Journal of Clinical Periodontology
Official Journal of The European Federation of Periodontology
Founded by the British, Dutch, French, German, Scandinavian, and Swiss Societies of Periodontology

J Clin Periodontol 2009; 36: 984–995 doi: 10.1111/j.1600-051X.2009.01475.x

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Partial least squares path modelling for relations between baseline factors and treatment outcomes in periodontal regeneration

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Tu Y-K, Gilthorpe MS, D'Aiuto F, Woolston A, Clerehugh V. Partial least squares path modelling for relations between baseline factors and treatment outcomes in periodontal regeneration. J Clin Periodontol 2009; 36: 984–995. doi: 10.1111/j.1600-051X.2009.01475.x.

Abstract

Background: Some clinical outcome variables in periodontal research are mathematically coupled, and it is not feasible to include all the mathematically coupled variables in an ordinary least squares (OLS) regression analysis. The simplest solution to this problem is to drop at least one of the mathematically coupled variables. However, this solution is not satisfactory when the mathematically coupled variables have distinctive clinical implications.

Material and Methods: Partial least squares (PLS) methods were used to analyse data from a study on guided tissue regeneration. Relationships between characteristics of baseline lesions and treatment outcomes after 1 year were analysed using PLS, and the results were compared with those from OLS regression.

Results: PLS analysis suggested that there were multiple dimensions in the characteristics of baseline lesion: vertical dimension was positively associated with probing pocket depth (PPD) reduction and clinical attachment level (CAL) gain, whilst horizontal dimension was negatively associated with the outcome. Baseline gingival recession had a negative association with PPD reduction but a small positive one with CAL gain.

Conclusion: PLS analysis provides new insights into the relationships between baseline characteristics of infrabony defects and periodontal treatment outcomes. The hypothesis of multiple dimensions in baseline lesions needs to be validated by further analysis of different datasets.

Key words: collinearity; mathematical coupling; partial least squares; periodontal regeneration; regression analyses

Accepted for publication 2 August 2009

Conflict of Interest and Source of Funding Statement

The authors declare that they have no conflicts of interest.
All authors except AW were funded by the UK government's Higher Education Funding Council for England (HEFCE). AW is currently supported by a PhD studentship from the Medical Research Council, UK. The first author currently holds a UK Research Council Fellowship.

Although the benefit of periodontal regeneration in the treatment of infrabony lesions is well established, it has also been noted that there are wide variations in the reported treatment effects (Needleman et al. 2006, Tu et al. 2008c). Many clinical studies therefore used multiple regression analyses to describe or explain the relationships between baseline characteristics of infrabony lesions and the treatment outcomes (Renvert et al. 1985, Tonetti et al. 1993, 1996, 1998, 2004, Falk et al. 1997, Trombelli et al. 1997, 2002, Mayfield et al. 1998, Cortellini & Tonetti 2000, Klein et al. 2001, Machtei 2001, Zucchelli et al. 2002, Ehmke et al. 2003, Silvestri et al. 2003, Sanz et al. 2004). One potential problem with the uses of multiple regression analysis is *collinearity*, i.e. the high correlations between explanatory variables (covariates) in the

regression models (Tu et al. 2004, 2005). For example, infrabony lesions with greater baseline pocket depths tended to have greater loss of attachment and have deeper infrabony defect measured surgically and radiographically. When there are more than two covariates that are highly correlated, this is called *multicollinearity* (Pedhazur 1997, Chatterjee et al. 2000, Glantz & Slinker 2001, Fox 2008). Collinearity and multicollinearity might distort the interpretation of regression models, and hence the role of each covariate, causing increased inaccuracy (as expressed through bias within the regression coefficients) and increased uncertainty (as expressed through the inflated coefficient standard errors) (Miles & Shelvin 2001).

A special type of multicollinearity within many areas of dentistry, and particularly within periodontal research, is the mathematical coupling of variables (Archie 1981, Andersen 1990, Tu et al. 2002, 2007), i.e. one or more covariate can be expressed as a mathematical equation of the other covariates. For example, clinical attachment level (CAL) is usually defined as the sum of probing pocket depth (PPD) and gingival recession (GR), i.e. CAL = PPD+GR. These three variables are therefore mathematically coupled and perfectly multicollinear. When these three variables are entered into multiple regression analysis as covariates, one of them will typically be removed by statistical software packages for mathematical computations to proceed. This is because to obtain the regression coefficients, the data matrix for covariates needs to be invertible (full-ranked), and a matrix with mathematically coupled covariates such as CAL, PPD and GR is not invertible (because one row or one column in the matrix can be expressed as a function of the other rows or columns) (Fox 2008).

The simplest way to resolve this problem of multicollinearity is to drop one or more of the mathematically coupled variable from the regression model; most computer software packages will do it automatically. In the example of mathematical coupling between CAL, PPD and GR, researchers may decide to use CAL and PPD as covariates, though these two variables are still highly correlated, i.e. collinear. Sometimes, it may not be straightforward to determine which variable should be left out in the regression model. Moreover, while one or more of the mathematically coupled variables may be considered redundant and better left out of regression models from a statistical point of view, it may not be the case from a clinical perspective. For instance, while PPD, CAL and GR are mathematically coupled, they are distinctive clinical entities, and this is why all of them are widely reported. Although only two of the three variables can be entered in a multiple regression model, this does not necessarily mean that the relationships between the outcome and the three variables can be derived from the relationships between the outcome and any two of them.

Within periodontal research, many clinical parameters that purport to be measures of baseline disease severity are highly correlated due partly to mathematical coupling (Tu et al. 2004, 2005). Therefore, alternative approaches may be required to overcome the multicollinearity problem in order to investigate the relationships between treatment outcomes and baseline disease characteristics. The aim of this study is to reanalyse multicollinear data from a clinical study on guided tissue regeneration (GTR) using partial least squares (PLS) analysis, a multivariate statistical method widely used in chemometrics and bioinformatics (Helland 1990, Phatak & de Jong 1997, Boulesteix & Strimmer 2007). In this study, PLS analysis is used to explore the relationships between baseline variables and multiple treatment outcomes, and some of its results are compared with those from ordinary least squares (OLS) regression.

Material and Methods

Data for re-analysis

We reanalysed data from a study evaluating the treatment effects of GTR with a resorbable membrane. Details of the study design and results have been published before (Falk et al. 1997). In summary, 203 lesions in 143 patients with infrabony defects $\geqslant$4 mm were treated. Clinical, radiographical and surgical measurements were undertaken at baseline, and clinical outcomes 1 year after treatments were evaluated. Original statistical analysis used single-level stepwise linear regression to test the associations between baseline disease characteristics and the treatment outcome CAL gain (Falk et al. 1997). Results showed that baseline CAL and infrabony defect depth had positive associations with CAL gain, i.e. lesions with greater attachment loss and deeper defects at baseline, the greater CAL gain was achieved. Lesions with wider defects and early exposure of barrier membranes had less CAL gain. The original data were not independent because some patients contributed more than one lesion, and therefore single-level linear regression was not appropriate from a statistical viewpoint. Nevertheless, re-analysis of the data using multilevel regression analysis indicated that the differences in the regression coefficients and their standard errors between single-level and multilevel analyses were negligible.

