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***FAST*TRACK – CLINICAL RESEARCH**
Congenital heart disease

Periodontitis treatment and progression of carotid intima-media thickness: a randomized trial

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Abstract

Background and Aims Intensive periodontal treatment (IPT) improves endothelial function in patients with periodontitis (PD). However, whether these changes can slow the progression of structural vascular remodelling remains unclear. This randomized clinical trial evaluated the impact of IPT on carotid intima-media thickness (cIMT) over 2 years (NCT03072342). Flow-mediated dilatation (FMD), blood pressure and pulse wave velocity (PWV) were assessed as secondary outcomes, while markers of inflammation, oxidative stress, and metabolomics were explanatory outcomes.

Methods 135 consecutive, otherwise healthy participants with PD, were enrolled in a single-blind, single-centre, controlled trial, and randomized to IPT (n = 68; including scaling, root planning, and, when appropriate, surgical corrective therapy) or control periodontal treatment (CPT, $n = 67$; including supra-gingival scaling and polishing). cIMT was assessed at baseline, 12 and 24 months post-therapy. Blood pressure, FMD, PWV, markers of inflammation, oxidative stress, and metabolomics were assessed at baseline and at 2, 6, 12, 18, and 24 months post-intervention.

Results After 24 months, cIMT was lower in the IPT vs the CPT group (−0.023 mm, 95% confidence interval −0.030.019 to −0.0227, $P < 0.0001$). FMD improved within 2 months in the IPT group and remained consistently higher than the CPT group throughout the study ($P < 0.0001$) correlating with the improved periodontal measurements at the same time points. No substantial differences were observed between groups in adverse events, anthropometric, blood pressure, PWV, or metabolomic markers. Among inflammatory and oxidative stress markers, glycoprotein acetyl was reduced in IPT compared with the CPT group participants ($P < 0.05$).

Conclusions IPT led to favourable structural changes in the vascular phenotype, underscoring the impact of PD on cardiovascular health and further highlighting the potential role of treating PD to improve cardiovascular outcomes.

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Structured Graphical Abstract

Key Question

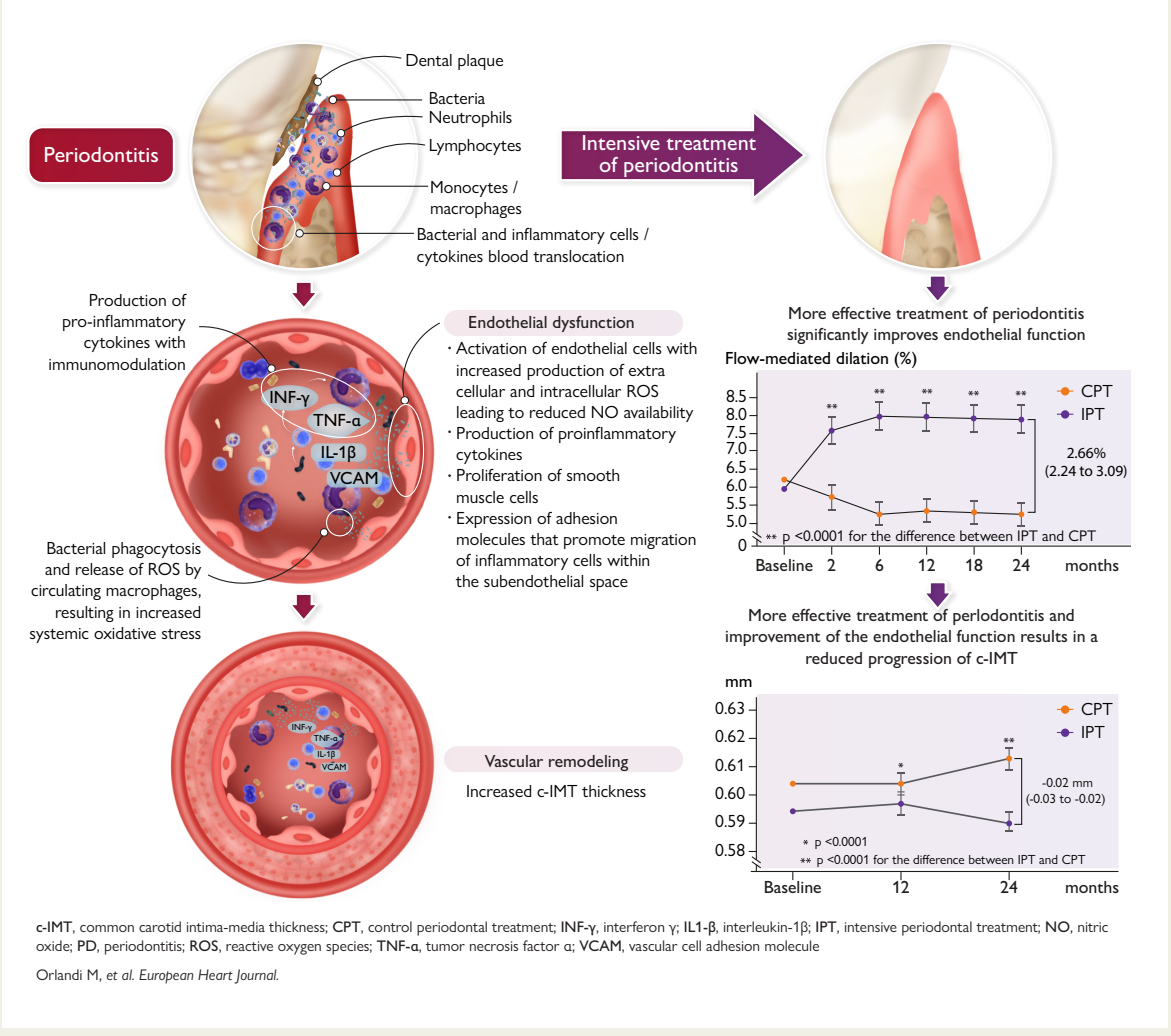
Can treatment of periodontitis (PD) reduce common carotid intima-media thickness (c-IMT)?

Key Finding

In this trial in 135 otherwise healthy participants with PD, patients allocated to intensive PD treatment exhibited less c-IMT progression and better flow flow-mediated dilation as compared to standard treatment.

Take Home Message

These findings suggest that cardiovascular prevention should include oral cavity assessment and PD treatment.



c-IMT, common carotid intima-media thickness; CPT, control periodontal treatment; INF-γ, interferon γ; IL1-β, interleukin-1β; IPT, intensive periodontal treatment; NO, nitric oxide; PD, periodontitis; ROS, reactive oxygen species; TNF-α, tumor necrosis factor α; VCAM, vascular cell adhesion molecule

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Impact of periodontitis on vascular health and changes in the endothelial function (assessed by flow mediated dilatation [FMD]) and common carotid intima-media thickness (cIMT) following treatment of periodontitis in the test (IPT) and control group (CPT). IPT, Intensive periodontal treatment; CPT, control periodontal treatment.

Keywords Periodontitis • Intima-media thickness • Endothelial function • Inflammation • Metabolomic

Introduction

Inflammation plays a central role in the development and progression of cardiovascular disease (CVD) and has emerged as a promising therapeutic target. Periodontitis (PD), a highly prevalent chronic inflammatory condition, affects over 40% of adults worldwide.[1] In both healthy individuals and patients with type 2 diabetes, effective treatment of PD has been shown to improve endothelial function and reduce systemic inflammation and oxidative stress.[2–4] In patients with type 2 diabetes,[2] such treatment improved metabolic control and renal function over 12 months, while in those with hypertension, blood pressure improved within 6 months.[5] These findings suggest that PD is a

widespread but unappreciated contributor to CVD morbidity and mortality. Its impact on arterial remodelling and long-term cardiovascular (CV) outcomes, however remains unclear.

