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CLINICAL RESEARCH

A 32-month evaluation of lithium disilicate cantilever resin-bonded fixed dental prostheses to replace a missing maxillary incisor

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ABSTRACT

Statement of problem. The absence of a tooth in the esthetic zone can cause emotional and social distress. The use of minimally invasive and visually pleasing lithium disilicate resin-bonded fixed dental prostheses (RBFDPs) may be a suitable option for replacing a missing maxillary incisor. However, the available literature on lithium disilicate cantilever RBFDPs is limited.

Purpose. This retrospective multicenter study assessed the survival and success rates of lithium disilicate anterior cantilever RBFDPs with an average follow-up period of 3 years up to 9 years.

Material and methods. RBFDPs delivered by 3 operators were clinically assessed for survival using a modified United States Public Health Service criteria list. The incidence density was determined for each criterion and operator. The standard error and 95% confidence interval were calculated for each incidence density difference (α=.05 for all analyses).

Results. A total of 108 RBFDPs were evaluated after a mean period of 32.45 months, ranging from 14 days to 111 months. None of the restorations exhibited failure, carious lesions, or fractures during the follow-up period. The primary reasons for reduced success rates were inflammation of the surrounding soft tissues and discoloration, with incidence densities of 0.074 and 0.057 per year, respectively. Significant differences were observed among RBFDPs from different operators for criteria that included adaptation, color match, marginal adaptation, polishability, surface staining, gingival health, and antagonist wear.

Conclusions. Cantilever lithium disilicate RBFDPs appear to be suitable for short-term restoration. RBFDPs exhibited visible changes after short-term follow-up. However, these changes did not result in failure. (J Prosthet Dent 2024;132:956-963)

The reported prevalence of tooth agenesis varies between 2.2% and 10.1%,[1] with the second premolar (23.0%) and lateral incisor (17.9%) being the most frequently absent maxillary teeth, apart from the third molars.[2] Lateral incisor agenesis is typically bilateral, and it negatively impacts facial esthetics with resulting emotional and social burdens.[3,4] Therefore, patients seeking dental treatment are motivated by a wish to enhance esthetics, improve social comfort, and reduce self-consciousness.[5]

Patients with tooth agenesis should be restored to a functional, healthy, and esthetically pleasing dentition using

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Clinical Implications

Cantilever lithium disilicate RBFDPs can be considered as a suitable treatment option for the restoration of a single missing tooth in the maxillary esthetic zone.

a conservative treatment approach.[4] Treatment options for tooth agenesis include an implant-supported restoration, orthodontic space closure, or a fixed dental prosthesis (FDP).[6] Successful osseointegration and sustained functionality with a single-tooth implant-supported restoration have been documented.[7–9] Moreover, adjacent teeth remain intact. Nevertheless, implant placement may be contraindicated for young patients still in a growth and development phase.[10,11] Furthermore, vertical skeletal modifications persist throughout an individual's lifetime, leading to differences in the inclination of the implant and neighboring teeth as someone ages, resulting in unsatisfactory esthetics.[12] Additionally, implant treatment is invasive and expensive compared with alternative treatment options.[13]

Orthodontic space closure may be initiated at a young age, with canine reshaping being the sole requirement in some patients after completion. Nevertheless, the substitution of canines for lateral incisors may present complications, including occlusal and facial discrepancies. For instance, a skeletal class III relationship may be exacerbated, or the upper lip support could be diminished. Additionally, the canine differs from the lateral incisor in terms of size, contour, color, and gingival profile and also possesses longer roots to facilitate lateral protection and guide articulation. Hence, the use of canine substitution alone may not always result in an optimal outcome.[14,15]

In situations where the adjacent teeth necessitate restoration because of caries or fracture, a conventional complete coverage FDP may be the preferred treatment option. However, because of the substantial removal of healthy dental tissue, complete coverage is not typically recommended for young patients.[16,17]

A resin-bonded fixed dental prosthesis (RBFDP) is a minimally invasive treatment option that is not contraindicated by continued craniofacial growth and enables the preservation of future treatment options.[18] Cantilever RBFDPs using a single abutment tooth have been reported to exhibit similar or lower complication rates than those incorporating 2 abutment teeth.[19–22] A single abutment tooth for an RBFDP is a minimally invasive approach that promotes the preservation of healthy dental tissue.[23]

