

RESEARCH AND EDUCATION

Bond strength comparison of chemically activated hard reline materials on CAD-CAM milled and conventional heat-polymerized PMMA denture bases



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ABSTRACT

Statement of problem. Comprehensive data are needed on the performance of chemically activated, chairside hard reline materials when used with computer-aided design and computer-aided manufacturing (CAD-CAM) milled polymethyl methacrylate (PMMA) denture bases and conventionally processed bases. This lack of data affects decisions regarding the chairside reline material to be used for improving the fit and retention of relined complete dentures.

Purpose. The purpose of this in vitro study was to evaluate and compare the shear bond strength (SBS) of 3 chemically activated, chairside hard reline materials on CAD-CAM milled and conventional heat-polymerized PMMA denture bases.

Material and methods. A total of 120 cylindrical specimens were prepared and divided into 2 groups: 60 specimens fabricated from CAD-CAM milled PMMA and 60 specimens fabricated from conventional heat-polymerized PMMA. Following thermocycling to simulate aging, the specimens were divided into 3 subgroups (n=20) and relined with 1 of 3 chemically activated reline materials: Ufi Gel, Rebase II, and Unifast. After 24 hours of storage at 37 °C, the SBS was determined using a universal testing machine. Adhesive, cohesive, and mixed failures were examined using a stereomicroscope and scanning electron microscope (SEM). Statistical analysis was conducted using the generalized linear model (GLM) with post hoc comparisons using the Holm-Bonferroni correction. Chi-squared tests evaluated failure mode differences, and Weibull analysis determined bond strength reliability ($\alpha=.05$).

Results. Ufi Gel and Unifast exhibited significantly higher SBS on CAD-CAM milled PMMA than conventional heat-polymerized PMMA ($P<.001$). Rebase II also showed a significant difference between both denture base types ($P=.001$), but its overall SBS was lower. Ufi Gel achieved the highest SBS, while Rebase II had the lowest across both denture base types. Weibull analysis revealed that CAD-CAM milled PMMA with Ufi Gel had the highest bond strength and reliability. Conversely, conventional heat-polymerized PMMA with Rebase II had the weakest performance, marked by the lowest bond strength and increasing failure rates. SEM analysis showed more cohesive and mixed failures with CAD-CAM milled PMMA, while adhesive failures were more prevalent in conventional heat-polymerized PMMA. No significant difference in failure types was observed between the 2 denture base materials ($P=.079$).

Conclusions. This study demonstrated that CAD-CAM milled PMMA provided better bond strength and reliability compared with conventionally processed PMMA, particularly when combined with Ufi Gel. Ufi Gel exhibited the highest bond strength and reliability, making it suitable for long-term clinical use. Unifast also performed well but had slightly lower bond strength, while Rebase II showed the weakest bond strength and more adhesive failures, indicating limited durability. These findings emphasize the importance of selecting effective reline materials to enhance denture retention, patient satisfaction, and longevity. (J Prosthet Dent 2025;133:889.e1-e9)

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Clinical Implications

Reline materials tested in this study demonstrated different bond strengths and reliability, with CAD-CAM milled PMMA generally providing better performance than conventional heat-polymerized PMMA. Clinicians should consider bond strength and failure resistance when selecting relining materials to enhance denture retention, patient satisfaction, and overall clinical outcomes.

The use of computer-aided design and computer-aided manufacturing (CAD-CAM) technology in denture manufacturing processes has expanded significantly,¹ enabling the milling of dentures from prepolymerized acrylic resin blocks fabricated using high-pressure and high-temperature procedures.^{1,2} CAD-CAM milled polymethyl methacrylate (PMMA) offers advantages, including reduced residual monomer,^{3–7} decreased porosity,^{8,9} diminished plaque accumulation,^{10–12} and improved surface quality.^{13–16} CAD-CAM technology has emerged as a compelling alternative to conventional heat-polymerized PMMA, providing benefits such as reduced treatment time, enhanced denture fit, reproducibility, and a streamlined workflow with fewer potential manufacturing errors.^{17–19} Additionally, improved mechanical properties^{18,20} and better adaptation with CAD-CAM milled PMMA dentures compared with conventional heat-polymerized PMMA dentures have been reported.^{4,21}