Carotid intima-media thickness (cIMT) and its rate of progression are established markers of structural remodelling of the arterial wall, closely associated with CV risk. A recent meta-analysis of randomized trials demonstrated that reducing cIMT progression by 0.01 mm/year corresponds to a 10% reduction in future CV events.[6]

We therefore conducted a randomized controlled trial (RCT) using the same validated protocol applied in previous studies to evaluate whether intensive treatment of PD could reduce cIMT progression over 2 years. To limit confounding, we recruited individuals with PD but without diagnosed CVD or other inflammatory conditions, and who were not on regular medications. The study addressed three key questions: (i) does effective treatment of PD reduce cIMT at 24 months?; (ii) what is the temporal relationship between treatment of PD and changes in vascular phenotypes, including endothelial dysfunction and arterial stiffness? and (iii) can changes in metabolic, inflammatory, or oxidative stress biomarkers explain changes in the vascular phenotypes after treatment of PD and help identify individuals who are most likely to benefit?

Methods

Study design

Consecutive patients diagnosed with severe, active PD at the UCL Eastman Dental Institute and Hospital were enrolled in a single-centre, randomized, controlled, single blind, parallel group clinical trial as previously reported.[7] Diagnostic criteria for severe, active PD were consistent with previous studies.[2,3] Exclusion criteria included: (i) hepatitis B or HIV infection, (ii) established CVD, (iii) chronic medication use (including anti-microbial), (iv) prior treatment of PD in the preceding 6 months), (v) immunodeficiency, (vi) pregnancy or breastfeeding, and (vii) limited mental capacity or language skills that would prevent understanding of and/or trial adherence.

Randomization

Following baseline assessment, patients were randomly assigned to receive either intensive (IPT) or control (CPT) periodontal treatment as previously reported.[7] Restricted randomization[8] on a 1:1 ratio between study groups was performed in terms of smoking status, gender, and PD severity. Treatment allocation was concealed in opaque envelopes disclosed to clinicians on the day of treatment.

Study intervention and assessments

Periodontal assessment and treatment followed validated protocols shown to improve endothelial function, diabetes control and circulating markers of inflammation and oxidative stress.[2–4]

Essential dental care, including oral hygiene instructions and removal of compromised teeth, was performed in both groups as previously reported.[7] A single trained/calibrated examiner collected medical, dental histories, and periodontal measurements at each visit.[7] Calibration was repeated every 6 months in each calendar year over the duration of the study. Briefly, periodontal measurements included gingival probing depth and recession of the gingival margin relative to the cemento-enamel junction at 6 sites per tooth. Supra-gingival dental plaque and gingival bleeding on probing were recorded. Whole-mouth number of periodontal lesions (probing depth >4 mm) and relative percentage of gingival bleeding [full mouth gingival bleeding scores; the number of sites with gingival bleeding on probing/total number of sites per mouth × 100] and dental plaque [full mouth plaque scores; the number of sites with visible detectable plaque/total number of sites per mouth × 100] were calculated. Tobacco exposure (defined as current, former, or never smoker following detailed interview), blood pressure, height, weight, waist circumference, and body fat mass (data not reported) were assessed at each visit. Medication use was assessed at baseline and updated at each subsequent visit (detailed medication log).

Patients in the IPT group received intensive periodontal treatment consisting of an initial single session of whole-mouth scaling of the root surfaces under local analgesia (no time limits were enforced for completing the session). At 2 months, those with good oral hygiene (dental plaque scores <20%) and ≥1 residual 6 mm periodontal pocket underwent corrective therapy.[7] Patients with sub-optimal oral hygiene received additional sub-gingival scaling under local analgesia. Thereafter, the IPT group received scaling sessions (no time limits) under local analgesia every 3 months. CPT patients received supra-gingival scaling and polishing at identical time points. At study end, CPT patients were offered comprehensive periodontal therapy as needed. Participants with progression of PD[9] received prompt specialist care and were withdrawn from the study, though no cases met this criterion.

Outcomes assessment

The primary outcome of the study was the between-group difference in cIMT at 24 months. Secondary outcomes included between-group differences in: (i) cIMT at 12 months and (ii) flow-mediated dilatation (FMD), blood pressure, and pulse wave velocity (PWV) at 24 months. Explanatory outcomes included inflammatory/oxidative stress/lipid biomarkers and periodontal clinical parameters. All vascular and laboratory assessments were acquired and analysed by two trained physicians or laboratory technicians, respectively, who were masked to the participants' treatment group allocation.

Primary outcome

Carotid intima-media thickness

cIMT was measured by ultrasound at baseline, 12 and 24 months after treatment of PD using a 12-MHz linear transducer (Acuson XP 128/10, Siemens). A validated protocol for cIMT acquisition was followed, as described previously.[2,10,11] Briefly, bilateral carotid artery images were recorded over ≥ 3 cardiac cycles. Post-processing was performed using semi-automated edge-detector software (Carotid Analyser, version 5.8.1). Mean cIMT was calculated from the three end-diastolic frames from lateral views. Using this protocol, we previously reported a coefficient of variation (CV) <5% for repeated cIMT measurements in diverse populations including children, adults with diabetes.[2,10,11] Intra- and inter-reader reproducibility were assessed using 10 randomly selected images. Intra- and inter-reader correlations coefficients were >0.9. Carotid plaques were defined as lesions >1.5 mm with abnormal shape or echogenicity.[12] One participant with an incidental carotid plaque at the cIMT measurement site was excluded from cIMT analysis.

Secondary outcomes

Flow- and glyceryl trinitrate-mediated dilatation

FMD was assessed at baseline, 2, 6, 12, 18, and 24 months post-treatment. Endothelium-dependent vasodilatation of the brachial artery was measured using high-resolution ultrasound with a 7-MHz probe (Acuson XP 128/10, Siemens). A standardized protocol was used to acquire continuous images at rest, during 5 min of forearm occlusion (250 mm Hg), and for 5 min post-deflation.[2,3,13] Vessel diameters were analysed *post hoc* using automated software (Brachial Tools, version 3.2.6, Medical Imaging Applications).[2] After 10 min of rest, endothelium-independent dilatation was assessed following 25 μg sub-lingual glyceryl trinitrate (GTN). This method has previously demonstrated sensitivity to FMD changes following PD treatment.[2,3]

Pulse wave velocity

Aortic stiffness was assessed using carotid-femoral (aortic) PWV via the Vicorder device (Smart Medical Limited). After 10 min of rest, cuffs were placed at the neck and thigh to record carotid and femoral waveforms.

Path length was measured from the suprasternal notch to the proximal edge of the thigh cuff. Subsequently, the cuffs were each inflated and high-quality waveforms were recorded simultaneously for 3 s. This procedure was repeated three times, and results were averaged. Foot-to-foot transit time was calculated using in-built device algorithms.

Blood pressure

Blood pressure was measured in triplicates using a validated device (Omron device M5-1, HEM-757A-E). The average of three readings was used for analysis.

Explanatory outcomes

Metabolomic and hs-CRP assay

Fasting blood samples were processed within 1 h of collection by staff blinded to group allocation. Plasma was aliquoted and stored at −70°C until batch analysis. Serum was analysed at each time point using a high-throughput 1H magnetic resonance (NMR) metabolomic platform (Nightingale Health, Helsinki, Finland) (List of markers in the Supplementary data). High-sensitivity C-reactive protein (hsCRP) was measured by immunoturbidimetry (Cobas Integra 700, Roche, Mannheim, Germany).

Oxidative stress

Oxidative stress was measured using the d-ROM test, which quantifies circulating hydroperoxides.[14] Results are expressed in Carratelli units (U Carr), where 1 U Carr corresponds to 0.08 mg/dL hydrogen peroxide. The intra-assay CV was 3%.

Statistical analysis

A minimum of 65 participants per group was required to detect a 0.02 mm difference in cIMT at 24 months between groups, assuming a standard deviation of 0.03 (based on previous trial data,[2]) $\alpha = .05$ and 95% power. A total of 140 participants were recruited to allow for 8% attrition.