Reanalysis of data using PLS methods

As there is no distributional assumption for PLS estimates (Wold 1982), the statistical assumption for independence of observations is not required for PLS (Chin 1999). Nevertheless, in order to compare PLS with OLS stepwise regression, we randomly selected one lesion from patients with multiple lesions. As a result, 143 lesions were used in the reanalysis. Seven baseline clinical, radiographical and intra-surgical variables were used as covariates in PLS analysis: PPD0 (baseline probing pocket depth in mm), CAL0 (baseline clinical attachment level in mm), GM0 (baseline gingival recession in mm), IBD (depth of infrabony defect in mm), RBL (distance between cemento-enamel junction to alveolar bone crest measured on digitalized radiographs), WIDTH (width of infrabony defects in mm) and CIRCUM (circumference of infrabony defects in degrees).

PLS model building strategy

We started with a basic PLS path model for PPD reduction or CAL gain by assuming that the seven baseline variables are all manifestations of one single latent (unobserved) variable, i.e. there is only one dimension in the baseline disease severity. Based on the results from the basic model, we extended the complexity of the path model by increasing the numbers of latent variables to be measured by different groups of baseline variables. One advantage of PLS, being a multivariate method, is that it can accommodate more than one outcome variable within a single model when seeking to understand the

inter-relationships between multiple treatment outcomes and baseline variables. Therefore, in the final model we included both outcomes in one PLS path model. As there are no distributional assumptions for PLS estimates, confidence intervals for path coefficients and associated *p*-values were derived using the bootstrap method with 500 random samplings. A concise non-technical explanation of PLS is provided in the Appendix A.

Reanalysis of data using OLS regression analysis

To compare results from some of the PLS analyses, data from 143 lesions were reanalysed using OLS regression. Backward stepwise algorithms were also used for variable selection. The criterion for variables to be removed from the model by backward elimination was significance level $p > 0.1$ from the *F*-test for the decrease in the explained outcome variance.

OLS stepwise regression analysis was undertaken using the statistical software package SPSS version 15 (SPSS Inc, Chicago, IL, USA). PLS analyses were undertaken using the statistical software XLSTAT version 2009 (Addinsoft, http://www.addinsoft.com). The statistical significance was set at 5% level throughout this study.

Results

A summary of baseline variables and treatment outcomes and the Pearson correlations among these variables are shown in Table 1. Table 2 shows the simple linear regression coefficients for each of the seven baseline variables when the outcome is PPD reduction or CAL gain.

OLS stepwise regression for PPD reduction and CAL gain

For PPD reduction, the positive bivariate association between the outcome and RBL (the coefficient in simple linear regression is 0.122) was reversed in multiple OLS regression models, whilst PPD0 and CAL0 showed positive associations with the outcome (Table 2). Backward stepwise regression kept GM0 in the final model, but the negative bivariate association (-0.127) between the outcome and GM0 was reversed (0.337, $p < 0.001$). Figure 1 shows the path diagram for multiple linear regression, where all baseline variables except GM0 were entered into OLS regression. Results show that the positive associations of RBL and IBD with the outcome were reversed, and the reversed association was statistically significant for RBL in both OLS regression models.

For CAL gain, the positive bivariate association between the outcome and RBL (0.113) was reversed and statistically significant in backward stepwise regression, while PPD0 and IBD showed positive associations with the outcome (Table 2). CAL0 was removed from the model by backward elimination, but GM0 was kept in the final model. When all baseline variables except GM0 were entered into OLS regression, the positive association between the outcome and RBL were reversed and statistically significant.

PLS path analysis for PPD reduction and CAL gain

PLS Path Model-1 (PLSPM-1)

Using PLS, we first hypothesized that there was a single latent variable for baseline lesions, which was measured by the seven baseline variables. The path diagram for this model (PLSPM-1) is shown in Fig. 2. The latent variable for baseline lesions (BASE) is a weighted composite of seven baseline measurements. The outer weights and loadings for all seven baseline variables are shown in Table 3. Outer weights are the weights for the construction of the PLS component, i.e. BASE is given as

$$\begin{aligned}\text{BASE} &= 0.494\text{PPD0} + 0.376\text{CAL0} \\ &+ 0.104\text{RBL} + 0.21\text{IBD} \\ &- 0.085\text{WIDTH} + 0.034\text{CIRCUM} \\ &- 0.079\text{GM0}.\end{aligned}$$

Outer loadings are the Pearson correlations between BASE and each of the seven variables. While PPD0, CAL0, RBL and IBD had high correlations with BASE, the other three had relatively low correlations. Because both manifest and latent variables have been standardized in PLS analysis, outer weights multiplied by the path coefficient can be interpreted as the standardized regression coefficients,

Table 1. Summary statistics for 143 infrabony lesions treated with guided tissue regeneration and Pearson correlation matrix amongst the treatment outcomes and baseline characteristics

	Summary statistics				Pearson correlation coefficients							
	min.	max.	mean	SD	PPD reduction	CAL gain	PPD0	CAL0	GM0	RBL	IBD	WIDTH
PPD reduction	0	11	5.56	2.12								
CAL gain	−1	9	4.79	2.01	0.774*							
PPD0	6	16	9.08	1.95	0.647*	0.469*						
CAL0	6	17	10.49	2.21	0.492*	0.529*	0.667*					
GM0	−4	6	1.41	1.71	−0.103	0.148	−0.279	0.529*				
RBL	8	19	11.93	2.36	0.136	0.132	0.502*	0.690*	0.318*			
IBD	3	16	6.34	1.87	0.275*	0.312*	0.598*	0.519*	−0.013	0.553*		
WIDTH	1	6	2.92	0.91	−0.111	−0.164	0.151	0.091	−0.055	0.339*	0.303*	
CIRCUM	60	360	133.78	58.86	0.045	0.11	0.087	0.220†	0.185†	0.235†	0.155	0.024

Min., minimum; max., maximum; SD, standard deviation; PPD0, baseline probing pocket depth in mm; CAL0, baseline clinical attachment level in mm; RBL, radiographical bone level in mm; IBD, infrabony defect depth in mm; WIDTH, width of infrabony defect in mm; CIRCUM, circumference of infrabony defect in degree; GM0, the distance between cemento-enamel junction and baseline gingival margin; GR, gingival recession after treatments.
*p-value < 0.001.
†p-value < 0.05.