One of the clinical challenges with complete dentures is the loss of retention caused by alveolar bone resorption and changes in underlying mucosal tissues.^{22,23} A suitable solution is to relining the denture base with a hard relining material,^{22,24} providing a cost-effective and timely way of enhancing denture retention.^{25–27} The chairside hard relining technique is particularly effective in improving denture fit and retention, making it an efficient option.^{25,26} Chemically activated hard relining materials, which typically contain methyl methacrylate (MMA) such as Unifast Trad have been widely used due to their strong adhesion to denture bases.^{28–30} However, MMA resins can have unpleasant odors, cause soft tissue irritation, and have an elevated polymerization temperature.^{31,32} To address these concerns, non-MMA resins such as Rebase II and Ufi Gel have been introduced, offering lower polymerization temperatures and reduced soft tissue irritation, making them suitable for chairside hard relining procedures.^{27,33} However, their adhesion to PMMA denture bases may be lower than that of MMA-based materials, possibly associated with their chemical composition, which can affect relining effectiveness.^{34,35} Comparable shear bond strength (SBS) between CAD-CAM milled and conventional heat-polymerized PMMA denture bases has been reported.^{36,37} However, other

studies have reported either greater or lower SBS with CAD-CAM milled PMMA denture bases, indicating variability in outcomes.^{3,38}

Given the frequent use of MMA and non-MMA chemically activated, hard relining materials for chairside relines, comprehensive data are needed on their attachment to both CAD-CAM milled and conventional heat-polymerized PMMA denture bases. This study aimed to compare the SBS of 3 chemically activated, chairside hard relining materials on these 2 types of PMMA denture bases. The null hypothesis was that no significant difference would be found in the SBS among the materials tested.

MATERIAL AND METHODS

A pilot study with 30 specimens, divided equally between CAD-CAM milled and conventional heat-polymerized PMMA denture bases, was conducted to estimate the study's sample and effect sizes. Each specimen was tested for SBS using the same protocols as described in this study, including thermocycling, yielding an effect size of $f=0.312$, calculated using a software program (G*Power version 3.1.9.4; Heinrich Heine University), resulting in a minimum requirement of 111 specimens for an 80% power with $\alpha=.05$. To enhance statistical power, the final sample size was increased to 120 specimens, with 20 specimens per subgroup. As the pilot results aligned with the initial assumptions, no significant modifications were made to the study design or methodology. The experimental workflow is illustrated in [Figure 1](#).

A total of 120 cylindrical specimens were fabricated and divided into 2 groups. The first group consisted of 60 specimens made from heat-polymerized PMMA (Vertex Rapid Simplified; Vertex Dental BV), which were processed using a compression molding technique. The second group consisted of 60 specimens made from CAD-CAM milled PMMA (Ivotion Base; Ivoclar AG) using a laboratory milling unit (PrograMill PM7; Ivoclar AG) ([Table 1](#)).

Each specimen was prepared in a $\varnothing 8 \times 4$ -mm custom cylindrical mold ([Fig. 2A](#)). For the conventional heat-polymerized PMMA group, the acrylic resin mixture was prepared at a 2.3 g powder to 1 mL liquid ratio by following the manufacturer's recommendations. The mixture was then poured into the custom cylindrical mold and invested in dental stone (Elite Base; Zhermack) using a dental flask (Hanau Flask Compress; Whip Mix Corp). The flask was placed under a bench press for 10 minutes to remove excess acrylic resin, followed by polymerization in a water bath (Wapo-Mat III; Wassermann) at 100 °C for 20 minutes. After a 30-minute cool-down to room temperature, the resin was removed