Baseline data were summarized using median and inter-quartile range for continuous outcomes and counts (percentages) for categorical variable. Analyses followed the intention-to-treat principle. Missing values were handled using last observation carried forward, and all primary and secondary analyses were repeated with *post hoc* linear digital inter-polation. A per-protocol analysis (data not shown) was also conducted, including participants who had at least one valid efficacy assessment and no protocol violations. Pre-specified comparisons for primary and secondary outcomes were hypothesis-driven and not adjusted for multiple testing. Exploratory and tertiary outcome analyses were considered hypothesis-generating, and likewise no formal corrections were made. All longitudinal outcomes (primary, secondary, and periodontal) were analysed using linear mixed-effect models with random intercepts. The models included the respective baseline measurement, treatment group (represented by one dummy variable), stage of study visit (i.e. 12 months, 24 months and also 2, 6, and 18 months, if available), and a treatment time inter-action term as explanatory variables. Additional co-variates included age, sex, ethnicity, smoking status, family history of CVD, and body mass index (BMI). Baseline values were not adjusted. Normality of outcomes was assessed using the Shapiro–Wilks test. Where appropriate, outcomes were log- or square-root-transformed; results were back-transformed for interpretation. We reported marginal means and 95% confidence intervals (CI) for each treatment group at each time point. Between-group differences in marginal means and their 95% CI were calculated, along with *P*-values for hypothesis testing. To address baseline differences in cIMT and improve interpretability of group effects over time, we additionally modelled the change from baseline to follow-up for each participant (further details are provided in the Supplementary Methods). Marginal means for change from baseline were estimated for each group at each visit and between-group differences in change scores were reported, along with 95% CI and *P*-values. Correlation between changes in vascular and biomarker endpoints was analysed using Spearman rank correlation. All statistical analyses were conducted using R software version 4.3.2. A two-sided *P*-value <.05 was considered statistically significant.

Role of the funding source

The funder contributed to study design but had no role in data collection, analysis, interpretation, or manuscript writing. The corresponding author had full data access and final responsibility for submission.

Results

Patients' characteristics

Between March 2013 and December 2017, 521 consecutive patients with PD were screened (*Figure 1*) and 135 were enrolled and randomized to IPT ($N = 68$) or CPT ($N = 67$).

Baseline characteristics were comparable between groups (*Table 1*). Participants were predominantly females, of white ethnicity, former smokers, and slightly overweight. Systolic and diastolic blood pressure values and lipid fractions were within normal ranges, as consistent with a low CV risk profile (*Table 1*). hsCRP values were <2 mg/L in both groups. No participants reported regular medication use at baseline or during follow-up.

No lifestyle, dietary, or anthropometric changes were reported during follow-up. PD severity and drop-out rates were similar between groups (9% of total loss to follow-up). Participants had comparable PD profiles (severity and extent) to those in our previous trials.[2] No serious adverse events occurred in either groups.

At the 2-month review, 42 participants in the IPT group underwent corrective periodontal treatment, the remainder received repeat IPT.

Periodontal measurements

At 24 months all periodontal indices—including dental plaque and gingival bleeding scores, probing pocket depths and clinical attachment levels—were substantially lower in the IPT group compared with CPT (see Supplementary data online, *Table S1*). Differences were already evident by 2 months and persisted throughout the study. The number of periodontal pockets ≥5 mm and ≥6 mm was also lower in the IPT group from 2 months onwards compared with CPT (see Supplementary data online, *Table S1*). No difference in number of teeth was observed between groups at all time points.

Carotid intima-media thickness

At 24 months, cIMT was lower in IPT group than in CPT (*Figure 2A* and *Table 2*). The adjusted between-group difference in cIMT at 24 months was −0.02 mm (95% CI −0.03 to −0.02 mm), controlling for baseline cIMT, age, sex, ethnicity, smoking status, family history of CVD, and BMI. The between-group differences in cIMT at 12 and 24 months corresponded to −1.22% and −3.86%, respectively, in favour of the IPT group. The analysis examining the changes in cIMT from baseline to 12 and 24 months confirmed a difference between the IPT and CPT groups (*Table 2*). Furthermore, compared with the IPT group, a higher number of patients in the CPT group experienced a progression of the cIMT at 12 and 24 months. Indeed, at 12 months, 11 patients in the CPT group experienced an increase of the cIMT ≥0.01 mm, compared with only 4 patients in the IPT group. At 24 months, in the CPT group 44 patients experienced an increase in the cIMT ≥0.01 mm, while 13 patients showed an increase of ≥0.02 mm compared with baseline. In the IPT group, only 1 patient had an increase in the cIMT ≥0.01 mm, and none had an increase of ≥0.02 mm from baseline to 24 months

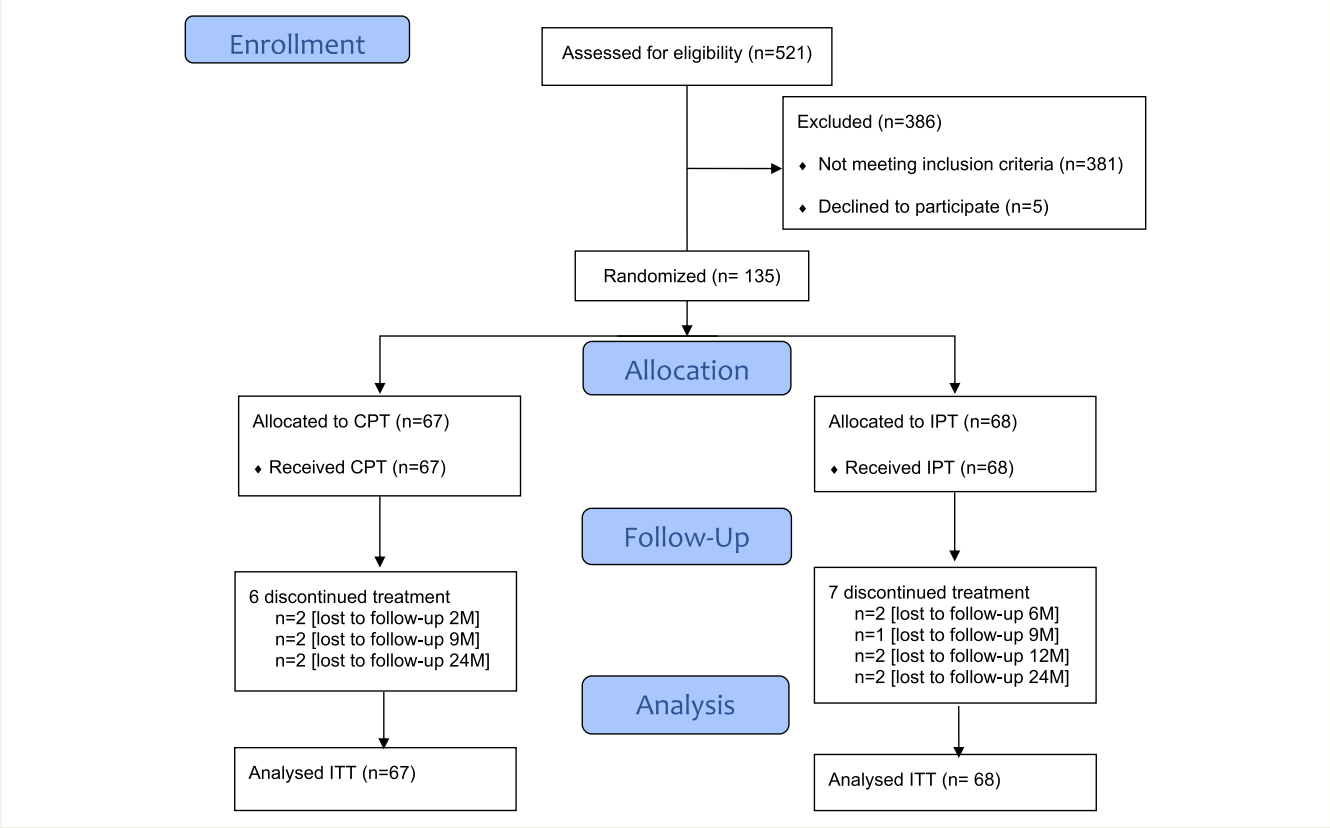

Figure 1 Study flowchart according to Consort recommendations

(see Supplementary data online, *Figure S1*). A *post hoc* analysis stratifying participants by the median values of cIMT at baseline showed consistent results with those of the primary analyses. Indeed, in both strata with thicker and thinner cIMT at baseline, the difference between IPT and CPT groups at 24 months was −0.02 mm (95% CI −0.03 to −0.02 mm; $P < .0001$).