Table 2. Results for PPD reduction and CAL gain from OLS backward stepwise regression and full multiple regression

	Coefficients	95% Confidence intervals	Standardized coefficients	*p*-value	VIF	Regression coefficients	95% confidence intervals	Standardized coefficients	*p*-value	VIF
	Outcome: PPD reduction					Outcome: CAL gain				
Simple linear regression						Simple linear regression				
PPD0	0.703	(0.565, 0.841)	0.647	<0.001		PPD0	0.484	(0.332, 0.636)	0.469	<0.001
CAL0	0.472	(0.333, 0.672)	0.492	<0.001		CAL0	0.482	(0.353, 0.611)	0.529	<0.001
RBL	0.122	(−0.026, 0.271)	0.136	0.105		RBL	0.113	(−0.028, 0.254)	0.132	0.116
IBD	0.312	(0.131, 0.493)	0.275	0.001		IBD	0.336	(0.165, 0.506)	0.312	<0.001
WIDTH	−0.259	(−0.645, 0.127)	−0.111	0.187		WIDTH	0.363	(−0.728, 0.001)	−0.164	0.051
CIRCUM	0.002	(−0.004, 0.008)	0.045	0.593		CIRCUM	0.004	(−0.002, 0.009)	0.110	0.192
GM0	−0.127	(−0.332, 0.078)	−0.103	0.221		GM0	0.174	(−0.020, 0.367)	0.148	0.078
Backward stepwise regression ($R^2 = 0.535$)						Backward stepwise regression ($R^2 = 0.442$)				
Intercept	0.720	(−0.730, 2.170)		0.333		Intercept	1.264	(−0.265, 2.793)		0.107	
PPD0	1.012	(0.841, 1.183)	0.931	<0.001	1.914	PPD0	0.782	(0.586, 0.978)	0.758	<0.001	2.301
RBL	−0.343	(−0.496, −0.190)	−0.382	<0.001	2.242	RBL	−0.375	(−0.540, −0.210)	−0.439	<0.001	2.368
WIDTH	−0.250	(−0.540, 0.040)	−0.107	0.094	1.195	IBD	0.164	(−0.02, 0.348)	0.152	0.082	1.856
GM0	0.337	(0.157, 0.517)	0.273	<0.001	1.646	WIDTH	−0.329	(−0.637, −0.021)	−0.148	0.038	1.235
						GM0	0.579	(0.389, 0.770)	0.493	<0.001	1.649
Full multiple regression ($R^2 = 0.537$)						Full multiple regression ($R^2 = 0.443$)				
Intercept	0.618	(−0.883, 2.119)		0.421		Intercept	1.169	(−0.397, 2.735)		0.146	
PPD0	0.705	(0.523, 0.887)	0.649	<0.001	2.167	PPD0	0.209	(0.019, 0.399)	0.203	0.033	2.167
CAL0	0.339	(0.157, 0.521)	0.353	<0.001	2.768	CAL0	0.573	(0.383, 0.763)	0.628	<0.001	2.768
RBL	−0.329	(−0.488, −0.170)	−0.366	<0.001	2.398	RBL	−0.380	(−0.547, −0.213)	−0.445	<0.001	2.398
IBD	−0.075	(−0.251, 0.101)	−0.066	0.409	1.863	IBD	0.160	(−0.024, 0.344)	0.149	0.090	1.863
WIDTH	−0.226	(−0.522, 0.070)	−0.097	0.138	1.238	WIDTH	−0.325	(−0.635, −0.015)	−0.146	0.042	1.238
CIRCUM	0.000	(−0.004, 0.004)	0.009	0.881	1.080	CIRCUM	0.001	(−0.003, 0.005)	0.039	0.561	1.080

The backward elimination criteria is *p*-value ⩾ 0.1. As baseline PPD (PPD0), CAL (CAL0) and GR (GM0) are mathematically coupled, GM0 is not included in the full multiple regression. VIF is the variance inflation factor for the diagnosis of collinearity.

PPD0, baseline probing pocket depth in mm; CAL0, baseline clinical attachment level in mm; RBL, radiographical bone level in mm; IBD, infrabony defect depth in mm; WIDTH, width of infrabony defect in mm; CIRCUM, circumference of infrabony defect in degree; GM0, the distance between cemento-enamel junction and baseline gingival margin; GR, gingival recession after treatments; VIF, variance inflation factor; SE, standard errors.

e.g.:

$$\begin{aligned}\text{PPDreduction} &= 0.596\text{BASE} + \text{error}\\ &= 0.596(0.494\text{PPD0} + 0.376\text{CAL0} + 0.104\text{RBL} + 0.21\text{IBD} - 0.085\text{WIDTH} + 0.034\text{CIRCUM} - 0.079\text{GM0}) + \text{error}\\ &= 0.294\text{PPD} + 0.223\text{CAL} + 0.062\text{RBL} + 0.125\text{IBD} - 0.051\text{WIDTH} + 0.02\text{CIRCUM} - 0.047\text{GM0} + \text{error}\end{aligned}$$

The direction of associations between covariates and PPD reduction in PLS analysis is consistent with those in the corresponding bivariate associations (i.e. the simple linear regression coefficients in Table 2), but only the weights (or regression coefficients) for PPD0, CAL0 and IBD were statistically significant. The model R^2 was 0.355, i.e. 35.5% of the variance in PPD reduction was explained by BASE, and this was smaller than in the OLS stepwise regression ($R^2 \approx 53\%$)

For CAL the regression coefficients, weights and loadings for all seven baseline variables are shown in Table 3. The latent variable for baseline lesions (BASE) is given as

$$\begin{aligned}\text{BASE} &= 0.372\text{PPD0} + 0.42\text{CAL0} + 0.105\text{RBL} + 0.248\text{IBD} - 0.13\text{WIDTH} + 0.087\text{CIRCUM} + 0.117\text{GM0}\end{aligned}$$

Therefore,

$$\begin{aligned}\text{CAL gain} &= 0.199\text{PPD} + 0.225\text{CAL} + 0.056\text{RBL} + 0.133\text{IBD} - 0.07\text{WIDTH} + 0.047\text{CIRCUM} + 0.063\text{GM0} + \text{error}\end{aligned}$$

While PPD0, CAL0, RBL and IBD had high outer loadings (i.e. correlations) with BASE, the other three had relatively low correlations. The direction of associations between covariates and CAL gain in PLSPM-1 is consistent with the simple linear regression in Table 2, but only the weights for PPD0, CAL0 and IBD were statistically significant. The R^2 was 0.287, i.e. 28.7% of the variance in CAL gain was explained by BASE, and this was smaller than in the OLS stepwise regression ($R^2 \approx 44\%$)