Traditionally, RBFDPs have been composed of a metal alloy framework, which can lead to reduced translucency and a grayish appearance of the abutment tooth, particularly the central incisor.[22] Furthermore, debonding of metal-ceramic RBFDPs has been reported to occur at a rate of 2.89%.[20,24] Nonmetal RBFDP alternatives include fiber-reinforced composite resins and ceramic materials. The advantages of fiber-reinforced composite resins include improved esthetics and low cost. However, degradation of the composite resin can decrease esthetics, and connector fracture is a common cause of failure subsequent to wear.[20,23] A survival rate of 73.4% after 4.5 years has been reported for fiber-reinforced composite resin RBFDPs.[25] Therefore, this treatment option is typically selected as a low-cost, short-term option.[23]

Zirconia ceramic offers several advantages, including high flexural strength and fracture toughness, biocompatibility, and favorable esthetics.[26] A survival rate of 98.2% after 10 years for anterior zirconia ceramic cantilever RBFDPs has been reported.[27] However, chipping of the ceramic veneer and debonding at an annual rate of 1.42% have been reported.[24] A significant benefit of glass-ceramic RBFDPs is that debonding has not been reported.[24] Additionally, a 100% survival rate for lithium disilicate glass-ceramic cantilever RBFDPs was reported in 2 different studies after a mean follow-up of 4 and 6 years.[28,29]

Lithium disilicate is an etchable glass-ceramic, which makes it suitable for adhesive luting. It is more fragile than zirconia, and, therefore, a larger connector size is required.[30] Additionally, its excellent esthetics make it suitable for monolithic restorations in the esthetic zone.[31] The flexural strength of lithium disilicate is around 400 to 500 MPa, which restricts its recommended use by the manufacturer to laminate veneers, inlays, onlays, and partial-coverage crowns.[32] However, clinical experience indicates that lithium disilicate cantilever RBFDPs can be used to replace a maxillary lateral incisor.[33] Since the manufacturer does not recommend the use of lithium disilicate for cantilevered RBFDPs, data on the long-term outcomes and success rate of such restorations are sparse.[28]

The aim of this patient-controlled study was to assess the survival and success rates of lithium disilicate cantilever RBFDPs replacing maxillary incisors based on incidence density. Furthermore, the study aimed to investigate whether there were any differences in the survival and success of the cantilever RBFDPs among operators. The null hypothesis was that no variations would exist among the restorations produced by different operators.[34]

MATERIAL AND METHODS

In this retrospective study, the survival and success of RBFDPs were evaluated. The RBFDPs had been placed by

3 experienced educators in restorative dentistry (M.M. M.G., G.J.B., G.T.) in different dental practices. The clinicians followed the same protocols, resulting in calibrated restorations. All patients that had been treated with lithium disilicate cantilever RBFDPs within these dental practices were included. The restorations were evaluated at the time of placement and during the patient's regular annual oral examination by 3 different observers (A.D., S.M., M.O.), independent of the operators, and calibrated before the clinical examination. The research protocol of this retrospective clinical study was assessed by the Medical Ethical Committee of the Institutional Review Board of the University Medical Center Groningen (METc communication M18.229771) and was considered not clinical research with human participants as meant in the Medical Research Involving Human Subjects Act (WMO).

All lithium disilicate cantilever RBFDPs replacing a missing maxillary incisor were from 3 different practices: Center for Special Care, Martini Hospital, Groningen (MH); Buijs Tandartsen (BT) Groningen; and a private practice in Paris (DPP). RBFDPs that had been initially placed as interim restorations and subsequently replaced by implant-supported prostheses were excluded from the study because such restorations were not removed because of failure.

The retainers were prepared for palatal chamfer or buccal laminate veneers on the adjacent canine or central incisor with a mesial extension. Pressed lithium disilicate (IPS e.max Press; Ivoclar AG) RBFDPs were fabricated by 2 different dental laboratory technicians who followed the same procedure and techniques according to the manufacturer's instructions for a 3-unit anterior partial fixed dental prosthesis. The connector dimension was 7×3 mm, and a miniwing was placed on the mesial side without bonding it to the tooth to prevent buccopalatal movement.