Secondary outcomes

Flow-mediated dilatation, glyceryl trinitrate-mediated dilatation, blood pressure, and pulse wave velocity

FMD was higher in the IPT group compared with CPT at 2 months (*Figure 2B* and *Table 2*). This difference persisted throughout follow-up: at 24 months, FMD was 2.7% (95% CI 2.2% to 3.1%) higher in IPT (7.9%, 95% CI 7.5 to 8.3) compared with the CPT (5.2%, 95% CI 4.9 to 5.6). No substantial group differences were observed in GTN-mediated dilatation, PWV, or blood pressure at any time point (*Table 2*).

Explanatory outcomes

hsCRP was lower in the IPT group compared with the CPT group at 24 months (*Figure 3A*). Glycoprotein acetyls (GlycA) declined early after IPT and closely mirrored FMD changes (*Figure 3B*). Between-group GlycA differences were evident by 6 months (IPT vs CPT: −0.05, 95% CI −0.08 to −0.02 mmol/L) and persisted at 24 months (IPT vs CPT: −0.05, −0.08 to −0.02 mmol/L) (*Figure 3B*). No other differences in metabolomic markers were detected (see Supplementary data online, *Table S2*). The d-ROM test showed lower reactive oxygen metabolites in IPT compared with CPT at 24 months (difference: −63 U Carr, 95% CI −88 to −37) (*Table 2*).

Exploratory analyses assessed correlations between cIMT, FMD, periodontal parameters, and biomarkers levels (Supplementary File). Changes in cIMT over 24 months correlated with FMD, GlycA, hsCRP, and d-ROM levels. Changes in cIMT and inflammatory markers also correlated with improvements in periodontal indices.

Discussion

This randomized trial demonstrated that intensive treatment of PD improves endothelial function, reduces systemic inflammation and oxidative stress, and may attenuate arterial wall remodelling (as measured by cIMT) in otherwise healthy individuals over 24 months (*Structured Graphical Abstract*). The absence of group differences in blood pressure and most metabolomic markers suggests these vascular improvements occurred independently of traditional CV risk factors. Importantly, structural changes in arterial wall appeared after sustained improvements in endothelial function and correlate with them, supporting the hypothesis that endothelial dysfunction contributes to vascular remodelling.

We previously showed that IPT reduces systemic inflammation (assessed by hsCRP) and oxidative stress (assessed by d-ROM test) when compared with control treatment (CPT).[2,4] In this study, we extend these findings by demonstrating that changes in cIMT correlate with changes in FMD, GlycA, hsCRP and oxidative stress. This suggests that durable improvements in endothelial function and reductions in inflammatory and oxidative burdens may mediate IPT-induced changes in

Table 1 Baseline characteristics of the study participants

	CPT ($n = 67$)	IPT ($n = 68$)
Age (years)	54 [48, 61]	56 [48, 59]
Sex		
Male	29 (43.3)	31 (45.6)
Female	38 (56.7)	37 (54.4)
Ethnicity		
White	40 (59.7)	39 (57.4)
Asian	11 (16.4)	15 (22.1)
African	11 (16.4)	6 (8.8)
Afro-Caribbean	2 (3.0)	7 (10.3)
Other	3 (4.5)	1 (1.5)
Smoking history		
Never	24 (35.8)	24 (35.3)
Current	15 (22.4)	15 (22.1)
Former	28 (41.8)	29 (42.6)
Family history of cardiovascular diseases		
Positive	28 (41.8)	24 (35.3)
Negative	39 (58.2)	44 (64.7)
Other clinical characteristics		
Body mass index (kg/m^2)	26.0 [22.9, 28.6]	25.9 [23.9, 28.4]
Total cholesterol (mmol/L)	4.95 [4.32, 5.54]	4.87 [4.40, 5.43]
LDL-cholesterol (mmol/L)	1.99 [1.69, 2.26]	1.96 [1.69, 2.37]
HDL-cholesterol mmol/L	1.42 [1.21, 1.60]	1.35 [1.16, 1.62]
Triglycerides (mmol/L)	1.02 [0.74, 1.34]	0.93 [0.74, 1.15]
Plasma glucose (mmol/L)	4.60 [4.31, 4.97]	4.50 [4.34, 4.82]
Primary outcome		
Common carotid-intima media thickness (mm)	0.58 [0.54, 0.65]	0.60 [0.54, 0.64]
Secondary vascular outcomes		
Flow-mediated dilatation (%)	6.0 [4.3, 9.0]	6.3 [3.7, 8.2]
Glyceryl trinitrate-mediated dilation (%)	17.4 [14.6, 22.0]	17.3 [14.5, 20.2]
Carotid-to-femoral pulse wave velocity (m/s)	7.2 [6.2, 8.2]	7.4 [6.5, 8.0]
Systolic blood pressure (mm Hg)	120 [110, 132]	122 [112, 133]
Diastolic blood pressure (mm Hg)	78 [72, 86]	79 [75, 83]
Periodontal outcomes		
Number of teeth (*n*)	28 [26, 29]	28 [26, 30]
Full mouth dental plaque score (%)	54 [41, 67]	58 [34, 72]
Full mouth gingival bleeding score (%)	49 [36, 67]	51 [42, 67]
Periodontal probing pocket depth (mm)	4.0 [3.6, 4.4]	3.9 [3.6, 4.5]
Clinical attachment level (mm)	4.9 [4.1, 5.6]	5.1 [4.3, 6.1]
Number of periodontal pockets (PPD >3 mm) (*n*)	80 [62, 99]	83 [69, 104]
Number of pockets PPD ≥5 mm	59 [42, 72]	60 [43, 81]

Continued

Table 1 *Continued*

	CPT ($n = 67$)	IPT ($n = 68$)
Number of pockets PPD ≥6 mm	29 [19, 42]	31 [19, 51]
Exploratory outcomes		
High-sensitivity C-reactive protein (mg/dL)	1.2 [0.8, 2.8]	1.2 [0.7, 2.9]
Glycoprotein acetyls (mmol/L)	0.80 [0.75, 0.87]	0.84 [0.76, 0.94]
dROM (U Carr)	340 [288, 408]	318 [279, 389]

Values are expressed as median [inter-quartile range] or *n* (%).
IPT, intensive periodontitis treatment; CPT, control periodontitis treatment; BMI, body mass index; PPD, probing pocket depth; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

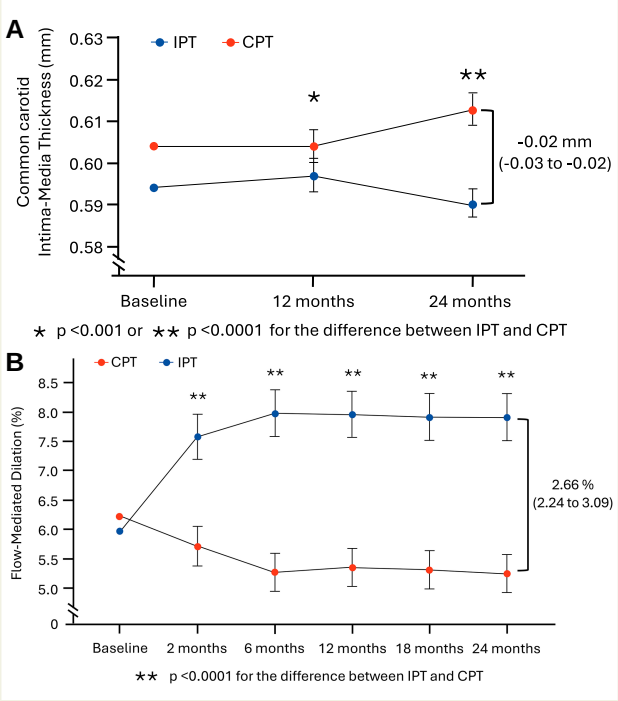

Figure 2 Changes in the vascular phenotype during the study period. (*A*) Changes in carotid intima-media thickness (cIMT) at 12 and 24 months following periodontal therapy. (*B*) Changes in the flow-mediated dilatation (FMD) induced by IPT and CPT during the clinical trial. Baseline values represent the observed mean cIMT while values reported for follow-up time points represent adjusted predictions, reflecting mean values derived from fixed effects. Error bars at each time point represent the 95% confidence intervals obtained from the fixed effect models.

cIMT. Collectively, these findings support a potential causal link between PD and vascular remodelling and provide insight into its underlying mechanisms. These results highlight the potential public health impact of promoting oral health to reduce the global morbidity and mortality burden related to CVD.

