

GENETIC TESTING IN THE MANAGEMENT OF PERIODONTAL DISEASES

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Abstract

The growing understanding of the role of genetic variation in chronic inflammation presents opportunities to identify high-risk individuals for early intervention before tissue damage occurs. An abnormal inflammatory response has been linked to cardiovascular disease (CVD) and specifically to diabetes, where there is an increased susceptibility to infections such as periodontal disease. Activation of interleukin-1 (IL-1) and of tumour necrosis factor- α (TNF- α) represents some of the earliest events in response to injurious challenges and increased levels may correlate with severity of inflammatory disease. Identification of genetic risk factors underlying chronic inflammation may therefore be of value when treating refractory periodontitis and possibly peri-implantitis. The detrimental effects on periodontitis of risk factors such as smoking, stress, bacterial infections and nutritional deficiencies appear to be greater in persons with a genetic predisposition to chronic inflammation. Early detection of gene mutations shown to be associated with the more severe forms of periodontitis and peri-implantitis, as part of a comprehensive cardiovascular genetic screening in conjunction with medical and lifestyle assessments, may therefore provide a more targeted approach to the management of these diseases.

Introduction

Chronic periodontitis driven by gene-environment interactions may increase the risk of other common diseases. A meta-analysis based on seven cohort studies has shown that periodontal infection significantly increases the risk of both cerebrovascular and coronary heart disease (Khader et al. 2004; Dumitrescu 2005), with insulin resistance as an important contributing factor. Large-scale longitudinal epidemiologic and intervention studies are necessary to validate this association and to determine causality (Scannapieco et al 2003). Cardiovascular diseases are responsible for 16.6 million deaths per annum worldwide, of which 7.1 million deaths are caused by coronary heart disease (Kapp 2002).

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Diabetics are at 2-4 times greater risk for the development of cardiovascular disease (CVD), the leading cause of diabetes-related deaths (Laakso 1999). Diabetes affects approximately 18 million individuals with an increase of approximately 1.3 million new cases a year in adults. Diabetes is strongly related to a hyper-inflammatory trait with increased susceptibility to infections, including periodontal diseases. Periodontitis is caused primarily by bacterial infection, although the host must be genetically susceptible. Periodontitis affects 7-15% of the adult population (Papapanou 1999) and, in subjects with metabolic dysregulation, may lead to systemic disease as a result of over-expression of inflammatory mediators. Thus both genetic and environmental factors influence the host response, which is essentially protective in nature, while an impaired immune response could worsen tissue destruction. There is large variation in the results of studies on the association between periodontitis and systemic diseases. Confounding and effect modification may explain this variation and need to be considered in the decision making process (Ylostalo et al 2006)

The fact that individual genetic factors are not determinants of the more prevalent forms of chronic periodontitis, challenges the usefulness of DNA testing. A review of the literature was undertaken to determine whether genetic testing could be of value as an adjunct to

diagnosis, as a predictor of, or as an aid to the management of periodontitis.

Heritable susceptibility

Dental diseases with a Mendelian inheritance pattern are relatively rare and inheritance cannot explain most common forms of periodontitis. A specific genotype pattern involving two polymorphisms of the interleukin-1 (IL-1) gene cluster with high levels of IL-1 production was shown to increase the risk of chronic periodontitis in the general population (Kornman et al. 1997). This composite genotype involves mutation -889G→T (in linkage disequilibrium with 4845) in the IL-1 α gene and mutation 3953C→T (previously numbered 3954) in the IL-1 β gene (Engelbrecht et al. 1999). In a recent study performed by Agerbaek et al. (2006), it was shown that a lower bacterial load is required in persons with the mutated composite IL-1 genotype to develop the same level of periodontitis as in mutation-negative individuals.

Studies are in progress to determine the impact of the IL-1 genotype on the periodontal status of the Xhosa population of South Africa. Research in different population groups is necessary as data from Caucasian populations cannot always be extrapolated across ethnic groups owing to population differences in allele frequencies and socio-demographic backgrounds.

Periodontitis and diabetes

Detection of variation in genes encoding the proinflammatory cytokines IL-1, IL-6 and tumour necrosis factor- α (TNF- α) may be particularly important in patients at risk of both periodontitis and diabetes, as cytokine production could be favourably modulated by supplementation with omega-3 fatty acids (Meydani et al. 1991) and vitamin E (Devaraj and Jialal 2000).

Grimble et al. (2002) have demonstrated that fish oil reduced TNF- α production to a greater extent in individuals with at least one A-allele of the TNF- α -308G→A polymorphism, which is associated with a 2-fold increase in transcription levels, compared with the more common G-allele. Co-existence of the -308A allele of the TNF- α gene and the -174CC genotype of the IL-6 gene demonstrated a significant decrease in insulin secretion and is highly predictive of conversion from insulin resistance to type II diabetes (Kubaszek et al. 2003). Persons with the -308A TNF- α gene variant have a 23% increased risk of developing obesity compared with controls and they showed significantly higher systolic arterial blood pressure and

plasma insulin levels (Sookoian et al. 2005).

