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Are Hill's criteria for causality satisfied for vitamin D and periodontal disease?

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There is mounting evidence that periodontal disease (PD) is linked to low serum 25-hydroxyvitamin D [25(OH)D] concentrations in addition to recognized risk factors like diet and smoking. This paper reviews this evidence using Hill's criteria for causality in a biological system. Evidence for strength of association, consistency, cohesion and 'dose-effects' [biological 'gradients'] include strong inverse correlations between serum 25(OH) and PD cross-sectionally and that PD is consistently more prevalent in darker vs. lighter skinned people and increases at higher latitudes with analogy for gingivitis and for disorders associated with PD whose risks also increase with hypovitaminosis D. Evidence for plausibility includes that vitamin D increases calcium absorption and protects bone strength; induces formation of cathelicidin and other defensins that combat bacterial infection; reduces tissue production of destructive matrix metalloproteinases actively associated with PD and that prevalence of PD varies with common vitamin D receptor polymorphisms. Experimental evidence from limited supplementation studies [using calcium and vitamin D] shows that supplementation reduces tooth loss. Thus, existing evidence for hypovitaminosis D as a risk factor for PD to date meets Hill's criteria for causality in a biological system. Further experimental evidence for effectiveness and temporality, preferably from randomized controlled trials of vitamin D supplementation [adjusting for other PD risk factors including diet and smoking to reduce confounding] are necessary to confirm causality. If confirmed, dentists and periodontists could perform a valuable service to their patients by discussing the importance of adequate vitamin D status and how to avoid deficiency.

Introduction

Periodontal disease (PD) is a chronic condition where bacterial biofilms adhere to the gingiva (periodontal tissues) leading to host responses within periodontal tissues, and inducing inflammatory damage resulting in breakdown of the connective tissue that anchors teeth to alveolar bone.[1] If left unchecked, PD leads to tooth loss. The proportion of the US population with PD in 1999–2004 according to the National Health and Nutrition Examination Survey (NHANES) increased from 3.8% for those aged 20–34 years to 10.4% for those aged 35–49 years and to 11.9% for those aged 50–64 years.[2] PD rates also varied with ethnicity at 5.8% in Whites, 16.8% in Blacks and 13.8% in Mexican-Americans.[2] However, another study, also based on NHANES, found 3.6% in Whites, 7.2% in Blacks and 4.4% for Mexican-Americans.[3] Overall, periodontitis affects almost 40% of the entire adult population in the UK.[4]

Since oral bacteria are important risk factors for PD,[5] and since activated vitamin D [1,25-dihydroxyvitamin D], through induction of cathelicidin (LL-37) and other defensins, effectively fights bacterial infections,[6] it seems reasonable to expect that maintenance of adequate repletion with vitamin D could reduce the risk of PD. The most convincing evidence would be provided by well-conducted randomized controlled trials (RCTs). However, there has been only one to date, and it provided evidence of a moderate benefit with respect to periodontal health for combined vitamin D and calcium supplementation.[7] A cross-sectional study in the United States found a significant inverse correlation between PD and serum 25-hydroxyvitamin D [25(OH)D] concentrations.[8] While useful, cross-sectional studies alone cannot establish a causal connection between low serum 25(OH)D concentrations and risk of PD.

Another way to examine causality in a biological system was proposed by A. Bradford Hill.[9] Hill designated nine criteria that could be evaluated: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy. Other researchers added the ruling out of confounding factors and bias.[10] Not all criteria need be satisfied, but the more that are, the stronger the case for causality. Some examples of applying Hill's criteria to examine causal links include dietary factors in the risk of Alzheimer disease,[11] the first paper to make such a link, and vitamin D as a risk reduction factor for several types of cancer nearly thirty years after the ultraviolet-B (UVB)-vitamin D-cancer hypothesis was proposed.[12]

This paper reviews the journal literature in order to address the question of whether the evidence supports a role for better supplies of vitamin D in reducing the risk of PD, using Hill's criteria for causality.