Two prior studies have examined the effect of the treatment of PD on cIMT. Piconi *et al.* reported reductions in inflammation and early atherosclerotic changes in 35 otherwise healthy individuals. Improvement in inflammatory and adhesion/activation biomarkers was accompanied by cIMT reduction following therapy.[15] Another trial involving 168 Aboriginal Australians assessed the effect of one session of non-surgical periodontal therapy on cIMT. It showed a difference in maximum cIMT but not mean cIMT at 12 months.[16] The absence of vascular functional or metabolomic data limit insights into mechanisms linking PD to vascular changes. Building on our previous work, we replicated a validated study protocol to investigate multiple vascular and systemic response to the treatment of PD.[2,3] To reduce confounding, we recruited participants not on regular medications, and conducted the study in a single centre, ensuring standardized procedures. We used a validated, reproducible protocol to measure cIMT that previously captured associations with endothelial dysfunction in pre-clinical populations.[10] This approach allowed us to replicate previously observed improvements in endothelial function and now provide evidence that PD may lie on the causal pathway for structural arterial changes, driven by endothelial function and systemic inflammation.

Previous meta-analyses and reviews have reported inconsistent findings regarding the association between cIMT reduction and lower CVD risk.[17–19] Although these findings raised question about the clinical relevance of cIMT,[20] methodologic flaws limited their conclusions.[21] Genetic studies have shown overlap between loci associated with cIMT and traits such as atherosclerotic plaques, coronary heart disease and stroke.[22] These data support cIMT as a surrogate for future CV and cerebrovascular risk. This reinforces the utility of cIMT in evaluating early CV prevention strategies in low-risk populations. Indeed, cIMT remains a widely used endpoint in prospective studies.[23,24] A recent systematic review and meta-analysis of 119 RCTs ($N = 100\,667$ patients and 12 038 incident CVD events) estimated that each 0.010 mm/year reduction in cIMT progression reduced CVD risk by ~10%.[6] In this low-risk population with PD, IPT produced comparable reductions in cIMT over 24 months. Whether this translates into reduced CV event rates remains to be confirmed in future outcome studies.

Our findings suggest that treatment of PD did not substantially affect arterial stiffness, as assessed by carotid-to-femoral PWV. This may reflect limited statistical power, as PWV was not the primary outcome. Notably, the SPARTE trial found that targeting arterial stiffness—beyond guideline-directed blood pressure control—did not reduce CV events.[25] These findings support the view that carotid-to-femoral PWV may reflect arterial wall remodelling but not necessarily plays a causal role in CVD pathogenesis.

The cIMT changes observed after IPT appeared to be largely independent of traditional CV and metabolomic risk factors. Prior studies have similarly shown that cIMT progression is only partly explained by conventional risk factors,[6] suggesting other contributors to vascular

Table 2 Absolute values, changes from baseline and between-group differences in the primary and secondary cardiovascular outcomes

	Absolute values (95% CI)				Change from baseline (95% CI)			
	CPT ($n = 67$)	IPT ($n = 68$)	Difference between groups	*P*-value	CPT ($n = 67$)	IPT ($n = 68$)	Difference between groups	*P*-value
Common carotid intima-media thickness (mm)								
12 months	0.60 (0.60 to 0.61)	0.60 (0.59 to 0.60)	−0.01 (−0.01 to −0.00)	<.001	−0.003 (−0.007 to 0.001)	−0.009 (−0.014 to −0.005)	−0.006 (−0.002 to −0.011)	.005
24 months	0.61 (0.61 to 0.62)	0.59 (0.59 to 0.59)	−0.02 (−0.03 to −0.02)	<.0001	0.006 (0.002 to 0.010)	−0.016 (−0.020 to −0.012)	−0.022 (−0.027 to −0.018)	<.0001
Flow-mediated dilatation (%)								
2 months	5.7 (5.4 to 6.1)	7.6 (7.2 to 8.0)	1.86 (1.43 to 2.28)	<.0001	−0.292 (−0.605 to −0.092)	0.661 (0.335 to 1.095)	1.831 (1.169 to 2.641)	<.0001
6 months	5.3 (4.9 to 5.6)	8.0 (7.6 to 8.4)	2.69 (2.27 to 3.12)	<.0001	−0.678 (−1.126 to −0.343)	1.143 (0.697 to 1.697)	3.582 (2.626 to 4.685)	<.0001
12 months	5.3 (5.0 to 5.7)	7.9 (7.6 to 8.3)	2.60 (2.17 to 3.03)	<.0001	−0.591 (−1.013 to −0.282)	1.010 (0.595 to 1.535)	3.146 (2.255 to 4.185)	<.0001
18 months	5.3 (5.0 to 5.6)	7.9 (7.5 to 8.3)	2.60 (2.17 to 3.02)	<.0001	−0.617 (−1.047 to −0.300)	0.937 (0.539 to 1.444)	3.074 (2.195 to 4.102)	<.0001
24 months	5.2 (4.9 to 5.6)	7.9 (7.5 to 8.3)	2.66 (2.24 to 3.09)	<.0001	−0.681 (−1.129 to −0.345)	0.975 (0.568 to 1.491)	3.284 (2.373 to 4.344)	<.0001
Glyceryl trinitrate (GTN)-mediated dilation (%)								
2 months	17.2 (16.5 to 18.0)	17.3 (16.6 to 18.1)	0.09 (−0.77 to 0.95)	.838	−0.359 (−0.891 to 0.024)	−0.227 (−0.709 to 0.134)	0.107 (−0.310 to 0.606)	.590
6 months	17.2 (16.4 to 17.9)	17.8 (17.0 to 18.6)	0.60 (−0.27 to 1.47)	.178	−0.518 (−1.113 to −0.090)	−0.121 (−0.561 to 0.242)	0.353 (−0.073 to 0.964)	.111
12 months	17.3 (16.5 to 18.0)	18.0 (17.3 to 18.8)	0.75 (−0.13 to 1.63)	.095	−0.481 (−1.060 to −0.064)	−0.054 (−0.468 to 0.321)	0.405 (−0.033 to 1.037)	.073
18 months	17.4 (16.7 to 18.2)	18.0 (17.2 to 18.7)	0.55 (−0.33 to 1.43)	.220	−0.475 (−1.052 to −0.060)	−0.091 (−0.519 to 0.276)	0.352 (−0.073 to 0.961)	.111
24 months	17.0 (16.3 to 17.7)	17.9 (17.2 to 18.7)	0.93 (0.06 to 1.80)	.035	−0.670 (−1.324 to −0.201)	−0.081 (−0.505 to 0.288)	0.546 (0.066 to 1.242)	.022
Carotid-to-femoral pulse wave velocity (m/s)								
2 months	8.6 (8.2 to 9.0)	8.6 (8.2 to 9.0)	−0.01 (−0.49 to 0.46)	.953	−0.028 (−0.285 to 0.217)	0.012 (−0.232 to 0.261)	0.040 (−0.243 to 0.343)	.765
6 months	8.5 (8.1 to 8.9)	8.7 (8.3 to 9.1)	0.18 (−0.29 to 0.66)	.441	−0.052 (−0.316 to 0.188)	0.058 (−0.179 to 0.319)	0.113 (−0.162 to 0.439)	.413
12 months	9.0 (8.6 to 9.1)	8.9 (8.5 to 9.3)	−0.06 (−0.55 to 0.43)	.813	0.165 (−0.073 to 0.456)	0.228 (−0.016 to 0.531)	0.054 (−0.227 to 0.363)	.687
18 months	9.1 (8.7 to 9.5)	9.2 (8.7 to 9.6)	0.06 (−0.44 to 0.56)	.819	0.237 (−0.010 to 0.547)	0.351 (0.083 to 0.685)	0.092 (−0.184 to 0.412)	.501
24 months	9.0 (8.6 to 9.4)	9.0 (8.6 to 9.4)	0.02 (−0.48 to 0.51)	.948	0.150 (−0.088 to 0.438)	0.275 (0.022 to 0.591)	0.109 (−0.168 to 0.436)	.432
Systolic blood pressure (mm Hg)								
2 months	123 (118 to 127)	121 (116 to 125)	−2.0 (−7.8 to 3.8)	.500	−0.060 (−0.865 to 0.659)	−0.552 (−1.733 to 0.134)	−0.464 (−1.862 to 0.335)	.264
6 months	122 (118 to 127)	113 (109 to 118)	−8.8 (−14.4 to −3.1)	.002	−0.006 (−0.769 to 0.749)	−0.627 (−1.866 to 0.082)	−0.618 (−2.163 to 0.208)	.159
12 months	122 (118 to 127)	120 (116 to 125)	−1.9 (−7.7 to 3.9)	.521	−0.011 (−0.778 to 0.740)	−1.227 (−2.921 to −0.265)	−1.203 (−3.306 to −0.127)	.021
18 months	122 (117 to 127)	122 (118 to 127)	0.3 (−5.6 to 6.1)	.924	−0.018 (−0.791 to 0.727)	−0.186 (−1.089 to 0.484)	−0.165 (−1.277 to 0.678)	.654
24 months	124 (119 to 128)	123 (118 to 127)	−1.1 (−7.0 to 4.8)	.705	0.563 (−0.125 to 1.750)	−0.083 (−0.906 to 0.626)	−0.693 (−2.309 to 0.155)	.123