PLS Path Model-2 (PLSPM-2)

Results from PLSPM-1 and the correlations in Table 1 indicated there to be more than one dimension in baseline lesions, hence more than one latent variable might be required to specify the multiple dimensions. We therefore hypothesized that there might be three dimensions (i.e. three latent composite

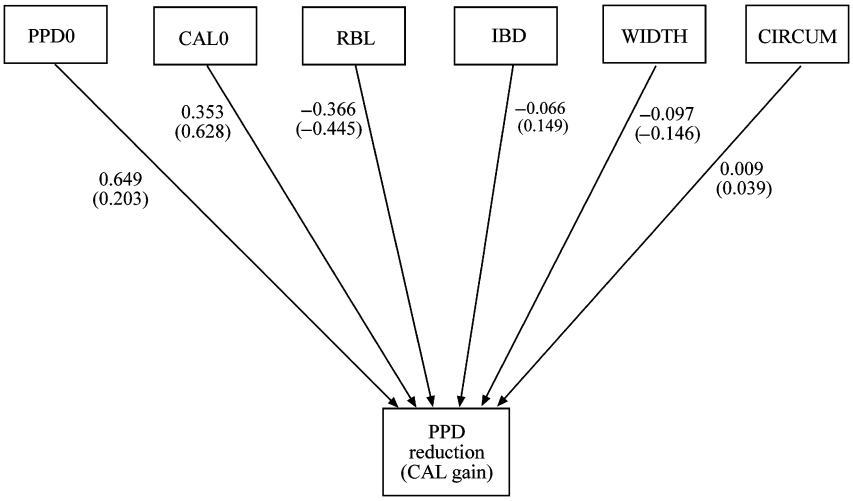

Fig. 1. Path diagram for multiple linear regression for PPD reduction or CAL gain. Arrows (i.e. paths) represent the relationships between the six covariates and each outcome. The values accompanying the arrows are the standardized regression coefficients for baseline variables when the outcome is PPD reduction, while those in parenthesis are standardized regression coefficients when the outcome is CAL gain. To simplify the presentation, the correlations between baseline variables are not shown.

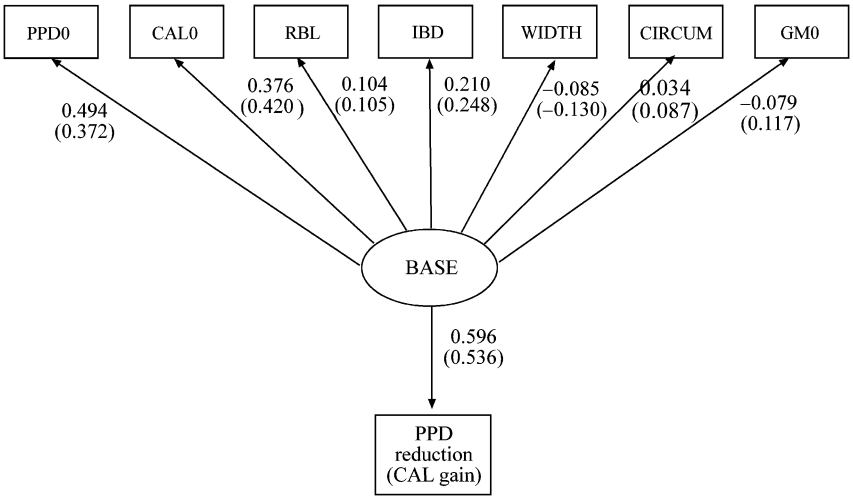

Fig. 2. Path diagram for PLSPM-1. Latent variables (in circles) are weighted composites of manifest variables (in squares). The value accompanying the arrows from a latent variable to an observed variable is the weight, while the value accompanying an arrow from a latent variable to another is a path coefficient. Values in parenthesis are results when the outcome is CAL gain.

variables) in baseline infrabony lesions: the vertical dimension, BASE-V (measured by PPD0, CAL0, RBL and IBD); the horizontal dimension, BASE-H (measured by WIDTH and CIRCUM); and the soft tissue dimension, BASE-G (measured by GM0). However, preliminary investigations revealed that BASE-H had a large positive correlation with WIDTH and a moderate negative correlation with CIRCUM, indicating that WIDTH and CIRCUM are unlikely to be indicators of the same dimension. We then hypothesized that a four-dimension model would be preferable, where we have the vertical dimension, BASE-V (measured by PPD0, CAL0, RBL and IBD); the horizontal dimension, BASE-H (measured by WIDTH); the circumferential dimension, BASE-C (measured by CIRCUM); and the soft tissue dimension, BASE-G (measured by GM0). For the three latent variables measured only by one observed variable, they are statistically equivalent to their indicator variables, e.g. BASE-H is just WIDTH. The path diagram for PLSPM-2 is shown in Fig. 3, and the results are given in Table 4.

For PPD reduction in PLSPM-2, BASE-V was positively associated with PPDRED (0.778, $p<0.001$), while both WIDTH (BASE-H) and GM0 (BASE-G) were negatively associated with PPD reduction. All these associations were statistically significant. CIRCUM (BASE-C) had no association with PPD reduction. The model R^2 was 0.41, which was larger than that in PLSPM-1.

For CAL gain in PLSPM-2, BASE-V had a positive association with CALGAIN (0.635, $p<0.001$), and WIDTH (BASE-H) had a negative association with the outcome (-0.615, $p<0.001$). Both were statistically significant. GM0 and CIRCUM had very small positive associations with CALGAIN. The model R^2 was 0.328, which was larger than that in PLSPM-1.

PLS Path Model-3 (PLSPM-3)

In a final path model, we attempted to analyse the associations between baseline variables and both treatment outcomes simultaneously by hypothesizing that PPD reduction after regenerative surgery was due partly to CAL gain, and this model is depicted in Fig. 4. As more than one outcome was included in the path model, the results from PLSPM-3 were not directly comparable to those from OLS regression, where the latter can only accommodate one outcome variable in each model. Results given in Table 5 showed that BASE-V had positive direct effects on both CAL gain (0.634, $p<0.001$) and PPD reduction (0.337, $p<0.001$), and WIDTH (BASE-H) had a larger negative direct effect on CAL gain (-0.609, $p<0.001$) than on PPD reduction (-0.168, $p=0.157$); GM0 (BASE-G) had a large negative direct effect on PPD reduction (-0.295, $p<0.001$) and a small positive direct effect on CAL gain (0.062, $p=0.466$); CIRCUM (BASE-C) had very small effects on both CAL gain and PPD reduction. CAL gain had a large direct effect on PPD reduction (0.696, $p<0.001$). This model revealed that 33% of the variance in CAL gain was explained by the three baseline latent variables, and 69.7% of the variance in PPD reduction was explained by the same three baseline latent variables plus CAL gain.