Results

Strength of association. Data from the National Health and Nutrition Examination Survey (NHANES) III survey, conducted

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in two phases between 1988 and 1994 were analyzed in terms of periodontal attachment loss as a function of serum 25(OH)D concentrations for males and females for two age groups, 20–49 years and >50 years. Associations were adjusted for age, race or ethnicity, smoking, diabetes, calcium intake, BMI, poverty income ratio, gingival bleeding, survey phase and dental examiner. The trends for those aged 20–49 years were not significant. For those >50 years, the standardized β coefficients varied from 0.39 (95% CI, 0.17–0.68) for 25(OH)D <40.2 nmol/L to 1.0 (reference) for 25(OH)D >85.6 nmol/L ($p_{for\ trend}$, 0.001) for males and 0.26 (95% CI, 0.09–0.43) ($p_{for\ trend}$, 0.001) for females.[8] Since these results were adjusted for many factors that affect risk of PD other than diet and vitamin D, they suggest a strong association of PD with poor vitamin D status.

Chronic marginal gingivitis, a chronic inflammation of the gingival tissues that is induced by bacterial dental plaque, is often associated with PD. In a related study using NHANES III data, Dietrich et al.[15] found a significant trend for prevalence of bleeding across quintiles of 25(OH)D; for the highest (32.4 nmol/L) vs. the lowest (99.6 nmol/L) the OR was 0.90 (0.86–0.95) after adjustment for the same factors as for PD but with the addition of vitamin C, hormone replacement therapy among women, missing teeth, full crown coverage and frequency of dental visits.

Consistency. While there are few studies of PD with respect to serum 25(OH)D concentrations, there are other studies that can be used to indicate the effect of vitamin D on PD risk. One such set of studies compares PD prevalence among African-Americans and White-Americans.[3,16-21] In the first of these studies, Blacks had an average of 78% of their sites with attachment loss and the average level of loss in those sites was approximately 4 mm, as compared to 65% and 3.1 min for Whites.[16] In a recent study in Brazil, lighter-skinned Black people (Pardos) and dark-skinned Black people (Pretos) presented higher levels of PD when compared with white people [odds ratio (OR) = 1.5; 95% CI 1.2; 1.8 and OR = 1.6; 95% CI 1.2; 2.1, respectively] even after controlling for age, gender, schooling, per capita income and geographic region.[21] While such studies should be examined to determine whether factors other than serum 25(OH)D concentration could explain the findings, the fact that the mean serum 25(OH)D values for African-Americans was 16 ng/mL [64 nmol/l] while that for White-Americans was 26 ng/mL [104 nmol/l][22] also supports the assumption that differences in vitamin D status [serum 25(OH)D concentration] could account for much of the disparity. A recent review concluded that differences in serum 25(OH) D levels between Black and White Americans could account for a large fraction of the health disparities observed.[23]

Temporality. This condition requires that beneficial effects should follow, not precede, the agent. This is generally the case for vitamin D. However, several papers have raised the possibility that low serum 25(OH)D concentrations measured for those who already have a disease or condition could reflect a changed lifestyle with less time spent out of doors, and, conversely, higher levels could be associated with increased outdoor activity, better health or the use of vitamin D supplementation because of its known or suspected health benefits. Two cross-sectional studies, one on PD,[8] the other on gingivitis,[15] are part of a much larger set of studies using the NHANES dataset. Nearly all of the 357 NHANES papers mentioning associations of disease state with serum 25(OH)D concentrations have been supported by other studies. In addition, PD does not generally cause sufferers to stay indoors as might be the case with cancer or cardiovascular disease. There have been no prospective studies, but the one RCT of calcium and vitamin D supplementation on the effect of tooth loss in the elderly found a modest protective effect.[7]

Mechanisms. The first mechanism that is proposed to explain the role of vitamin D in reducing the risk of PD and gingivitis is induction of LL-37 and defensins by 1,25-dihydroxyvitamin D. This mechanism has been found to explain how solar UVB and vitamin D reduce the risk of tuberculosis.[24,25] Markers of higher vitamin D repletion have also been found to be associated with reduced risk of influenza,[26] pneumonia[27] and septicemia.[28,29] There are several good reviews of this mechanism.[6,30-33] A recent study found that saliva from orally healthy individuals is capable of protecting LL-37 from proteolysis by *Porphyromonas gingivalis,* a bacterium associated with periodontitis. This protective activity was found to be necessary to enable the direct bactericidal activity of LL-37 (as tested on *E. coli*) in the presence of virulence-associated proteases of *P. gingivalis*.[34]