Continued

Table 2 *Continued*

	Absolute values (95% CI)				Change from baseline (95% CI)			
	CPT ($n = 67$)	IPT ($n = 68$)	Difference between groups	*P*-value	CPT ($n = 67$)	IPT ($n = 68$)	Difference between groups	*P*-value
Diastolic blood pressure (mm Hg)								
2 months	79 (77 to 82)	77 (74 to 80)	−2.4 (−6.0 to 1.1)	.183	0.215 (−0.416 to 1.091)	−0.486 (−1.561 to 0.160)	−0.806 (−2.399 to 0.042)	.067
6 months	76 (73 to 79)	77 (75 to 80)	1.7 (−1.8 to 5.2)	.344	−0.154 (−0.986 to 0.491)	−0.453 (−1.504 to 0.186)	−0.259 (−1.370 to 0.495)	.474
12 months	79 (76 to 82)	77 (74 to 80)	−1.5 (−5.1 to 2.0)	.398	0.018 (−0.690 to 0.753)	−0.900 (−2.273 to −0.102)	−0.935 (−2.642 to −0.028)	.041
18 months	80 (77 to 83)	79 (76 to 82)	−0.8 (−4.4 to 2.8)	.657	0.239 (−0.389 to 1.132)	−0.056 (−0.820 to 0.631)	−0.309 (−1.463 to 0.438)	.403
24 months	81 (79 to 85)	80 (77 to 83)	−1.9 (−5.6 to 1.8)	.031	0.770 (0.028 to 2.045)	0.205 (−0.430 to 1.077)	−0.468 (−1.764 to 0.282)	.233
High-sensitivity C-reactive protein (mg/L)								
2 months	2.4 (2.0 to 2.9)	1.9 (1.6 to 2.4)	−0.46 (0.05 to −0.96)	.075	0.172 (−0.069 to 0.467)	−0.213 (−0.520 to 0.033)	−0.421 (−0.845 to −0.095)	.008
6 months	2.3 (1.9 to 2. 8)	2.0 (1.6 to 2.5)	−0.26 (−0.75 to 0.23)	.303	0.089 (−0.150 to 0.364)	−0.124 (−0.409 to 0.115)	−0.224 (−0.589 to 0.060)	.128
12 months	2.0 (1.6 to 2.4)	2.0 (1.6 to 2.4)	0.00 (−0.45 to 0.46)	.987	−0.117 (−0.399 to 0.121)	−0.144 (−0.434 to 0.095)	−0.024 (−0.330 to 0.267)	.855
18 months	2.4 (2.0 to 2.9)	1.9 (1.6 to 2.4)	−0.45 (−0.96 to 0.05)	.076	0.178 (−0.063 to 0.475)	−0.155 (−0.447 to 0.085)	−0.361 (−0.766 to −0.048)	.021
24 months	2.7 (2.2 to 3.2)	1.6 (1.3 to 2.0)	−1.05 (−1.57 to −0.53)	<.001	0.468 (0.172 to 0.839)	−0.461 (−0.831 to −0.166)	−1.145 (−1.784 to −0.652)	<.0001
Glycoprotein acetyls (mmol/L)								
2 months	0.83 (0.80 to 0.85)	0.83 (0.80 to 0.85)	0.00 (−0.08 to 0.03)	.957	0.004 (−0.021 to 0.029)	−0.014 (−0.039 to 0.011)	−0.017 (−0.047 to 0.011)	.231
6 months	0.83 (0.81 to 0.85)	0.78 (0.76 to 0.80)	−0.05 (−0.08 to −0.02)	<.001	0.005 (−0.020 to 0.030)	−0.062 (−0.088 to −0.035)	−0.067 (−0.098 to −0.037)	<.0001
12 months	0.82 (0.80 to 0.84)	0.78 (0.76 to 0.80)	−0.04 (−0.07 to −0.01)	.004	−0.006 (−0.032 to 0.019)	−0.061 (−0.088 to −0.035)	−0.054 (−0.085 to −0.025)	<.001
18 months	0.83 (0.80 to 0.85)	0.78 (0.76 to 0.80)	−0.05 (−0.08 to −0.02)	<.001	0.003 (−0.022 to 0.028)	−0.059 (−0.085 to −0.033)	−0.062 (−0.092 to −0.032)	<.0001
24 months	0.83 (0.80 to 0.85)	0.78 (0.76 to 0.80)	−0.05 (−0.08 to −0.02)	<.001	0.001 (−0.024 to 0.026)	−0.062 (−0.088 to −0.036)	−0.063 (−0.093 to −0.033)	<.0001
d-ROM (U Carr)								
2 months	352 (329 to 377)	332 (310 to 354)	−20.5 (−48.3 to 7.3)	.148	1.537 (−0.174 to 6.556)	0.343 (−1.180 to 2.929)	−0.890 (−5.734 to 0.885)	.325
6 months	354 (331 to 378)	324 (303 to 347)	−29.4 (−57.0 to −1.8)	.037	0.939 (−0.536 to 4.774)	−0.388 (−3.063 to 1.108)	−1.692 (−8.592 to 0.324)	.126
12 months	335 (313 to 359)	333 (311 to 356)	−2.6 (−29.7 to 24.50)	.850	0.276 (−1.333 to 2.801)	0.127 (−1.597 to 2.297)	−0.133 (−3.037 to 2.145)	.847
18 months	326 (305 to 349)	339 (317 to 363)	13.2 (−13.8 to 40.2)	.338	−0.746 (−4.199 to 0.706)	0.920 (−0.524 to 4.619)	2.352 (−0.063 to 10.944)	.062
24 months	340 (318 to 364)	277 (260 to 297)	−62.8 (−88.2 to −37.5)	<.0001	−0.296 (−2.860 to 1.297)	−13.846 (−42.447 to −4.073)	−10.453 (−39.810 to −2.214)	<.001

Values are reported as mean (95% CI). All outcomes were modelled using multi-level linear regression with random intercepts. The models included the respective baseline measurement, treatment group (represented by one dummy variable), stage of study visit (i.e. 12 months, 24 months, etc.), and a treatment-time inter-action term as explanatory variables (co-variates). Additional co-variates included age, sex, ethnicity, smoking status, family history of cardiovascular disease, and body mass index.

IPT, intensive periodontitis treatment; CPT, control periodontitis treatment.