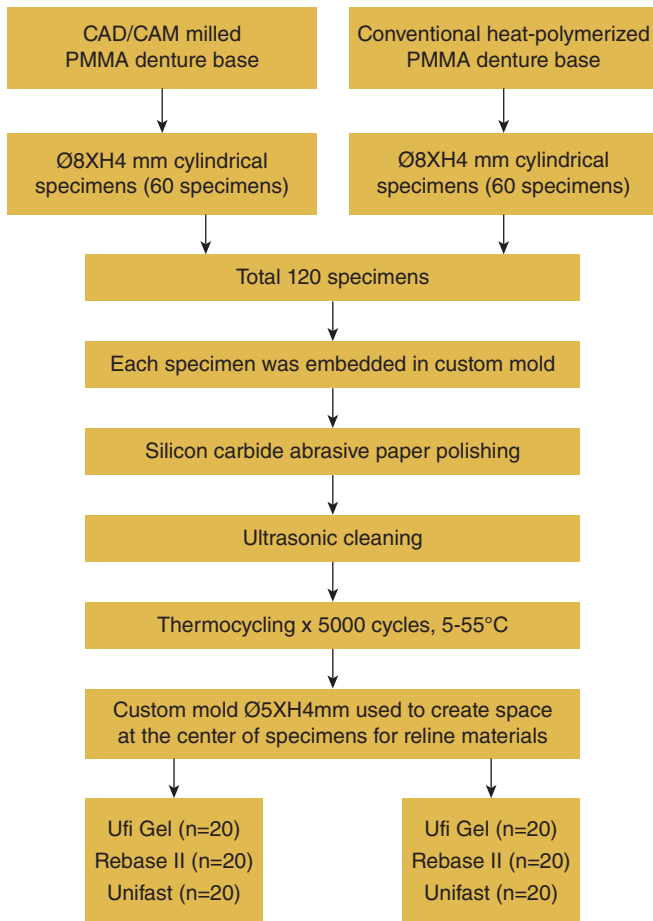


Figure 1. Experimental workflow for evaluating shear bond strength of reline materials on CAD-CAM milled and conventional heat-polymerized PMMA denture bases. CAD-CAM, computer-aided design and computer-aided manufacturing; PMMA, polymethyl methacrylate.

from the flask. All specimens were then embedded in clear, chemically activated MMA resin (Meliodent; Kulzer GmbH) in Ø20×30-mm polyvinyl chloride tubes (PVC tube; Pipe Industry Co), positioned perpendicularly, and centered with a custom positioning device (Fig. 2B). The specimens were inspected to ensure that

they met size specifications and that they were free from voids or fractures.

The specimens were polished using a precision polishing machine (Machine-Nano2000; PACE Technologies) with 600-grit silicon carbide paper (SiC Grinding Paper; Buehler) at 200 rpm to produce a smooth and uniform surface.³⁹ After polishing, the specimens were ultrasonically cleaned in distilled water (VGT-1990QTD; Comcube) at 40 kHz and 25 °C for 10 minutes.³⁹ Subsequently, the specimens were thermocycled (Thermocycler THE 1400; SD Mechatronik) from 5 to 55 °C with 30 seconds dwell time for 5000 cycles, simulating 6 months of denture aging.^{39,40}

After thermocycling, the specimens were divided equally into 3 subgroups (n=20) of 1 of 3 chemically activated hard reline materials (Table 1): Unifast (Unifast Trad; GC Corp), Rebase II (Rebase II; Tokuyama Dental Corp), and Ufi Gel (Ufi Gel; VOCO). A custom stainless-steel split mold along with a corresponding ring-shaped tape was placed on each specimen to create a 5-mm-cylindrical space at the center (Fig. 3).²⁷ The reline materials were prepared according to the manufacturer’s recommendations (Table 1) and applied to the mold space. The specimens were then polymerized by placing a glass slide (Microscope slide 7101; Sail CO) and a 1000-g steel pendulum (1000 G Standard weight F1; JP electronics scale)^{3,37} on top of the mold until polymerization was complete.^{3,37} All specimens were stored in distilled water at 37 °C for 24 hours by following the International Organization for Standardization (ISO) specification 11405:2003 guidelines.⁴¹

The SBS testing was conducted using a universal testing machine (EZ-S; Shimadzu) at a crosshead speed of 0.5 mm/minute.²⁷ A compressive load was applied using a knife-edged blade parallel to the base and reline interface (Fig. 4). SBS was calculated by dividing the failure force by the adhesion surface area ($F=N/A$), where F is SBS (MPa), N is the maximum force exerted on the specimen (N), and A is the bonding area (mm²).