Table 3. Results from PLSPM-1 for PPD reduction and CAL gain

	Estimates	SE	*p*-value		Estimates	SE	*p*-value
	PPD reduction				CAL gain		
Outer weights				*Outer weights*			
BASE				BASE			
PPD0	0.494	0.053	<0.001	PPD0	0.372	0.044	<0.001
CAL0	0.376	0.037	<0.001	CAL0	0.42	0.042	<0.001
RBL	0.104	0.055	0.057	RBL	0.105	0.061	0.087
IBD	0.21	0.044	<0.001	IBD	0.248	0.049	<0.001
WIDTH	−0.085	0.099	0.391	WIDTH	−0.13	0.092	0.157
CIRCUM	0.034	0.063	0.587	CIRCUM	0.087	0.071	0.219
GM0	−0.079	0.069	0.258	GM0	0.117	0.07	0.094
Outer loadings				*Outer loadings*			
BASE				BASE			
PPD0	0.935	0.029	<0.001	PPD0	0.808	0.061	<0.001
CAL0	0.845	0.069	<0.001	CAL0	0.938	0.037	<0.001
RBL	0.682	0.104	<0.001	RBL	0.732	0.093	<0.001
IBD	0.739	0.087	<0.001	IBD	0.719	0.085	<0.001
WIDTH	0.128	0.188	0.495	WIDTH	0.07	0.19	0.711
CIRCUM	0.201	0.134	0.135	CIRCUM	0.294	0.126	0.02
GM0	0.024	0.14	0.867	GM0	0.289	0.134	0.031
Path coefficients				*Path coefficients*			
PPD reduction				CAL gain			
BASE	0.596	0.068	<0.001	BASE	0.536	0.071	<0.001
R^2	0.355			R^2	0.287		

PPD0, baseline probing pocket depth in mm; CAL0, baseline clinical attachment level in mm; RBL, radiographical bone level in mm; IBD, infrabony defect depth in mm; WIDTH, width of infrabony defect in mm; CIRCUM, circumference of infrabony defect in degree; GM0, the distance between cemento-enamel junction and baseline gingival margin; GR, gingival recession after treatments; SE, standard errors.

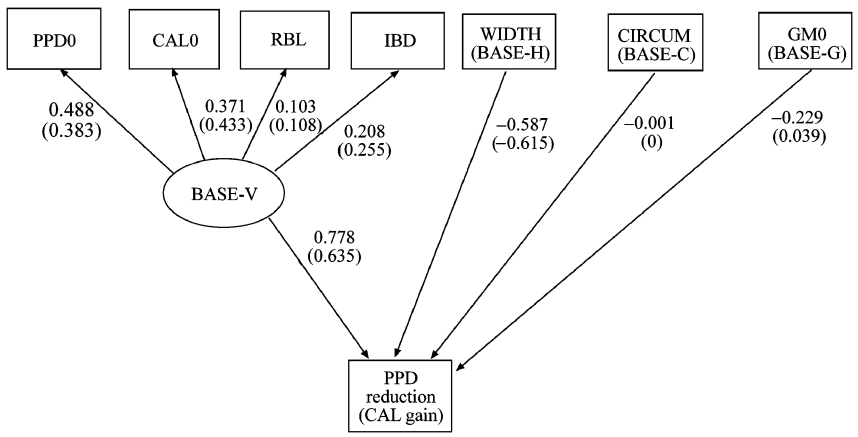

Fig. 3. Path diagram for PLSPM-2. As BASE-G has only one manifest variable, GM0, BASE-G is equivalent to GM0. For the same reason, BASE-H is equivalent to WIDTH, and BASE-C to CIRCUM. The value accompanying the arrows from a latent variable to an observed variable is the weight, whilst the value accompanying an arrow from a latent variable to another is a path coefficient. Values in parenthesis are results when the outcome is CAL gain.

Discussion

One recent study found relatively high degree of variability in clinical outcomes in the treatments of infrabony lesions after periodontal regeneration or flap operation (Aichelmann-Reidy & Reynolds 2008). A systematic review on GTR in the treatment of infrabony lesions also found wide variations in the reported benefits of GTR compared with periodontal flap operation, and further research was recommended to address the issue of variability and to identify characteristics of the lesions or the patients associated with a beneficial outcome (Needleman et al. 2006). In the periodontal literature, OLS regression analysis was used to identify factors affecting periodontal treatment outcomes after regenerative procedures (Tonetti et al. 1993, 1996, 1998, 2004, Falk et al. 1997, Trombelli et al. 1997, Klein et al. 2001, Zucchelli et al. 2002, Silvestri et al. 2003, Sanz et al. 2004, Tsitoura et al. 2004). These factors are usually baseline clinical or radiographical measurements of periodontal lesions, which are in general highly correlated. Because these variables are mixed measurements of the underlying lesions and measured with error, a larger number of variables will therefore provide a more comprehensive understanding of periodontal lesions. Nevertheless, we need statistical methods to extract and summarize useful information from these measurements to test their associations with the treatment outcomes after periodontal regeneration. Principal component analysis (Jolliffe 2002, Jackson 2003), structural equation modelling (SEM) (Loehlin 2004, Tu et al. 2008a) and PLS are three of the most commonly used statistical method to extract information from such complex collinear data. In this study, PLS path modelling showed that vertical measurements of infrabony lesions had positive associations with treatment outcomes, whilst horizontal measurements had negative effects. Gingival recession was negatively related to pocket reduction, but no such relation with attachment gain was observed. Due to mathematical coupling among PPD, CAL and gingival recession, the associations between baseline gingival recession and treatment outcomes were rarely tested and discussed in previous literature using OLS regression.

PLS analysis has been used in chemical engineering as a data reduction and variable selection method, and recently it has been further developed and applied to bioinformatics (Helland 1990, Phatak & de Jong 1997, Wold et al. 2001, Boulesteix & Strimmer 2007). Compared with OLS regression, estimates from PLS analysis are more robust to the problem of multicollinearity (Wold et al. 1984, Næs et al. 2002). For instance, the negative regression coefficients for RBL in OLS regression (all statistically significant) were contrary to expectations and contrary to those for other vertical measurements of baseline lesions, such as PPD0 and CAL0. The reverse associations in multiple regression indicated great imprecision in estimating the independent contribution of RBL to the explanation of treatment outcomes using OLS regression, thereby giving rise to uncertainty in interpreting the association between RBL and treatment outcomes.

