].

Considering these premises, Damgaard *et al.* recently questioned whether standard blood donations from subjects with periodontitis are more likely to contain viable bacteria[14]. This question is of current importance, because every year 100 million blood units are transfused, and transfusion-transmitted infections are still cause of post-transfusion morbidity and mortality[15,16]. The possible causes of these infections could be the transient immunosuppression caused by the transfusion, contamination during the venipuncture, and the presence of bacteria in the transfused blood units[17].

Donor deferral criteria related to oral diseases are regularly applied in blood donor centres. For example, in accordance with Italian law[18], potential donors are deferred from making donations for 48 hours after minor dental interventions such as dental hygiene, for 1 week after healing from a dental extraction, devitalisation or minor surgery and for 4 months after major surgery with bone implants. However, these deferral criteria might not be sufficient.

In order to avoid transfusion-transmitted infections, the platelet fraction of blood samples from donors are systematically subjected to standard screening protocols, such as the BacT/ALERT test, to determine the presence of any bacterial contamination[19]. However, the large discrepancy between the relatively high rates of transfusion-transmitted infections and the low rates of bacterial contamination in the platelet fraction supports the idea that the plasma and red blood cell fractions could also be sources of bacteria.

In order to investigate this issue, Damgaard *et al.*, performed a cross-sectional study in which the blood from 60 self-reportedly healthy donors was microbiologically analysed. All procedures were performed in order to avoid any external contamination, especially during the venipunctures. Standard testing for bacterial contamination was also performed[14]. Subsequently, samples from plasma and red blood cells were cultured under aerobic and anaerobic conditions for 7 days. The findings were compared with clinical and radiological data, evaluating a possible correlation between the presence of bacteria in the blood samples and the periodontal status of the donors. A trained operator performed the periodontal examination, by means of a millimetre-scaled periodontal probe at six points for each tooth and then classified periodontal patients, according to the American Academy of Periodontology (AAP) and European Federation of Periodontology (EFP) criteria[20]. Forty-eight percent of the population in the study were affected by periodontitis.

The microbiological results were very interesting. Although none of the donors resulted positive at the BacT/ALERT test, the presence of contaminated samples was found in many cases and resulted mainly from plates inoculated with red blood cells. Bacterial contamination was found in 62% of blood samples from donors affected by periodontitis and in 10% of those with a healthy periodontium. The relative risk of contaminated blood samples from donors with periodontitis was 6.4 compared with the risk in donors without this disease. Interestingly, the donors with an apparently healthy periodontium in whom a bacterial contamination was found, at radiological examination showed the presence of at least one periapical radiolucency, which was probably caused by an infected root canal.

The bacterial species most frequently found in both populations were *Cutibacterium acnes*, followed by *Staphylococcus caprae/capitis* and *Staphylococcus epidermidis*. Other species, *Staphylococcus hominis*, *Staphylococcus lugdunensis* and *Bacillus mycoides*, were found only in donors with periodontitis. These results are very important, because these species were previously associated with nosocomial infections[21]. These species are not strictly periodontal pathogens; however, we cannot ignore that the relative risk of blood contamination in donations from subjects with periodontitis is significantly higher. We agree with the hypothesis of Damgaard *et al.* that the existence of an oral inflammation, supported by periodontitis or periapical inflammation, could favour the presence of bacteria in the blood stream, thanks to the increase of connective tissue loosening and endothelial permeabilisation. The absence of typical periodontal pathogens in the blood samples could be related to their killing by the immune system in the whole blood preparations during the overnight storage, while commensal bacteria, such as *Staphylococcuss spp.* and *Cutibacterium acnes*, are tolerated.

It is important to increase awareness, among both medical staff and blood donors, of the link between periodontal

disease and blood contamination. Furthermore, it would be desirable for blood donors to undergo periodic periodontal screening, in order to diagnose any periodontal disease early and treat it before proceeding with the blood donation. We believe that this topic should be investigated further, with the aim of minimising the risk of nosocomial infections, also considering that patients who undergo blood transfusions are usually immunosuppressed and consequently at high risk of bacteraemia.

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