The restorations were adhesively luted under dental dam isolation[35] after etching with 9% hydrofluoric acid (Porcelain Etch; Ultradent Products, Inc), cleaning with 35% phosphoric acid (Ultra-Etch; Ultradent Products, Inc), ultrasonic cleaning in distilled water, and the application of silane (Bis-Silane; Bisco). The restoration was heated at 100 ℃ for 3 minutes in an oven (DI-500 Oven; Coltène). The prepared enamel was abraded with 29-μm aluminum oxide (Aqua-Care; Velopex), etched with 35% phosphoric acid (Ultra-Etch; Ultradent Products, Inc), and coated with an adhesive (OptiBond FL Adhesive; Kerr Corp). The RBFDPs were luted with a composite resin (Enamel Plus HFO UD1; Micerium) and heated to 55 ℃ (Ena Heat; Micerium).

The performance of the RBFDPs was assessed according to modified United States Public Health Service (USPHS) criteria (Table 1).[36] Survival was defined as a prosthesis that was in situ at the time of evaluation. Any occurrence of debonding was registered. If any of the criteria listed in Table 2 necessitated the replacement of the restoration, it was defined as a failure.[37] A mirror, explorer, periodontal probe (Standard Set-Up; Hu-Friedy), operating light (SingLED; Planmeca), and dental floss (Reach waxed Floss; Johnson & Johnson) were used for the assessment. For every criterion, the most appropriate restoration score was assigned. The period in which a restoration was in situ was defined as the duration between the date of placement (T0) and the date of the last clinical assessment (T1). The duration in situ for each RBFDP was recorded. A clinical example of an RBFDP at T0 and T1 is illustrated in Figure 1.

The evaluations were transferred anonymously from the patient's record to a dataset with an electronic data capture software program (Research Electronic Data Capture; version 1.2; Vanderbilt University). The exact number of days between T0 and T1 was calculated with a spreadsheet (Excel; version 14.7.3; Microsoft Corp) to determine the number of days at risk.

To evaluate the association between the scores of the modified USPHS assessment criteria and the occurrence of changes in RBFDPs, the incidence density per criterion was determined over the total population and for each group (MH, BT, DPP). The difference in incidence density among the groups was then calculated. Since the degree, severity, and exact timing of the occurrence of changes per criterion of the modified USPHS assessment form could not be determined retrospectively, the ratings per criterion were reduced to a binary score of 1 (change occurred) or 0 (change did not occur).

The total number of assessments in which changes occurred was recorded as the number of incidents (a). To determine the period at risk across the entire population, the days at risk (N) for all 3 groups were added together. By using the formula $(r) = (a/N) \times 365$, the annual incidence density was calculated.[38] The 95% confidence interval (CI) was calculated using the formula *95% CI* $(e^{\ln r - z_{1-\frac{\alpha SE}{2}}}, e^{\ln r + z_{1-\frac{\alpha SE}{2}}})$.[38] The annual incidence density (r) was calculated for each group by using this formula. Next, the incidence density difference ($(r)_{diff}$) per year among groups was calculated by using the formula.

$(r)_{diff} = |(r)_x - (r)_y|$.[38] In order to determine the differences among groups, 3 pairwise (x-y) comparisons (BT-DPP, DPP-MH, and BT-MH) were performed. For each incidence density difference, the standard error was calculated with the formula $SE = \sqrt{a_1/N_1^2 + a_2/N_2^2}$, and the corresponding 95% CI for each comparison was calculated with the formula.

95% CI $((r)_{diff} \pm z_{(1-\alpha/2)} \times SE)$[38] ($\alpha$=.05 for all analyses).

RESULTS

A total of 108 RBFDPs were evaluated, 43 in the MH group, 31 in the BT group, and 34 in the DPP group. An

Table 1. Modified USPHS assessment criteria

Category	Score	Criterion
1. Adaptation of the restoration	0	Restorations contour is continuous with existing anatomical form and margins
	1	Restoration is slightly under or over contoured
	2	Marginal overhang or tooth structure (dentin or enamel) is exposed
	3	Restoration is missing, traumatic occlusion or restoration cause pain in tooth or adjacent tissue
2. Caries	0	No visible caries
	1	Caries contiguous with the margin of the restoration
3. Color Match	0	No mismatch in color, shade, or translucency between restoration and tooth structure
	1	Mismatch within the normal range of tooth
	2	Mismatch outside the normal range of tooth
	3	Esthetically displeasing color, shade, and translucency
4. Marginal Adaptation	0	Excellent continuity at resin – enamel interface; no ledge formation, no discoloration
	1	Slight discoloration at resin – enamel interface; ledge at interface
	2	Moderate discoloration at resin – enamel interface measuring 1 mm or greater
	3	Recurrent decay at margin
5. Polishability	0	Smooth and highly shiny, similar to enamel
	1	Smooth and satin, highly reflective
	2	Rough and shiny, satin, somewhat reflective
	3	Rough and dull or satin, not reflective
6. Surface Staining	0	Absent
	1	Present
7. Gingival Health	0	Excellent response, no inflammation
	1	Slight inflammation of gingival tissue
	2	Moderate to severe gingival inflammation
8. Proximal Contact Points	0	Present
	1	Absent
9. Fracture Resistance	0	No fracture of the restoration
	1	Small lines of the restoration
	2	Small chip (1/4 of restoration)
	3	Moderate chip (1/2 of restoration)
	4	Severe chip (3/4 of restoration)
	5	Loose restoration
10. Fracture Tooth	0	No fracture of the tooth
	1	Small lines in the tooth
	2	Small chip (1/4 of the crown)
	3	Moderate chip (1/2 of the crown)
	4	Fracture crown on cement-dentin junction
	5	Crown – root fracture
11. Wear Antagonist	0	No wear
	1	Wear
12. Wear Restoration	0	No wear
	1	Wear