Table 4. Results from PLSPM-2

	Estimates	SE	*p*-value		Estimates	SE	*p*-value
	PPD reduction				CAL gain		
Outer weights				*Outer weights*			
BASE-V				BASE-V			
PPD0	0.488	0.053	<0.001	PPD0	0.383	0.042	<0.001
CAL0	0.371	0.038	<0.001	CAL0	0.433	0.057	<0.001
RBL	0.103	0.057	0.070	RBL	0.108	0.073	0.139
IBD	0.208	0.042	<0.001	IBD	0.255	0.05	<0.001
Correlations (outer loadings)				*Correlations (outer loadings)*			
BASE-V				BASE-V			
PPD0	0.912	0.015	<0.001	PPD0	0.879	0.023	<0.001
CAL0	0.876	0.029	<0.001	CAL0	0.895	0.025	<0.001
RBL	0.719	0.07	<0.001	RBL	0.740	0.076	<0.001
IBD	0.749	0.061	<0.001	IBD	0.769	0.06	<0.001
Path coefficients				*Path coefficients*			
PPD reduction				CAL gain			
WIDTH (BASE-H)	−0.587	0.156	<0.001	WIDTH (BASE-H)	−0.615	0.159	<0.001
CIRCUM (BASE-C)	−0.001	0.002	0.612	CIRCUM (BASE-C)	0.000	0.002	0.992
GM0 (BASE-G)	−0.229	0.083	0.006	GM0 (BASE-G)	0.039	0.085	0.646
BASE-V	0.778	0.082	<0.001	BASE-V	0.635	0.085	<0.001
R^2	0.41			R^2	0.328		

PPD0, baseline probing pocket depth in mm; CAL0, baseline clinical attachment level in mm; RBL, radiographical bone level in mm; IBD, infrabony defect depth in mm; WIDTH, width of infrabony defect in mm; CIRCUM, circumference of infrabony defect in degree; GM0, the distance between cemento-enamel junction and baseline gingival margin; GR, gingival recession after treatments; SE, standard errors.

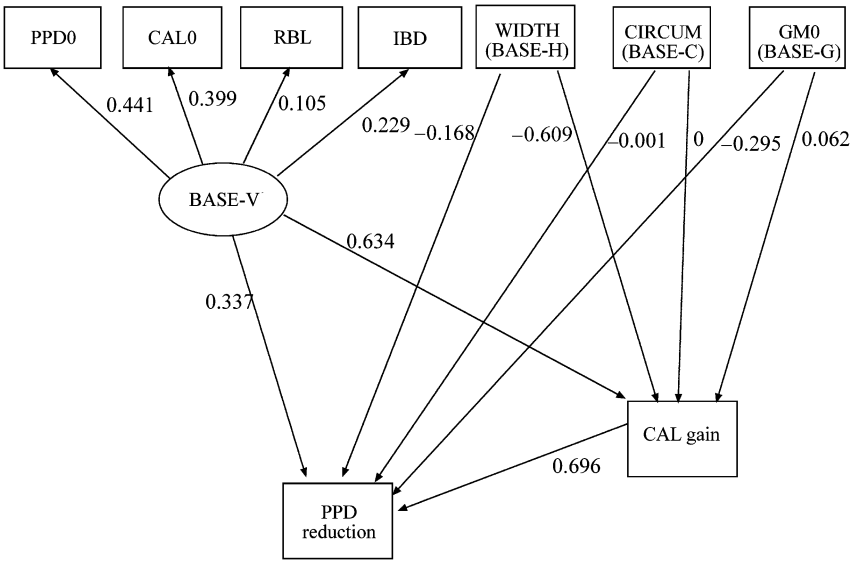

Fig. 4. Path diagram for PLSPM-3. As BASE-G has only one manifest variable, GM0, BASE-G is equivalent to GM0. For the same reason, BASE-H is equivalent to WIDTH, and BASE-C to CIRCUM. The value accompanying the arrows from a latent variable to an observed variable is the weight, whilst the value accompanying an arrow from a latent variable to another is a path coefficient.

Although the model R^2 was greater in the final stepwise regression models, this does not necessarily mean that these models have greater predictive ability (Thompson 1995). Several simulation studies comparing the performances of stepwise OLS, PCA and PLS regression in the analysis of highly collinear data revealed that in general PLS regression outperforms stepwise OLS and PCA regression in terms of recovery of true regression coefficients, prediction of outcomes, and stabilization of model estimations (Wold et al. 1984, Garthwaite 1994, Chong & Jun 2005, Kiers & Smilde 2007). Stepwise regression models may explain a larger amount of variance in the outcomes for this specific dataset than PLS, but this good predictive ability is less likely to be replicated by the same variables in different datasets (Thompson 1995), i.e. statistical models given by stepwise regression are less consistent and not reliable in the prediction of treatment outcomes. The model R^2 reported in the final stepwise regression generally overestimates its predictive ability (Thompson 1995). One interesting finding of this study is that while the negative regression coefficients for RBL suggests a problem of collinearity, its variance inflation factor (VIF) values, a commonly used diagnostic tool for collinearity, remained small, while regression textbooks typically suggested VIF > 10 as a threshold value for collinearity (Pedhazur 1997, Glantz & Slinker 2001, Miles & Shelvin 2001, Fox 2008). According to this criterion, collinearity was not a problem in our OLS regression models, yet it apparently is.

When collinearity is genuinely not a problem and there are no measurement errors in any covariates, OLS regression is the best method of model estimations, as it yields unbiased and consistent results (Kiers & Smilde 2007, Fox 2008). However, for highly collinear data, alternative regression methods may be required to provide more consistent results with smaller standard deviations than those from OLS regression (Hastie et al. 2001). When perfect multicollinearity is caused by mathematical coupling, only PLS and PCA regression can provide model estimates for the relationship between the outcome and coupled covariates. This does not mean that PLS or PCA regression is a panacea for multicollinearity, and therefore researchers can enter all the variables they have at hand without seriously considering their relative importance in both the explanation and prediction of the outcome. PLS may be applied as an exploratory method, guiding our covariate selection and model building. Results from PLS regression may also help with generating new theory and hypotheses that will then be confirmed or modified by further data collection and analysis.