Debonded surfaces were inspected using a stereomicroscope (SZ 61; Olympus) at ×30 magnification and

Table 1. Specifications of denture base resins and hard reline materials used

Denture Bases	Processing Procedure	Specimens	Lot no.			
			Powder	Liquid	Adhesive	
Ivotion Base Disc Pink	CAD-CAM milling process	60	YB3KD7			
Vertex Rapid Simplified	Compression-molding technique. Heat processed at 100 °C, 20 min	60	WX161P02			
Reline materials	Lot no.		Composition			
			Powder	Liquid	Adhesive	Direction for use
Ufi Gel	2213589		PEMA	1,6-HDMA	Acetone, 2-HEMA	Apply adhesive and air-dry for 30 s. Then apply mixed resin onto surface.
Rebase II	068ZE0		PEMA	AAEMA, 1,9-NDMA	Ethyl-acetate Acetone	Apply adhesive and leave for 20 s. Then apply mixed resin onto surface
Unifast	L2110061,P2106171		PMMA	MMA	-	Apply mixed resin to surface directly

1,6-HDMA, 1,6-hexanediol dimethacrylate; 1,9-NDMA, 1,9-nonanediol dimethacrylate; 2-HEMA, 2-hydroxyethyl methacrylate; AAEMA, acetooxyethyl methacrylate; CAD-CAM, computer-aided design and computer-aided manufacturing; HEMA, hydroxyethyl methacrylate; MMA, methyl methacrylate; PEMA, polyethyl methacrylate; PMMA, polymethyl methacrylate.

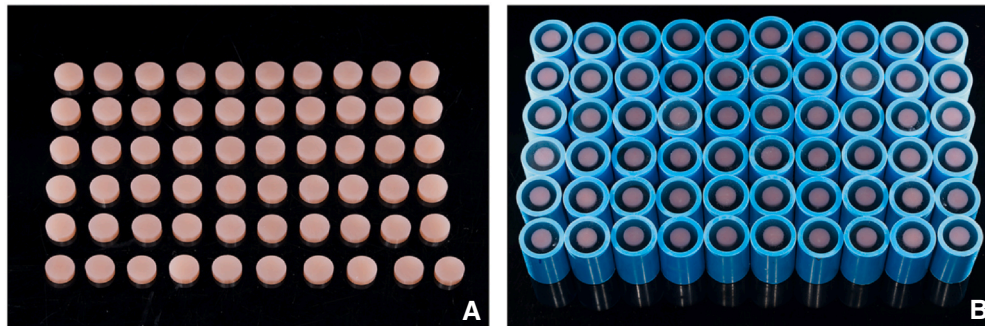


Figure 2. Specimen preparation. A, 60 Cylindrical CAD-CAM milled PMMA specimens. B, CAD-CAM milled PMMA specimens embedded in custom resin molds. CAD-CAM, computer-aided design and computer-aided manufacturing; PMMA, polymethyl methacrylate.



Figure 3. Application of chemically activated chairside hard reline material on CAD-CAM milled PMMA specimen. CAD-CAM, computer-aided design and computer-aided manufacturing; PMMA, polymethyl methacrylate.



Figure 4. Specimen mounted in universal testing machine for shear bond strength testing.

further examined with a scanning electron microscope (SEM) (Quanta 250; FEI Co.) at 10 kV and $\times 100$ magnification to evaluate the bonded interface.⁴² Adhesive failures were recorded when the fracture occurred at the interface between the reline material and the denture base, indicating bond failure. Cohesive failures were noted when the fracture occurred within the reline

material or denture base, indicating material failure. Mixed failures were identified when the fracture occurred both at the bonded interface and within the reline material or denture base, indicating a combination of adhesive and cohesive failures.

Data were analyzed using the generalized linear model (GLM) with a gamma distribution and log link function to account for the nonnormal distribution and heteroscedasticity of the SBS data, confirmed through the Shapiro-Wilk test ($P=.003$) and Levene test ($P=.005$). The GLM was used to evaluate the effects of reline materials, denture base materials, and their interaction on SBS. Post hoc pairwise comparisons were conducted using the Holm-Bonferroni correction to control for Type I error inflation. Failure types were analyzed using a chi-squared test to determine significant differences in failure modes across groups. Additionally, Weibull analysis was conducted to determine the characteristic bond strength and failure reliability of the material combinations. All statistical analyses were performed using statistical software programs (R Statistics version 4.3.3; The R Project for Statistical Computing, Python version 3.9.13; Python Software Foundation) ($\alpha=.05$ for all tests).