Matrix metalloproteinases (MMPs). MMPs are enzymes that assist in modulation of interstitial tissue by digestion of its supportive matrix, especially collagen and MMP-9, in particular, is known to be present in large amounts in active PD,[35] as it is in active atheromatous plaque and this enzyme is inhibited by tissue inhibitor of matrix metallopreoteinase-1 (TIMP-1). Higher plasma MMP-3, MMP-8 and MMP-9 concentrations have been found in PD patients compared with healthy controls (all $p < 0.05$).[36] Furthermore, a study of British Bangladeshi adults, free of known diabetes or major illness, showed that a year of modest vitamin D supplementation led to a decrease in plasma circulating matrix metalloproteinase 9 (MMP-9) by -69% and of CRP by -23%.[37] Activated vitamin D has also been shown to suppress the increases in MMP9 formation induced in white cells by tubercle bacilli[38] as well as of MMP-3.[39] MMP-3 is associated with acute coronary syndrome[40] and unstable coronary disease.[41] Increases in circulating MMP-9 are seen in acute coronary events and associated with increases in cardiovascular disease risk factors[42] though this was not confirmed by Kaplan et al.[43] Since vitamin D modulates MMP9 in bone, and bone formation,[44] this second mechanism provides a possible link through which vitamin D status could influence both gum disease, tooth attachment and preservation of alveolar bone as well as cardio vascular disease and general bone health.

Vitamin D receptors. Vitamin D receptors (VDRs) are found in nearly every cell of the body. The hormonal metabolite of vitamin D, 1,25-hydroxyvitamin D, is the ligand that activates them by fitting into a specific cleft in the VDR. Ligand-bound VDRs heterodimerize with the retinol X receptor to induce many of the effects of vitamin D through binding of the VDR; RXR complex to vitamin D response elements in the promoter regions of target genes, leading to modulation of expression of many of the 1,000 or more target genes. In about two-thirds of cases, they activate or enhance gene expression, and in the other third, they reduce

gene expression. Much of the action of vitamin D is achieved through the VDRs. There are many VDR polymorphisms, *Bsm*I, *Apa*I, *Taq*I and *Fok*I being the best known. VDR polymorphisms appear to be associated with variation in expression of various other genes even though polymorphisms such as *Apa*I, *Bsm*I, *Fok*I and *Taq*I are in non expressed portions of the VDR gene, possibly due to variation in the induction of tertiary structure of the VDR.[45] Investigations of disease associations with VDR polymorphisms can give an indication of whether vitamin D status may affect a given health or disease outcome. For PD, the VDRs that have received the most attention are *Apa*I, *Bsm*I, *Fok*I and *Taq*I (reviewed in ref. 46–52).

The question arises whether these polymorphisms could be related to effects on alveolar bone through calcium metabolism or by the ability to combat bacterial infection. To address that question, Pubmed was searched for papers on VDR, osteoporosis and infectious diseases. Papers were found for bones,[53,54] osteoporosis,[55] *Mycobacterium malmoense* pulmonary disease,[56] tuberculosis,[57,58] acute lower respiratory tract infection,[59] insulin secretory capacity,[60] type 1 diabetes,[61,62] lepromatous leprosy,[63] *Staphylococcus aureus* infection[64] and advanced prostate cancer.[65,66] For bones, the TT allele frequency was higher for those with higher mean forearm and spine bone mass density.[53] For tuberculosis, the Tt allele was found associated with better response to treatment,[56,57,67] as was the AA genotype.[68] Thus, these studies suggest that these polymorphisms are important for both functions but do not allow any distinction to be made between the roles of calcium metabolism and bactericidal efficacy.

Supplementation studies. There has been one small RCT of vitamin D and calcium supplementation and risk of PD. In this study, 11 of the 82 subjects (13%) taking supplements and 17 of the 63 subjects (27%) taking placebo lost one or more teeth (OR = 0.4; 95% CI: 0.2 to 0.9). During the 2-year follow-up period, 31 of the 77 subjects (40%) with total calcium intake of at least 1,000 mg per day lost one or more teeth compared with 40 of the 68 subjects (59%) who consumed less (OR = 0.5; 95% CI: 0.2 to 0.9).[7] Since both vitamin D and calcium were used, it is difficult to distinguish between the effects of the two supplements.