Mathematical coupling of data is a common problem in clinical dental research, and to the best of our knowledge this study is the first to use PLS analysis to overcome this problem. Results from the initial PLS analysis

Table 5. Results from PLSPM-3

	Estimates	SE	*p*-value
Weights (outer weights)			
BASE-V			
PPD0	0.441	0.045	<0.001
CAL0	0.399	0.042	<0.001
RBL	0.105	0.059	0.074
IBD	0.229	0.043	<0.001
Correlations (outer loadings)			
BASE-V			
PPD0	0.897	0.017	<0.001
CAL0	0.885	0.024	<0.001
RBL	0.729	0.075	<0.001
IBD	0.759	0.058	<0.001
Path coefficients			
CAL gain			
WIDTH (BASE-H)	−0.609	0.159	<0.001
CIRCUM (BASE-C)	0.000	0.002	0.987
GM0 (BASE-G)	0.062	0.084	0.466
BASE-V	0.634	0.084	<0.001
PPD reduction			
WIDTH (BASE-H)	−0.168	0.118	0.157
CIRCUM (BASE-C)	−0.001	0.002	0.471
GM0 (BASE-G)	−0.295	0.060	<0.001
BASE-V	0.337	0.071	<0.001
CALGAIN	0.696	0.060	<0.001
R^2			
PPD reduction	0.330		
CAL gain	0.697		

PPD0, baseline probing pocket depth in mm; CAL0, baseline clinical attachment level in mm; RBL, radiographical bone level in mm; IBD, infrabony defect depth in mm; WIDTH, width of infrabony defect in mm; CIRCUM, circumference of infrabony defect in degree; GM0, the distance between cemento-enamel junction and baseline gingival margin; GR, gingival recession after treatments; SE, standard errors.

(PLSPM-1) show that all four vertical measurements of baseline disease characteristics (PPD0, CAL0, RBL and IBD) have a positive association with PPD reduction and CAL gain, and three of these associations are statistically significant (Table 4). These findings are consistent with those from simple linear regression (Table 2). It is intriguing to note that while GM0 may also be considered as a vertical measurement, it had only a small negative association with PPD reduction and a small positive association with CAL gain; both associations were not statistically significant. Outer loadings (i.e. correlations with BASE) in Table 4 revealed that BASE was highly positively correlated with the four vertical measurements of baseline lesions (PPD0, CAL0, RBL and IBD), yet it had relatively low correlations with GM0, despite PPD0, CAL0 and GM0 being mathematically coupled. This suggests that there was more than one dimension in BASE, and treating these baseline variables as a single group by constructing just one latent variable may mask the multi-dimensional characteristics of baseline lesions. Arranging variables into several groups to capture different dimensions in baseline lesions could improve further the prediction of PLS path model, confirmed in PLSPM-2 in which BASE-H (WIDTH) had a statistically significant negative association with both outcomes while BASE-G (GM0) had a significant negative association with PPD reduction. These statistically significant negative associations were obscured in the simplified model PLSPM-1.

Another limitation of OLS regression is that it is not possible to analyse associations between baseline variables and multiple treatment outcomes simultaneously. Only multivariate methods, such as PLS and SEM, are able to undertake such analyses. When both PPD reduction and CAL gain were analysed in the PLSPM-3, it appeared that the negative association between WIDTH and PPD reduction was mediated by the association between WIDTH and CAL gain, i.e. the wider the baseline lesions, less CAL gain was observed, and hence less PPD reduction was attained. On the other hand, GM0 had a direct association with PPD reduction, indicating that less PPD reduction was to be observed in lesions with greater gingival recession at baseline. In contrast, there was a small positive association between GM0 and CAL gain. While GM0 had a negative association with PPD reduction in PLSPM-1, neither its weight nor its loading was statistically significant. Lesions with greater baseline gingival recession might have shallower baseline pocket depths and consequently less PPD reduction caused by post-surgical gingival recession. However, this does not adversely affect the changes in attachment level. Baseline gingival recession may partly reflect the residual periodontal inflammation; therefore lesions with less gingival recession may achieve greater PPD reduction without actually attaining greater attachment gain. Additional measurements of gingival tissue, such as the length of keratinized gingivae, thickness of gingival flap or tensions during suturing (Pini Prato et al. 2000) would be helpful in increasing our understanding of the role of gingival tissue in periodontal regenerative procedures. This also applies to the measurement of other dimensions in baseline lesions with only a single indicator in this study (e.g. WIDTH and CIRCUM).

Several vertical measurements, such as the angle of infrabony defects (Klein et al. 2001, Tsitoura et al. 2004), the depth of 3-wall, 2-wall and 1-wall components (Tonetti et al. 1996, Parashis & Tsiklakis 2000), and the distance between the cemento-enamel junction to the bottom of infrabony defects (Tonetti et al. 1996), were not available in this dataset. The inclusion of all these measurements in OLS regression would exacerbate the already intricate problem of multicollinearity and probably give rise to more confusion than clarification of the associations between baseline lesion characteristics and treatment outcomes. However, the greater number of manifest variables for latent variables in PLS path analysis (or other latent variables methodology), the greater the predictive power of a PLS model because of its ability to handle multicollinearity. Nevertheless, like all statistical methods, PLS analysis should be guided by clinical knowledge and biological theory, and results from exploratory analyses should be cross-validated by other studies. We welcome periodontal researchers to corroborate and further improve our models.

The aim of this study was to test the associations between baseline characteristics of infrabony lesions and treatment outcomes, and this is why variables such as the early exposure of barrier membrane (EXPOSURE: yes *versus* no), which was included in the original analysis by Falk et al. (1997), were excluded in the PLS analysis. Although variables included in our analysis are all continuous, both continuous and categorical variables such as EXPOSURE can be included in the PLS path analysis as explanatory variables. We have conducted further analysis with the inclusion of EXPOSURE as an independent latent variable in PLSPM-3, and the results showed that early exposure had a significantly adverse effect on CAL gain (path coefficient: -0.235, 95% CI: -0.375, 0.072) but a small positive effect on PPD reduction (0.046, 95% CI: -0.035, 0.129). The associations between treatment outcomes and baseline characteristics of infrabony lesions remained similar to those reported in Table 5.

One statistical issue related to the application of PLS in periodontal research is worthy of comment. PLS components are simply weighted composites of covariates, and as a result there is no distributional assumption for PLS coefficients (Chin 1999). Resampling methods (such as bootstrap) are needed to obtain confidence intervals and *p*-values. Although the assumption for the independence of observations, which is crucial for OLS regression, is not required in PLS regression for the construction of weighted components, this issue has not been fully investigated in the statistical literature. This is also why, in this study, we selected only one lesion from each patient with multiple lesions. Further theoretical investigation is to be undertaken to clarify this issue for multilevel dental data.

Acknowledgement

Data reanalysed in this study were kindly made available by Dr. Lars Laurell. His generosity and open-mindedness toward the reanalysis of his data are greatly appreciated.