RESULTS

Significant differences in SBS were observed among the 3 chemically activated hard reline materials on both CAD-CAM milled and conventional heat-polymerized PMMA denture bases ($P=.002$) (Table 2). Comparisons of mean SBS and standard deviation for each reline

Table 2. Results of generalized linear model (GLM) evaluating effects of reline materials, denture base materials, and their interaction on shear bond strength

	X ²	df	P
Reline materials	124.1	2	<.001
Denture base materials	89.3	1	<.001
Reline materials×Denture base materials	12.1	2	.002

Table 3. Mean, standard deviation, and post hoc pairwise comparisons using Holm-Bonferroni correction for each reline material across both denture base types

Reline Materials	Shear Bond Strength (Mean ±SD) (MPa)		P
	CAD-CAM Milled PMMA	Conventional Heat-polymerized PMMA	
Ufi Gel	11.40 ±2.34	8.31 ±2.13	<.001
Rebase II	6.26 ±1.20	4.75 ±1.24	.001
Unifast	10.10 ±2.29	5.52 ±1.35	<.001
P	<.001	<.001	

CAD-CAM, computer-aided design and computer-aided manufacturing; PMMA, polymethyl methacrylate; SD, standard deviation.

material across both types of denture bases are shown in Table 3. Ufi Gel and Unifast exhibited significantly higher SBS on CAD-CAM milled PMMA compared with conventional heat-polymerized PMMA ($P<.001$), while Rebase II also demonstrated a significant difference ($P=.001$) but had overall lower SBS than Ufi Gel and Unifast. Ufi Gel had the highest mean SBS for both CAD-CAM milled PMMA (11.40 ±2.34 MPa) and conventional heat-polymerized PMMA (8.31 ±2.13 MPa) denture bases. In contrast, Rebase II had the lowest mean SBS for both CAD-CAM milled PMMA (6.20 ±1.20 MPa) and conventional heat-polymerized PMMA (4.75 ±1.24 MPa) denture bases.

Comparing different hard reline materials on CAD-CAM milled PMMA (Table 4), Ufi Gel had significantly higher SBS than Rebase II ($P<.001$). Similarly, Unifast exhibited significantly higher SBS than Rebase II ($P<.001$). While Ufi Gel showed higher SBS than Unifast, this difference was not statistically significant ($P=.176$). For conventional heat-polymerized PMMA (Table 4), Ufi

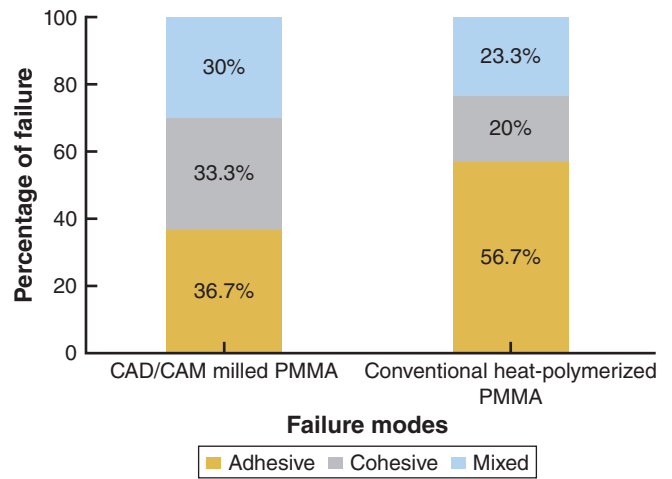


Figure 6. Distribution of failure modes between reline materials and denture bases: CAD-CAM milled PMMA versus conventional heat-polymerized PMMA. CAD-CAM, computer-aided design and computer-aided manufacturing; PMMA, polymethyl methacrylate.

Gel exhibited significantly higher SBS than both Rebase II ($P<.001$) and Unifast ($P<.001$). Although Unifast had a higher SBS compared with Rebase II, the difference was not statistically significant ($P=.127$).

The SEM analysis of fractured surfaces revealed various failure types (Fig. 5). Adhesive failures were found more frequently with conventional heat-polymerized PMMA (56.7%) compared with the CAD-CAM milled PMMA (36.7%) (Fig. 6). Cohesive and mixed failures were more commonly observed with CAD-CAM milled PMMA (33.3% and 30.0%, respectively) compared with the conventional heat-polymerized PMMA

Table 4. Post hoc pairwise comparisons using Holm-Bonferroni correction for reline materials within denture base materials