Genetic testing for risk management

DNA testing is not recommended for diagnosis of periodontitis, but may be useful to facilitate clinical management of patients with chronic inflammatory disease. Identification of persons at increased risk of aggressive periodontitis and peri-implantitis may predict general deregulation of the inflammatory response, with concomitant increased risk of other chronic disorders such as coronary heart disease, type II diabetes, dementia and certain types of cancer. A family history of any of these diseases would strongly suggest that genetic testing combined with medical and nutritional therapy may be appropriate (Kotze and Badenhorst 2005).

Conclusion

For multi-factorial diseases such as chronic periodontal diseases, no single gene mutation will allow a definitive diagnosis or certain risk prediction. In such a complex disease model, a single functional gene polymorphism can modulate disease progression over time but is not solely sufficient to cause periodontal disease. Genetic testing would therefore be most useful for subjects with periodontal disease as one component of a spectrum of diseases which might be targeted for intervention for risk reduction at the gene-environment level. At this level the information gained from genetic testing could assist health professionals to personalise the treatment of their patients.

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References

- Agerbaek MR, Lang NP and Persson PG. Microbiological composition associated with Interleukin-1 Gene Polymorphism in subjects undergoing supportive Periodontal Therapy. *Periodontology* 2000; 2006; 40: 130–143.
- Devaraj S, Jialal I. Low-density lipoprotein postsecretory

modification, monocyte function, and circulating adhesion molecules in type 2 diabetic patients with and without macrovascular complications: the effects of alpha-tocopherol supplementation. *Circulation* 2000; 102: 191-196.

Dumitrescu AL Influence of periodontal disease on cardiovascular diseases. *Rom J Intern Med.* 2005; 43(1-2):9-21

Engebretson S, Lamster I, Herrera-Abreu M, Celenti RS, Timms JM, Chaudhary AG, di Giovine FS, Kornman KS. The influence of interleukin gene polymorphism on expression of interleukin-1 β and tumor necrosis factor-alpha in periodontal tissue and gingival crevicular fluid. *J Periodontol* 1999; 70: 567-573.

Grimble RF, Howell WM, O'Reilly G, Turner SJ, Markovic O, Hirrell S, East JM, Calder PC. The ability of fish oil to suppress tumor necrosis factor- α production by peripheral blood mononuclear cells in healthy men is associated with polymorphisms in genes that influence tumor necrosis factor- α production. *Am J Clin Nutr* 2002; 76: 454

Kapp C. World Health Report charts way forward on CV disease prevention. *Lancet Neurol* 2002; 1: 461.

Khader YS, Albashaireh ZS, Alomari MA. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: a meta-analysis. *J Periodontol.* 2004; 75:1046-53.

Kornman KS, Crane A, Wang HY, di Giovine FS, Newman MG, Pirk FW, Wilson Jr. TG, Higginbottom FL, Duff GW, Kubaszek A. Promoter polymorphisms of TNF- α (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes. *Diabetes* 2003; 52: 1872-1876.

Laakso M. Hyperglycemia as a risk factor for cardiovascular disease in type II diabetes. *Prim Care* 1999; 26: 829-839.

Meydani SN, Endres S, Woods MM, et al. Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. *J Nutr* 1991; 121: 547-555.

Michalowicz BS, Diehl SR, Gunsolley JC, Sparks BS, Brooks CN, Koertge TE, Califano JV, Burmeister JA, Schenkein HA. Evidence of a substantial genetic basis for risk of adult periodontitis. *J Periodontol* 2000; 71: 1699-1707.

Offenbacher S. Periodontal diseases: Pathogenesis. *Ann Periodontol* 1996; 1: 821-878.

Papapanou PN. Epidemiology of periodontal diseases: an update. *J Int Acad Periodontol* 1999; 1: 110-116.

Scannapieco A.F., Bush R.B., Paju S. Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systematic review. *Ann Periodontol* 2003 8:38-53.

Sookoian SC, Gonzalez C, Pirola CJ. Meta-analysis on the G-308A tumor necrosis factor alpha gene variant and phenotypes associated with the metabolic syndrome. *Obes Res* 2005; 13:2122-31.

Southerland JH, Taylor GW, Moss K, Beck JD, Offenbacher S. Commonality in chronic inflammatory diseases: periodontitis, diabetes and coronary artery disease. *Periodontology* 2000, 2006; 40: 130-143

Ylostalo P.V. and Knuutila M.L. Confounding and effect modifications. Possible explanation for variation in the results on the association between oral and systemic disease. *J Clin Periodontol* 2006, 33: 104-108



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