Table 2. Scores and associated criteria assessed as failure

Category Modified USPHS	Score	Criterion
1. Adaptation of the restoration	3	Restoration is missing, traumatic occlusion or restoration cause pain in tooth or adjacent tissue
4. Marginal adaptation	3	Recurrent decay at margin
9. Fracture resistance	3	Moderate chip (1/2 of restoration)
9. Fracture resistance	4	Severe chip (3/4 of restoration)
9. Fracture resistance	5	Loss of restoration
10. Fracture tooth	3	Moderate chip (1/2 of the crown)
10. Fracture tooth	4	Fracture crown on cement-dentin junction
10. Fracture tooth	5	Crown-root fracture

additional 23 RBFDPs were lost to follow-up. The study population comprised 71 women and 37 men aged 16 to 75 years. The follow-up period ranged from 14 days to 111 months, with a mean of 32.45 months and a median of 25 months. The survival rate of the lithium disilicate RBFDPs was 100% in the absence of restoration, debonding, or repairs.

The computation of the annual incidence density with the corresponding 95% CI for each criterion of the modified USPHS assessment form across all 3 groups is shown in Table 3. For criterion 2, Caries and criterion 10, Tooth Fracture, no alterations were identified in any of the 3 groups, and the incidence density was set at 0.000 for these criteria. The 95% CI does not apply here.

The variation in incidence density per criterion of the modified USPHS assessment form among the 3 groups, along with the corresponding 95% CI is shown in Table 4. In the comparison between the BT and DPP groups, alterations were observed in criteria 5 and 9 in the BT group, while no alterations were observed in the DPP group. For criterion 5, the value 0 was not contained within the 95% CI, indicating a statistically significant difference for that criterion. For the remaining criteria, the value 0 fell within the computed 95% CI, indicating no statistically significant difference for these criteria.

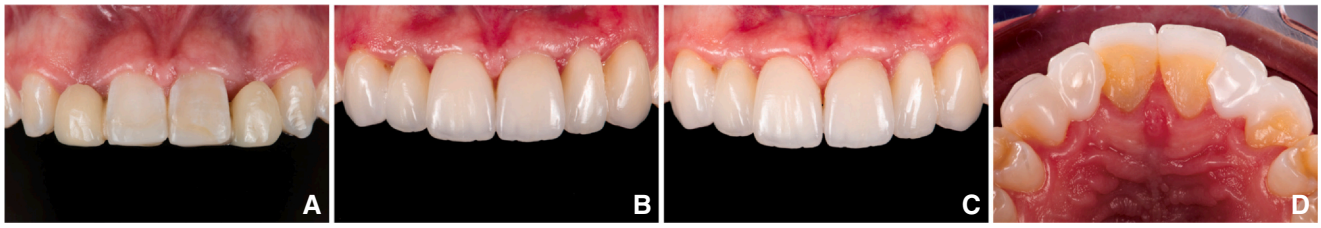

Figure 1. Lithium disilicate anterior cantilever RBFDPs (palatal wing and laminate veneer retainer) from canine to laterals (central incisor veneer). A, Initial situation. B, Restoration placement. C, D, Clinical assessment (32 months). RBFDP, resin-bonded fixed dental prosthesis.