In a related cross-sectional study of chronic periodontitis in relation to calcium and vitamin D supplementation in Illinois and Missouri, a comparison was made of 23 subjects who had been taking vitamin D (≥400 IU/day) and calcium (≥1,000 mg/day) supplementation for >18 months (takers) and 28 subjects who were taking neither vitamin D nor calcium supplementation and had dietary intakes of calcium <1,000 mg/day and of vitamin D <400 IU/day (non-takers). The mean values of vitamin D and calcium intakes for the takers were 1,049 (781–1,317) IU/d and 1,769 (1,606–1,933) mg/day and 156 (117–195) IU/d and 642 (505–779) mg/d for the non-takers. Measures of periodontitis were consistently higher in non-takers than in takers [$p < 0.05$], despite the small numbers of subjects[69] and despite the fact that participants had been enrolled in periodontal maintenance programs for >6 months before supplementation, which may have reduced the potential for benefits from vitamin D and calcium.

Table 1. Regression results for tooth loss for data in Dunning (1953)[71]

Number of states	UVB (β, p)	Urban (β, p)	T July (β, p)	Adj. R^2, F, p
48	-0.72*	0.39*		0.64, 42*
47	-0.55*		-0.25, 0.08	0.52, 26*
47		0.37, 0.001	-0.60	0.48, 22*

*$p < 0.001$.

Analogies with dental caries in the U.S. Dental caries is analogous to PD in that it is caused by oral bacteria.[5] There are two studies on the effect of sunlight on risk of dental caries on adolescents and young men from the early-to-mid twentieth century. In the first, it was reported that adolescent males between the ages of 12 and 14 years had half as many carious lesions in the sunny west (3,000 hours of sunlight/year) than those in the much less sunny northeast (<2,200 hours of sunlight/year) whilst the rates in the portions of the country with intermediate annual hours of sunlight fell between those for the extremes of sun exposure.[70] In the second study, dental condition rankings were developed for young men entering the armed forces for World War I and World War II.[71] The northeast had the worst ranking, while states near Texas had the best ranking. A simple ecological analysis of the rankings using summertime UVB[72] and urban residence for 1,960 found an adjusted $R^2 = 0.64$ standardized coefficient beta for UVB = -0.72, $p < 0.001$, and for urban residence the adjusted $R^2 = 0.39$, $p < 0.001$ (See **Table 1**).

Confounding factors: smoking, diet and calcium intake. The most important recognized factors for PD are age (greater than 40 years), smoking,[73] diet[74,75] and calcium intake.[76] However, even when these factors are included in studies examining links between PD and systemic and infectious diseases, there is often a large portion of causation unaccounted for.

Bone mineral density (BMD) is linked to calcium, diet and smoking, as well as other factors. Many studies have found PD and osteoporosis to be comorbid.[77-80] However, osteoporosis may not be directly linked to dietary calcium intake because national diets high in calcium are also high in animal sources of protein,[81] which lowers the pH of the digestive tract, reducing calcium absorption and thus increasing calcium removal from bone.[82] Studies of correlations of changes in BMD with changes in PD status may provide some insight into the relative roles of the various factors. In a study in Pennsylvania, "absolute BMD and percentage change in BMD were similar in dentate and edentulous women. We found no difference in BMD or in absolute or percentage change in BMD between women with or without periodontal disease" and the authors concluded. "Little evidence exists for an association between edentulousness, periodontal disease and longitudinal changes in BMD."[83] "In a cohort of 1,347 (137 edentulous) older men followed for an average of 2.7 year after recruitment from the Osteoporotic Fractures in Men Study, random half-mouth dental measures included clinical attachment loss (CAL), pocket depth (PD), calculus, plaque and bleeding. BMD was measured at the hip, spine and whole-body, by dual-energy X-ray absorptiometry,

and at the heel by ultrasound. After adjustment for age, smoking, race, education, body mass index and calculus, there was no association between number of teeth, periodontitis, periodontal disease progression, and either BMD or annualized rate of BMD change."[84] However, both of these studies were short-term in nature. Longer-term studies are probably required to find links. For example, in studies of measured and imputed maternal serum 25(OH)D and bone mineral density in the offspring aged nine years, both the estimated exposure to UVB radiation during late pregnancy and the maternal use of vitamin D supplements contributed to maternal 25(OH)-vitamin D concentration ($p < 0.0001$ and $p = 0.01$, respectively) which in turn contributed to childhood bone mass ($p = 0.03$).[85,86] In adults, supplementation has led to lesser reductions in BMD over time[87] and to reductions in fracture rates with 5 years of supplementation at ~820 IU/day.[88]