Denture Base Materials	Reline Materials	Mean Diff	SE	95% Confidence Intervals		P
				Lower	Upper	
CAD-CAM milled PMMA	Rebase II-Ufi Gel	0.548	0.04	0.468	0.627	<.001
	Rebase II-Unifast	0.617	0.04	0.528	0.707	<.001
	Ufi Gel-Unifast	1.127	0.08	0.963	1.291	.176
Conventional heat-polymerized PMMA	Rebase II-Ufi Gel	0.571	0.04	0.488	0.654	<.001
	Rebase II-Unifast	0.860	0.06	0.735	0.985	.127
	Ufi Gel-Unifast	1.506	0.11	1.288	1.725	<.001

CAD-CAM, computer-aided design and computer-aided manufacturing; PMMA, polymethyl methacrylate; SE, standard error.

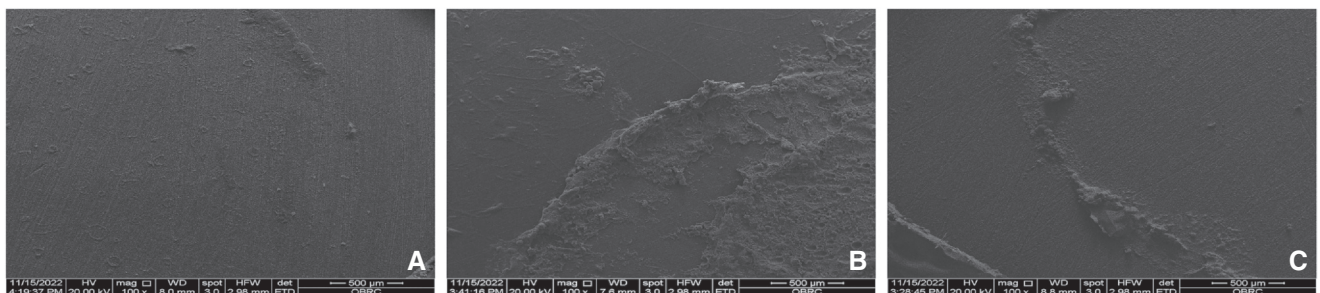


Figure 5. Scanning electron microscope images at bonding interface on CAD-CAM milled PMMA denture base at ×100 magnification. A, Adhesive failure. B, Cohesive failure. C, Mixed failure. CAD-CAM, computer-aided design and computer-aided manufacturing; PMMA, polymethyl methacrylate.