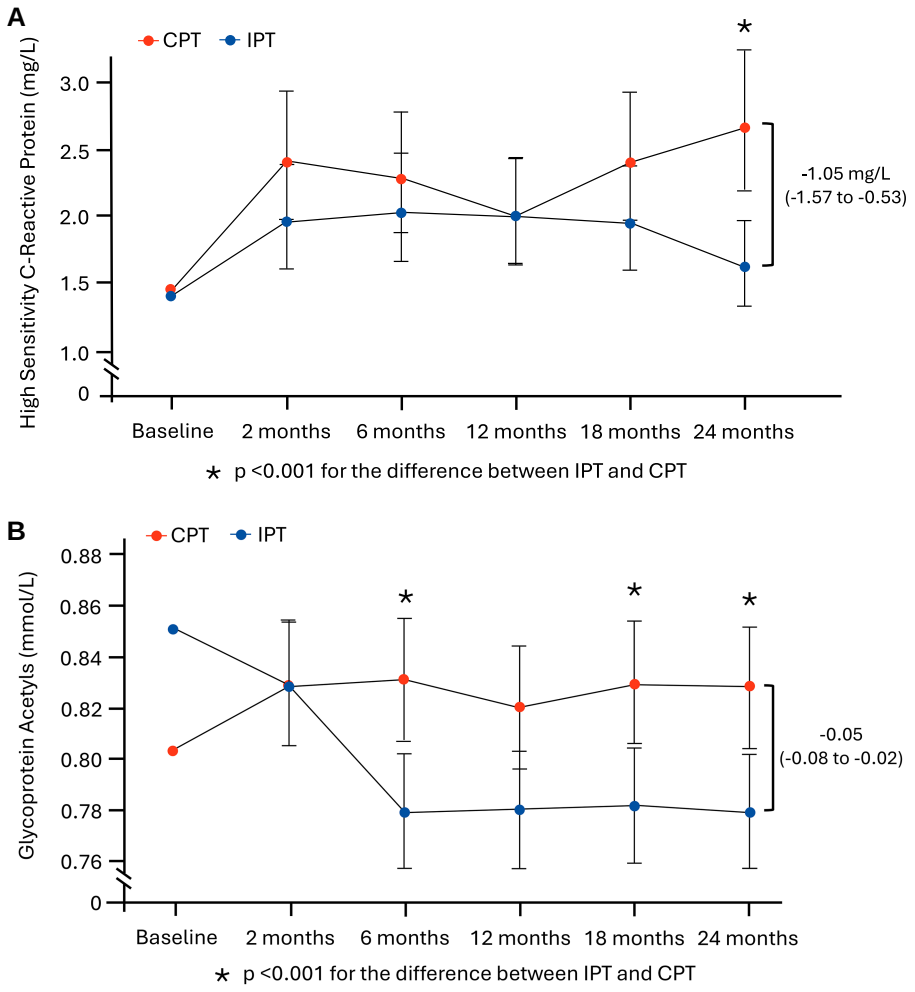

Figure 3 Changes in inflammatory markers during the study period. Changes in (*A*) high-sensitivity C-reactive protein (hsCRP) and (*B*) glycoprotein acetyl A at 2, 6, 12, 18, and 24 months following periodontal therapy. Baseline values represent the observed mean carotid intima-media thickness while values reported for follow-up time points represent adjusted predictions, reflecting mean values derived from fixed effects. Error bars at each time point represent the 95% confidence intervals obtained from the fixed effect models.

remodelling. Inflammation and oxidative stress are increasingly recognized as key modulators of vascular health. In our study, changes in cIMT correlated with reductions in inflammatory and oxidative stress biomarkers. These associations were observed in participants with hsCRP <2 mg/L—a level indicative of low but potentially relevant residual inflammatory risk.[26] However, GlycA levels declined earlier and more closely mirrored changes in FMD than hsCRP, suggesting superior sensitivity to vascular improvement. We have previously shown that GlycA reflects low-grade inflammation linked to adverse CV risk profiles, even in otherwise healthy participants.[27] Other large cohorts-including the Women's Health Study,[28] PREVEND,[29] MESA,[30] and JUPITER[31] have reported that GlycA independently predicts incident CV events. These findings suggest that GlycA may serve as biomarker to identify patients with PD most likely to derive CV benefit from the treatment of PD. Although mechanistic pathways remain speculative, we previously reported that accelerated biological ageing—reflected in biomarker profiles—was associated with faster vascular remodeling[32] and more pronounced in patients with PD, potentially due to elevated systemic oxidative stress.[14,33] We also demonstrated that the link between vascular ageing and inflammation persists even in individuals with low inflammatory burden.[34] Taken together, our data support the hypothesis that vascular remodelling not explained by traditional CV risk factors may reflect vascular ageing driven by chronic inflammation and oxidative stress.

This study has several limitations that should be acknowledged. Being a single-centre trial, findings may be influenced by local procedures and may not be fully generalizable. The absence of group differences in metabolomic markers or PWV may reflect limited power for detecting secondary outcomes. Patient-reported outcomes were not collected, which might have provided additional context on vascular health and quality of life. Although cIMT changes fell within the 'normal' ranges, their clinical relevance may be questioned. However, studies have shown that even cIMT values within 'normal' ranges can predict CV events, particularly in younger individuals, where they improve risk stratification beyond traditional scores.[35–37] To further assess the impact of baseline cIMT on the study results, we conducted a *post hoc* stratified analysis. The observed treatment effects remained robust, confirming the consistency of our findings. Finally, no correction for

multiple comparisons was applied to exploratory analyses, increasing the potential for type I error. These findings should be viewed as hypothesis-generating and warrant replication in future studies. Strengths include a rigorous, validated imaging protocol for both FMD and cIMT, and the successful execution of a well-controlled RCT in patients with severe PD. We also employed metabolomics to explore potential mechanisms underlying the vascular benefits of IPT.

Conclusions

Treatment of PD improves endothelial function, lowers systemic inflammation and oxidative stress, and favourably modifies structural vascular health. These effects may translate into reduced long-term CV risk.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

The data supporting the results presented in this report are available upon reasonable request from the corresponding author.

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Ethical Approval

Ethical approval was granted by the London Queen Square Ethics Committee (06/Q0512/107) in accordance with the Declaration of Helsinki. The written informed consent was obtained from all participants.

Pre-registered Clinical Trial Number

The trial was registered on Clinicaltrial.gov with the number NCT03072342.