Correlation with other diseases. PD has itself been linked to many systemic and infectious diseases,[89-92] including many types of cancer,[93,94] carotid atheroma,[95] cardiovascular disease,[96,97] diabetes mellitus,[98,99] pneumonia[100] and rheumatoid arthritis.[101] Lower serum 25(OH)D concentrations have been found associated with risk of many types of chronic and infectious diseases in the past few years.[102] Such diseases include many types of cancer,[12,103-105] cardiovascular disease,[106] diabetes mellitus[106] and pneumonia.[107] Thus, the hypothesis that PD was a risk factor for the diseases associated with it was proposed. A number of other hypotheses have been postulated, including common susceptibility, systemic inflammation with increased circulating cytokines and mediators, local infection and cross-reactivity or molecular mimicry between bacterial antigens and self-antigens.[90]

In many association studies, commonly accepted risk factors for PD, such as smoking, were included in the analysis but did not explain the association. There is some evidence from intervention trials that periodontal therapy, which decreases the intraoral bacterial bioburden and reduces periodontal inflammation, can have a significant impact on systemic inflammatory status.[108] However, it has not been established that treating PD reduces the risk of any of the associated diseases.[109]

Another hypothesis is that a high carbohydrate diet increases both the risk of PD and of systemic diseases such as diabetes and cardiovascular disease, thereby explaining the link between the two.[74] Indeed, there is evidence that added sugar intake is a risk factor for cardiovascular disease.[110-113]

An alternative hypothesis, proposed here, is that low serum 25(OH)D concentrations increase the risk of both PD and of diseases associated with PD. **Table 2** includes examples of studies of PD with other diseases known to be associated with low serum 25(OH)D, namely cardiovascular disease, coronary heart disease, cognitive impairment, pneumonia, and many types of cancer. If this is the case, vitamin D supplementation for those with PD may prove to reduce the risk of the associated diseases.

Recently it was proposed that signaling through the receptor for advanced glycation end products (RAGE) might explain the periodontal-systemic disease link. This receptor, which is frequently associated with proinflammatory responses, has been shown to be activated by various ligands such as high mobility group box-1 (HMGB1/amphoterin), amyloid fibrils, transthyrein, Mac-1 (Integrin Mac-1), as well as advanced glycation end products (AGEs), and recent studies indicate that signaling through RAGE is implicated as an underlying condition in diverse pathologies. It was recently demonstrated that hormonal vitamin D can blunt the deleterious impact of AGEs on endothelial cells, which provides further support for the vitamin D hypothesis.[116-117]

Discussion

This paper reviews the evidence for the association of PD with low serum 25(OH)D concentrations. The more important evidence includes:- strong inverse correlation between serum 25(OH)D and both PD and gingivitis cross-sectionally; consistent data showing higher prevalence of PD in darker as compared to lighter -skinned people living in the same geographical locations. Several feasible mechanisms for this association are presented; that vitamin D increases calcium absorption and upregulates intracellular calcium; induces production of cathelicidin and other defensins with bacteriocidal effects on oral bacteria and reduces production of MMPs, especially of the MMP9 found in high concentrations in active PD. In addition, PD severity varies with two common VDR polymorphisms. Limited studies of vitamin D and calcium supplementation report reduced tooth loss with combined supplementation but could not distinguish between the effects of vitamin D and those of calcium. Analogy with dental caries include; that higher solar UVB exposure correlated inversely with dental caries in young men in the United States in the early-to-mid twentieth century; that there is co-morbidity of caries with systemic and infectious diseases for which low serum 25(OH)D concentration is a risk factor. The more commonly recognized risk factors for PD, such as age, diet and smoking, can confound studies related to serum 25(OH)D concentration but studies of co-morbid diseases with PD not examining serum 25(OH)D, suggest that these associations are not fully accounted for by the classical risk factors.