Table 3. Incidence density per year for total population (*r*) with corresponding 95% CI

Category modified USPHS	(*a* / *N*) × 365	(*r*)	95% CI
1. Adaptation	(16/108 300) × 365	0.054	[0.033; 0.087]
2. Caries	(0/108 300) × 365	0.000	
3. Color match	(17/108 300) × 365	0.057	[0.036; 0.091]
4. Marginal adaptation	(12/108 300) × 365	0.040	[0.023; 0.070]
5. Polishability	(4/108 300) × 365	0.013	[0.005; 0.036]
6. Surface staining	(10/108 300) × 365	0.034	[0.018; 0.062]
7. Gingival health	(22/108 300) × 365	0.074	[0.050; 0.111]
8. Proximal contact points	(5/108 300) × 365	0.017	[0.007; 0.040]
9. Fracture resistance	(1/108 300) × 365	0.003	[0.000; 0.024]
10. Tooth fracture	(0/108 300) × 365	0.000	
11. Wear antagonist	(15/108 300) × 365	0.051	[0.031; 0.083]
12. Wear restoration	(9/108 300) × 365	0.030	[0.016; 0.058]

The comparison between the DPP and MH groups revealed no changes in criteria 2, 5, 9, and 10 between the 2 groups. However, changes were observed in the DPP group for criteria 3, 6, and 7, but not in the MH group. The value 0 does not fall within the 95% CI for criteria 1, 3, 4, 6, 7, and 11, indicating a statistically significant difference for these criteria. Conversely, for criteria 8 and 12, the value 0 falls within the calculated 95% CI, indicating no statistically significant difference.

Differences in incidence density between the BT and MH groups were observed, as criteria 3, 5, 6, 7, and 9 exhibited changes in the BT group that were not present in the MH group. For criteria 3, 5, 6, and 7, the difference was statistically significant, as the value 0 falls outside the 95% CI. Conversely, the difference in criteria 1, 4, 8, 9, 11, and 12 was not statistically significant.

DISCUSSION

In this retrospective study, the incidence density-based survival and success of RBFDPs were examined, and potential differences among RBFDPs placed by different operators were evaluated. As hypothesized, differences in the occurrence of changes among RBFDPs placed by different operators were observed. All 108 RBFDPs were assessed based on 12 criteria of the modified USPHS assessment form. Some changes were observed, but no restoration failure occurred. The survival rate of the lithium disilicate RBFDPs was 100% after a mean follow-up period of 32.45 months, up to a maximum of 111 months.

No changes were observed for criterion 2, Caries and criterion 10, Tooth Fracture across all groups. This finding was consistent with that of another clinical study on lithium disilicate cantilever RBFDPs in which no instances of secondary caries were observed after a mean observation period of 46.57 months.[29] The criterion of tooth fracture was not addressed in that study. However, in another study involving zirconia cantilever RBFDPs, a single occurrence of caries was observed, and no instances of tooth fracture were reported.[39] The total period at risk in the study was 61.8 months, and the survival rate was reported to be 91.1%.[39] However, it should be noted that the zirconia cantilever RBFDPs investigated in this study were not restricted to the maxillary anterior region. The restoration's location might impact the survival rate.[34]

The criteria with the highest incidence densities were criterion 7, Gingival Health (r=0.074) and criterion 3, Color Match (r=0.057). The changes noted in Gingival Health were characterized as inflammation of the surrounding gingiva according to the modified USPHS assessment form criteria. Previous studies that observed gingival inflammation around restorations reported compromised gingival health around restorations in most participants. However, no relationship between gingival inflammation and irritation from restorative materials was demonstrated.[40] In relation to criterion 3, Color Match, previous studies on lithium disilicate restorations indicated that, in

Table 4. Incidence density difference per year $(r)_{|BT-DPP|}$, $(r)_{|DPP-MH|}$, and $(r)_{|BT-MH|}$ between MH $(r)_{MH}$, BT $(r)_{BT}$, and DPP $(r)_{DPP}$ groups with corresponding 95% CI