References

1. Sanz M, D'Aiuto F, Deanfield J, Fernandez-Avilés F. European workshop in periodontal health and cardiovascular disease-scientific evidence on the association between periodontal and cardiovascular diseases: a review of the literature. *Eur Heart J Suppl* 2010;**12**:B3–12.
2. D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, *et al.* Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. *Lancet Diabetes Endocrinol* 2018;**6**:954–65. https://doi.org/10.1016/s2213-8587(18)30038-x
3. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, *et al.* Treatment of periodontitis and endothelial function. *N Engl J Med* 2007;**356**:911–20. https://doi.org/10.1056/NEJMoa063186
4. D'Aiuto F, Nibali L, Parkar M, Patel K, Suvan J, Donos N. Oxidative stress, systemic inflammation, and severe periodontitis. *J Dent Res* 2010;**89**:1241–6. https://doi.org/10.1177/0022034510375830
5. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, Nosalski R, Pelka P, Nowakowski D, *et al.* Causal association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. *Eur Heart J* 2019;**40**:3459–70. https://doi.org/10.1093/eurheartj/ehz646
6. Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao L, *et al.* Carotid intima-Media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100 667 patients. *Circulation* 2020;**142**:621–42. https://doi.org/10.1161/circulationaha.120.046361
7. Matuliene G, Pjetursson BE, Salvi GE, Schmidlin K, Brägger U, Zwahlen M, *et al.* Influence of residual pockets on progression of periodontitis and tooth loss: results after 11 years of maintenance. *J Clin Periodontol* 2008;**35**:685–95. https://doi.org/10.1111/j.1600-051X.2008.01245.x
8. Altman DG, Bland JM. How to randomise. *BMJ* 1999;**319**:703–4. https://doi.org/10.1136/bmj.319.7211.703
9. Tonetti MS, Claffey N. Advances in the progression of periodontitis and proposal of definitions of a periodontitis case and disease progression for use in risk factor research. Group C consensus report of the 5th European workshop in periodontology. *J Clin Periodontol* 2005;**32**:210–3. https://doi.org/10.1111/j.1600-051X.2005.00822.x
10. Halcox JP, Donald AE, Ellins E, Witte DR, Shipley MJ, Brunner EJ, *et al.* Endothelial function predicts progression of carotid intima-media thickness. *Circulation* 2009;**119**:1005–12. https://doi.org/10.1161/CIRCULATIONAHA.108.765701
11. Marcovecchio ML, Chiesa ST, Bond S, Daneman D, Dawson S, Donaghue KC, *et al.* ACE inhibitors and statins in adolescents with type 1 diabetes. *N Engl J Med* 2017;**377**:1733–45. https://doi.org/10.1056/NEJMoa1703518
12. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, *et al.* Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American society of echocardiography carotid intima-Media thickness task force. Endorsed by the society for vascular medicine. *J Am Soc Echocardiogr* 2008;**21**:93–111; quiz 189-190. https://doi.org/10.1016/j.echo.2007.11.011
13. Charakida M, de Groot E, Loukogeorgakis SP, Khan T, Lüscher T, Kastelein JJ, *et al.* Variability and reproducibility of flow-mediated dilatation in a multicentre clinical trial. *Eur Heart J* 2013;**34**:3501–7. https://doi.org/10.1093/eurheartj/eht223
14. Masi S, Salpea KD, Li K, Parkar M, Nibali L, Donos N, *et al.* Oxidative stress, chronic inflammation, and telomere length in patients with periodontitis. *Free Radic Biol Med* 2011;**50**:730–5. https://doi.org/10.1016/j.freeradbiomed.2010.12.031
15. Piconi S, Trabattoni D, Luraghi C, Perilli E, Borelli M, Pacei M, *et al.* Treatment of periodontal disease results in improvements in endothelial dysfunction and reduction of the carotid intima-media thickness. *FASEB J* 2009;**23**:1196–204. https://doi.org/10.1096/fj.08-119578
16. Kapellas K, Maple-Brown LJ, Jamieson LM, Do LG, O'Dea K, Brown A, *et al.* Effect of periodontal therapy on arterial structure and function among aboriginal Australians: a randomized, controlled trial. *Hypertension* 2014;**64**:702–8. https://doi.org/10.1161/HYPERTENSIONAHA.114.03359
17. Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, *et al.* Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. *J Am Coll Cardiol* 2010;**56**:2006–20. https://doi.org/10.1016/j.jacc.2010.05.059
18. Goldberger ZD, Valle JA, Dandekar VK, Chan PS, Ko DT, Nallamothu BK. Are changes in carotid intima-media thickness related to risk of nonfatal myocardial infarction? A critical review and meta-regression analysis. *Am Heart J* 2010;**160**:701–14. https://doi.org/10.1016/j.ahj.2010.06.029
19. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen TP, *et al.* Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet* 2012;**379**:2053–62. https://doi.org/10.1016/S0140-6736(12)60441-3
20. Simon A, Megnien JL, Chironi G. The value of carotid intima-media thickness for predicting cardiovascular risk. *Arterioscler Thromb Vasc Biol* 2010;**30**:182–5. https://doi.org/10.1161/ATVBAHA.109.196980
21. Bots ML, Taylor AJ, Kastelein JJ, Peters SA, den Ruijter HM, Tegeler CH, *et al.* Rate of change in carotid intima-media thickness and vascular events: meta-analyses cannot solve all the issues. A point of view. *J Hypertens* 2012;**30**:1690–6. https://doi.org/10.1097/HJH.0b013e32835644dc
22. Franceschini N, Giambartolomei C, de Vries PS, Finan C, Bis JC, Huntley RP, *et al.* GWAS and colocalization analyses implicate carotid intima-media thickness and carotid plaque loci in cardiovascular outcomes. *Nat Commun* 2018;**9**:5141. https://doi.org/10.1038/s41467-018-07340-5

23. Charakida M, Khan T, Johnson W, Finer N, Woodside J, Whincup PH, *et al.* Lifelong patterns of BMI and cardiovascular phenotype in individuals aged 60-64 years in the 1946 British birth cohort study: an epidemiological study. *Lancet Diabetes Endocrinol* 2014;**2**: 648–54. https://doi.org/10.1016/S2213-8587(14)70103-2
24. van der Linden IA, Roodenburg R, Nijhof SL, van der Ent CK, Venekamp RP, van der Laan SEI, *et al.* Early-life risk factors for carotid intima-Media thickness and carotid stiffness in adolescence. *JAMA Netw Open* 2024;**7**:e2434699. https://doi.org/10.1001/jamanetworkopen.2024.34699
25. Laurent S, Chatellier G, Azizi M, Calvet D, Choukroun G, Danchin N, *et al.* SPARTE study: normalization of arterial stiffness and cardiovascular events in patients with hypertension at Medium to very high risk. *Hypertension* 2021;**78**:983–95. https://doi.org/10.1161/hypertensionaha.121.17579
26. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, *et al.* Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;**377**:1119–31. https://doi.org/10.1056/NEJMoa1707914
27. Chiesa ST, Charakida M, Georgiopoulos G, Roberts JD, Stafford SJ, Park C, *et al.* Glycoprotein acetyls: a novel inflammatory biomarker of early cardiovascular risk in the young. *J Am Heart Assoc* 2022;**11**:e024380. https://doi.org/10.1161/jaha.121.024380
28. Akinkuolie AO, Buring JE, Ridker PM, Mora S. A novel protein glycan biomarker and future cardiovascular disease events. *J Am Heart Assoc* 2014;**3**:e001221. https://doi.org/10.1161/jaha.114.001221
29. Gruppen EG, Riphagen IJ, Connelly MA, Otvos JD, Bakker SJ, Dullaart RP. Glyca, a pro-inflammatory glycoprotein biomarker, and incident cardiovascular disease: relationship with C-reactive protein and renal function. *PLoS One* 2015;**10**:e0139057. https://doi.org/10.1371/journal.pone.0139057
30. Duprez DA, Otvos J, Sanchez OA, Mackey RH, Tracy R, Jacobs DR Jr. Comparison of the predictive value of GlycA and other biomarkers of inflammation for total death, incident cardiovascular events, noncardiovascular and noncancer inflammatory-related events, and total cancer events. *Clin Chem* 2016;**62**:1020–31. https://doi.org/10.1373/clinchem.2016.255828
31. Akinkuolie AO, Glynn RJ, Padmanabhan L, Ridker PM, Mora S. Circulating N-linked glycoprotein side-chain biomarker, Rosuvastatin therapy, and incident cardiovascular disease: an analysis from the JUPITER trial. *J Am Heart Assoc* 2016;**5**:12. https://doi.org/10.1161/jaha.116.003822
32. Masi S, D'Aiuto F, Martin-Ruiz C, Kahn T, Wong A, Ghosh AK, *et al.* Rate of telomere shortening and cardiovascular damage: a longitudinal study in the 1946 British birth cohort. *Eur Heart J* 2014;**35**:3296–303. https://doi.org/10.1093/eurheartj/ehu226
33. Masi S, Gkranias N, Li K, Salpea KD, Parkar M, Orlandi M, *et al.* Association between short leukocyte telomere length, endotoxemia, and severe periodontitis in people with diabetes: a cross-sectional survey. *Diabetes Care* 2014;**37**:1140–7. https://doi.org/10.2337/dc13-2106
34. Masi S, Nightingale CM, Day IN, Guthrie P, Rumley A, Lowe GD, *et al.* Inflammation and not cardiovascular risk factors is associated with short leukocyte telomere length in 13- to 16-year-old adolescents. *Arterioscler Thromb Vasc Biol* 2012;**32**:2029–34. https://doi.org/10.1161/ATVBAHA.112.250589
35. Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the carotid atherosclerosis progression study (CAPS). *Stroke* 2006;**37**:87–92. https://doi.org/10.1161/01.STR.0000196964.24024.ea
36. Ge J, Jing F, Ji R, Tian A, Su X, Li W, *et al.* Age-related trends in the predictive value of carotid intima-Media thickness for cardiovascular death: a prospective population-based cohort study. *J Am Heart Assoc* 2023;**12**:e029656. https://doi.org/10.1161/JAHA.123.029656
37. Eikendal AL, Groenewegen KA, Anderson TJ, Britton AR, Engström G, Evans GW, *et al.*Common carotid intima-media thickness relates to cardiovascular events in adults aged<45 years. *Hypertension* 2015;**65**:707–13. https://doi.org/10.1161/HYPERTENSIONAHA.114.04658