Thus, the evidence for hypovitaminosis D as a risk factor for PD meets the criteria for causality in a biological system proposed by Hill[9] and discussed by Weed[10] reasonably well even though some of his criteria are better satisfied than others. The cross-sectional evidence for this association and for variation with vitamin D polymorphisms supports the suggestion of causality as do the results of the single randomized controlled trial of vitamin D supplementation for PD though the benefits could not be distinguished from those of the calcium given. The fact that there are recognized mechanisms by which hypovitaminosis D tissue can worsen the risks of gingival inflammation, worsen tissue destruction, increase bone loss and reduce the efficiency of defensive mechanisms after bacterial infection, also supports the likelihood of causality.

Thus, there is consistent evidence using Hills Criteria, that hypovitaminosis D is a risk factor for PD but further evidence, either from randomized controlled trials of vitamin D supplementation or careful prospective studies, is required in order to determine whether hypovitaminosis D is causal for PD.

Table 2. Associations of periodontal disease with chronic and infectious diseases themselves known to be associated with hypovitaminosis D

Disease or health outcome	Study parameters	Findings:- Risk/Odds/Hazard Ratio [95% confidence interval]	Reference
Cardiovascular disease	215 epidemiological studies, 47 were observational 29 of these suitable for meta-analysis. 16,720 subjects in cross-sectional studies, 1,464 cases, 1,726 controls and 147,821 in cohort studies.	Pooled OR calculated from 22 case-control & cross-sectional studies 2.35 [1.87; 2.96; $p < 0.0001$]. RR for incident cardiovascular disease in the 7 cohort studies = 1.34 [1.27; 1.42; $p < 0.0001$].	96
Coronary heart disease	Meta-analysis of risk of PD with elevated markers of systemic bacterial exposure Total N of subjects = 12,074	OR = 1.75 [1.32; 2.34; $p < 0.001$]	114
Cognitive function	NHANES 2001 to 2002. 803 dentate participants aged 60 or older, completing periodontal and cognitive examination.	OR = 0.69 [0.51; 0.94] per/standard deviation (SD) increase in the DSST score	115
Pneumonia	Cohort study of 277 men and 420 women aged 80 years old examined in Japan in 1997.	OR for death from pneumonia (adjusted) = 3.9 in those with 10 or more teeth and with pockets >4 mm deep vs. those with 10 or more teeth but without pockets.	100
Cancers	Cohort study with 48,375 men and 18 years of follow-up were available (1986 to January 31, 2004; median follow-up 17.7 yrs), during which time 5,720 incident cancer cases were documented (excluding nonmelanoma skin cancer and nonaggressive prostate cancer).	By cancer site, significant associations for those with periodontal disease were found for lung (1.36 [1.15–1.60]), kidney (1.49 [1.12–1.97]), pancreas (1.54 [1.16–2.04]) and haematological cancers (1.30 [1.11–1.53]). Fewer teeth at baseline (0–16) marked OR for lung cancer of 1.70 [1.37–2.11], for those with 0–16 teeth vs. those with 25–32 teeth. In never-smokers, periodontal disease was associated with increases in total (1.21 [1.06–1.39]) and haematological cancers (1.35 [1.01–1.81]). But not for lung cancer (0.96 [0.46–1.98]).	93
	Review of approximately 40 studies	The most consistent risk increases were seen for oral and esophageal cancers in periodontal disease. Gastric and pancreatic cancers were associated in some but not all studies. Lung, prostate, hematologic and other cancers were not consistently associated or there were too few studies for analysis.	94

Materials and Methods

This paper is a review of the peer reviewed medical literature. The primary data source was www.pubmed.gov. The search terms were used with 'periodontal disease' or 'periodontitis' in searching this database. Since some of the evidence relates to vitamin D receptor (VDR) polymorphisms the search was extended to additional diseases linked to variation in VDR polymorphisms. The *Bsm*I, *Apa*I, *Taq*I and *Fok*1 VDR polymorphisms have received the greatest attention with respect to PD and other diseases,[13,14] so they were the ones included in searching for links to other diseases. In addition, a limited search was made for reports of large studies or meta-analyses discussing links between PD and systemic and infectious diseases.

Disclosure

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