Category modified USPHS	$(r)_{MH}$	$(r)_{BT}$	$(r)_{DPP}$	$(r)_{|BT-DPP|}$ [95% CI]		$(r)_{|DPP-MH|}$ [95% CI]		$(r)_{|BT-MH|}$ [95% CI]	
1. Adaptation	0.020	0.057	0.084	0.027	[−0.048; 0.101]	0.064	[0.003; 0.126]	0.037	[−0.019; 0.095]
2. Caries	0.000	0.000	0.000						
3. Color match	0.000	0.103	0.075	0.028	[−0.057; 0.113]	0.075	[0.023; 0.126]	0.103	[0.036; 0.170]
4. Marginal adaptation	0.010	0.034	0.075	0.041	[−0.024; 0.105]	0.065	[0.010; 0.120]	0.024	[−0.019; 0.068]
5. Polishability	0.000	0.046	0.000	0.046	[0.001; 0.091]			0.046	[0.001; 0.091]
6. Surface staining	0.000	0.069	0.037	0.032	[−0.035; 0.098]	0.037	[0.001; 0.074]	0.069	[0.014; 0.124]
7. Gingival health	0.000	0.115	0.112	0.003	[−0.093; 0.098]	0.112	[0.049; 0.175]	0.115	[0.044; 0.185]
8. Proximal contact points	0.020	0.023	0.009	0.014	[−0.023; 0.050]	0.011	[−0.022; 0.043]	0.003	[−0.038; 0.045]
9. Fracture resistance	0.000	0.011	0.000	0.011	[−0.011; 0.034]			0.011	[−0.011; 0.034]
10. Tooth fracture	0.000	0.000	0.000						
11. Wear antagonist	0.010	0.046	0.093	0.047	[−0.026; 0.121]	0.083	[0.023; 0.144]	0.036	[−0.013; 0.085]
12. Wear restoration	0.010	0.046	0.037	0.009	[−0.049; 0.066]	0.027	[−0.014; 0.069]	0.036	[−0.013; 0.085]

most situations, superficial discoloration was associated with calculus discolored by food or insufficient oral hygiene.[41,42] Moreover, another study investigating lithium disilicate restorations reported no significant alterations in color because of the restorative material.[43] In the present study, it was observed that in half of the situations where a change in Color Match was reported, a change in Gingival Health was also noted. These findings suggest that the discoloration and mild gingival inflammation in these RBFDPs might have been associated with poor oral hygiene.

In the comparison between the BT and DPP groups, a statistically significant difference was found only for criterion 5, Polishability. Significant differences were found between the DPP and MH groups for criteria 1, Adaptation, 3, Color Match, 4, Marginal Adaptation, 6, Surface Staining, 7, Gingival Health, and 11 'Wear Antagonist. The criteria 3, 5, 6, and 7 also significantly differed between the BT and MH groups. The causes of these differences among restorations were not identified. However, other studies on lithium disilicate restorations suggested that factors such as oral hygiene, evaluation of oral hygiene, and indication of additional dental cleanings may have an impact.[40–42,44] A recent study[34] examined 31 472 restorations from 11 different practices and practitioners and reported a significant discrepancy in the survival rates of restorations across the practices. Several significant factors that were reported to affect the differences in restoration survival rates included the operator's expertise, patient age, parafunctional habits, overall health status, periodontal health, susceptibility to caries, restoration location, and size of the restoration.

None of the RBFDPs in the present study failed. However, the restorations were evaluated after different follow-up intervals corresponding to different in situ or at-risk periods. Therefore, the evaluation period may not be sufficient for some restorations, and changes may occur in the future. Additionally, there may have been some variability among the independent and calibrated evaluators, which could have played a role.

Limitations of this retrospective study include the absence of a control group, impeding the ability to compare treatment outcomes with those of alternative approaches such as implant-supported FDPs or FDPs with complete coverage retainers. Additionally, influencing factors such as parafunctional habits, overall health, and susceptibility to caries were not recorded. Future studies should include a prospective design with a control group that incorporates patient characteristics such as age and parafunctional habits, as well as patient-reported outcomes to gain insights into patient satisfaction and quality of life.

CONCLUSIONS

Based on the findings of this patient-controlled multicenter study, the following conclusions were drawn:

1. Cantilever lithium disilicate RBFDPs were found to be suitable as a treatment option with high survival in the short term.
2. Although changes in success were observed during the follow-up, none of the evaluated restorations failed.
3. The incidence of changes varied among RBFDPs placed by different operators for the following criteria: Adaptation, Color Match, Marginal Adaptation, Polishability, Surface Staining, Gingival Health, and Wear Antagonist.

PATIENT CONSENT

Written informed consent was obtained from each participant before enrollment in the study.

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Joyce A. Jonker: Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **Gil Tirlet:** Conceptualization, Data curation, Investigation. **Alex Dagba:** Data curation. **Solène Marniquet:** Data curation. **Marinus Ouwerkerk:** Formal analysis, Investigation, Data curation, Writing - original draft. **Marco S. Cune:** review and editing. **Marco M. M. Gresnigt:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing - review and editing.

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