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Appendix 1

Principal component analysis

PLS analysis can be viewed as a variant of principal component analysis (PCA). PCA extracts components (known as principal components) using a mathematical technique known as singular value decomposition in matrix algebra, which requires the calculation of eigenvectors and eigenvalues (Jolliffe 2002, Jackson 2003). For p variables, $\chi_1, \chi_2, \ldots, \chi_p$, each principal component, pc_i, are weighted composites of p covariates:

$$pc_i = w_{i1}x_1 + w_{i2}x_2 + \cdots + w_{ip}x_p,$$

where w_{ij} ($j = 1$ to p) is the weight for covariate χ_p in pc_i. Suppose there are five covariates without perfect multicollinearity, five principal components, which are weighted combinations of the original five covariates, can be extracted. There are two mathematical constraints in the extraction of principal components: (1) the sum of squared weight is unity, i.e. $w_{i1}^2 + w_{i2}^2 + \cdots + w_{ip}^2 = 1$ and (2) the correlations between each pair of principal components are zero. Note that in the construction of principal components, variables, $\chi_1, \chi_2, \ldots, \chi_p$, are usually in standardized form, i.e. they have zero means and standard deviations of one. PCA can be undertaken using raw variables without standardization, but the results (i.e. the weights) are different. The extracted principal components are ordered by the amount of variances in the variables explained by the components, i.e. the first principal component explains more variance than the second, and the second explains more than the third, etc. The first few principal components, which explain most of the covariate variances, are then selected as the new covariates, and the outcome variable is regressed on these principal components. If all five principal components are selected as covariates, the results (i.e. regression coefficients and R^2) from PCA regression are equivalent to those from OLS multiple regression. When the outcome is only regressed on the first few components, the results will be different. Usually, problems in multiple regression due to multicollinearity, such as the wrong sign for regression coefficients (e.g. a positive association in simple regression becomes negative in multiple regression), can be rectified. A potential caveat of PCA regression approach is that the extraction of prin-

cipal components does not take into account the covariates' relationships with the outcome. In extreme cases, while the retained principal components might explain most of the variance across the covariates, they may have very small associations with the outcome (Hadi & Ling 1998).

PLS analysis

In contrast to PCA, PLS extracts components that are weighted combinations of the original covariates by also taking into account of their correlations with the outcome. In other words, in PCA, the extraction of components is independent of the outcome variable(s), whilst in PLS, different components are extracted for different outcomes. The extraction of PLS components operates under the same constraints: (1) the sum of squared weight is unity and (2) the correlations between each pair of PLS components are zero (Phatak et al. 1992). When there are five covariates without perfect multicollinearity, five PLS components can be extracted, and they are also independent of each other. PLS components are ordered according to the amount of variance in the outcomes that has been explained, i.e. the first PLS component has a higher correlation with the outcomes than the second PLS component, and the second has a higher correlation than the third, etc. In PLS, the first PLS component explains most of the variance in the outcome that can be explained by all the original variables (i.e. the variances of the outcome explained by OLS regression), and the outcome variable is then regressed on the PLS component. If all five PLS components are used as new covariates, the results (i.e. regression coefficients and R^2) from the PLS regression are equivalent to those from PCA regression and OLS regression. The advantage of PLS over PCA is that the extracted components explain most of the covariance between the outcome and covariates, and as a result, the caveat of PCA regression previously discussed does not occur. In fact, PLS can be viewed as a middle ground between OLS regression (i.e. the usual multiple linear regression) and PCA regression (Stone & Brooks 1990). When covariates are highly correlated, results from PLS will be closer to those from PCA regression, and when covariate are less correlated, results from PLS will be closer to those from OLS regression.

PLS components, such as those in Figs 1–3, are often called latent variables in the literature of SEM, and variables contributing to these latent variable constructions are called manifest variables (Loehlin 2004, Tu et al. 2008a, b). Although it may be argued that because the latent variables in PCA and PLS are simply weighted composites of observed variables, these latent variables are not strictly unobservable (i.e. they are not ''latent''). In this study, however, to avoid confusions and improve readability, we call all PLS composites latent variables.

Mathematical coupling and PLS

As explained in the introduction, one or more of the mathematically coupled variables has to be removed for OLS regression to proceed with model estimations. However, this is not a problem for either PCA or PLS regression. Suppose CAL, PPD, GR, IBD (infrabony defect depth measured during surgery) and RBL (the distance from cemento-enamel junction to alveolar bone crest in digitalized radiographs) are selected as covariates. Since CAL, PPD and GR are mathematically coupled, at least one of them has to be removed in an OLS regression analysis. In PCA and PLS, the mathematical coupling among the three variables means that only four components can be extracted from the five covariates, but each of the four components is a combination of the five original covariates. In other words, even if all four components are used as new covariates in subsequent analysis, the results from PCA and PLS will be different from OLS regression, because in PCA and PLS, regression coefficients for all five original covariates can be estimated (while only regression coefficients for four covariates can be estimated in OLS regression).

PLS path (structural equation) modelling

PLS algorithms were first devised by a Swedish econometrician and statistician, Hermann Wold in 1960s, and when maximum likelihood-based SEM was proposed in 1970s, Wold extended his PLS algorithms to PLS path modelling (Wold 1982). PLS path modelling has since been widely used in the social sciences such as marketing, psychology and education, as an alternative to maximum likelihood-based SEM (Chin & Newsted 1998, Chin 1999). PLS components are treated as latent variables in PLS path modelling, and a PLS path model has two elements: inner and outer models. The inner model describes the relationships (i.e. path coefficients) among latent variables, and this is analogous to the structural model in SEM. To facilitate interpretation, the variances of latent variables are scaled to be unity, and therefore the interpretation of PLS path coefficients is analogous to the standardized multiple regression coefficients in OLS regression. The outer model describes the relationships between latent variables and their manifest variables, and this is analogous to the measurement model in SEM. Outer weights are the weights in the construction of latent variables. Correlations reported in this study (Tables 3–5) are the correlations between latent and manifest variables, and they are called outer loadings in some software packages. The statistical theory behind PLS path modelling is rather mathematical (Tennenhaus et al. 2005), and a less technical introduction can be found in Haenlein & Kaplan (2004).

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Clinical Relevance

Scientific rationale for the study: 'Many studies have attempted to test the associations between the baseline characteristics of infrabony lesions and the treatment outcomes of periodontal regeneration, aiming to identify important predictors for successful treatment results. However, high correlations among these baseline variables pose a challenge for using OLS regression to identify these predictors. This study proposes a novel approach to this problem using PLS analysis.

Principal findings: The vertical dimension of baseline infrabony lesions measured clinically or surgically had a strong positive association with pocket reduction and attachment level gain. The horizontal dimension measured by the width of infrabony defect had a negative association with treatment outcomes. Lesions with greater gingival recession at baseline were expected to have less pocket reduction after treatments, but baseline gingival recession did not affect attachment level gain.

Practical implications: Deeper and narrower infrabony lesions are expected to achieve greater pocket reduction and attachment level gain. Baseline gingival recession does not adversely affect attachment level gain. More baseline variables should be measured in the future research in order to provide better understanding of the complex associations between baseline variables and treatment outcomes.