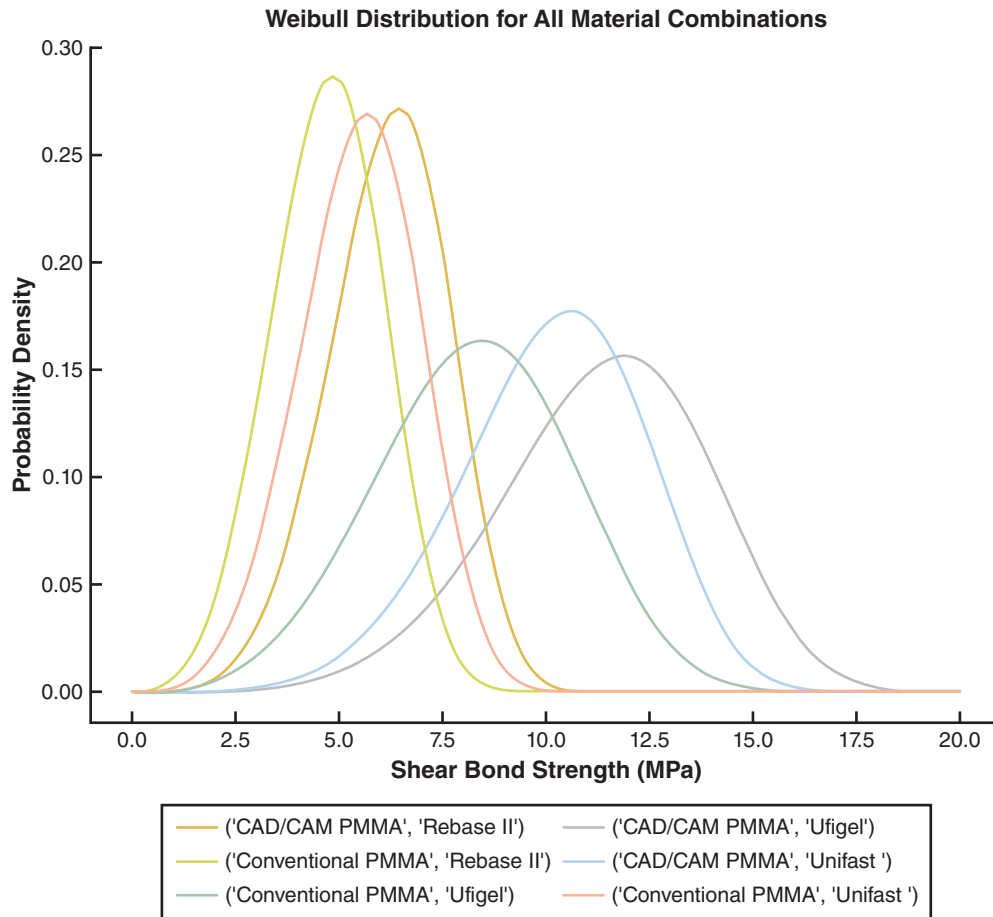


Figure 7. Weibull analysis assessed failure reliability and characteristic bond strength for all different denture base and reline material combinations.

(20.0% and 23.3%, respectively) (Fig. 6). No statistically significant difference in failure types was found between the types of denture base materials ($P=.079$). Weibull analysis revealed that CAD-CAM milled PMMA combined with Ufi Gel had the highest bond strength, with a slower increase in failure probability as bond strength increased, indicating greater reliability. In contrast, conventional heat-polymerized PMMA combined with Rebase II had the weakest performance, characterized by a lower bond strength and a moderately increasing failure rate (Fig. 7).

DISCUSSION

The 3 chemically activated chairside hard reline materials were selected for study because of their prevalent use. Variations in their chemical compositions and adhesive properties influenced the overall bond strength to denture bases. The null hypothesis that no significant difference would be found in the SBS among the materials tested was rejected, as significant differences in SBS were observed among the 3 reline materials in both types of denture bases ($P=.002$). Ufi Gel and Unifast had

significantly higher SBS on CAD-CAM milled PMMA compared with conventional heat-polymerized PMMA ($P<.001$). Similarly, Rebase II also had higher SBS on CAD-CAM milled PMMA compared with conventional PMMA ($P=.001$). These findings were consistent with those of previous studies which reported that SBS is typically higher in CAD-CAM milled PMMA than in heat-polymerized PMMA when bonded to chemically activated hard reline materials after thermocycling.^{3,38}

Several factors may have contributed to the differences in the SBS between the types of denture bases in this study. First, the CAD-CAM milling process used prefabricated PMMA resin blocks, which exhibit superior mechanical and physical properties,⁷⁻⁹ including reduced residual monomer release,³⁻⁷ lower porosity,^{8,9} stronger cross linkage between polymer chains,^{9,12} and decreased water absorption compared with conventional heat-polymerized PMMA.^{5,6,10,11,24} Consequently, CAD-CAM milled PMMA demonstrated greater bond stability during thermocycling, attributed to its lower water absorption,^{3,9} which led to higher bond strength and better durability over time.^{3,38} Heat-polymerized PMMA denture bases have been reported to release residual monomer into water and tend to absorb water

during thermocycling.^{5,32,33,40} The absorbed water molecules in the resin polymer network act as plasticizers, softening the resin and increasing its elasticity, ultimately weakening the bond.^{10,11,32,33} Variations in the coefficient of thermal expansion (CTE) among denture base resins during thermocycling may also cause differential shrinkage and expansion, leading to cyclic stress at the bonded interface and further decreased bond strength.^{11,12}

The ability of the reline material to penetrate the denture base is another key factor that may affect bond strength and is influenced by the molecular size of the solvent in the reline material.⁴³ During relining, monomers penetrate the PMMA surface and polymerize to form an interpenetrating polymer network that ensures a durable bond.^{37,43} In this study, Ufi Gel, a non-MMA reline material, had the highest SBS. This result is likely because of its low molecular weight monomers and adhesives like 1,6-hexanediol dimethacrylate (1,6-HDMA), acetone, and 2-hydroxyethyl methacrylate (2-HEMA).^{35,44} Acetone and HEMA have been reported to improve adhesion through enhanced surface wetting and penetration, resulting in better bond formation.^{34,45} Conversely, Rebase II, despite being a non-MMA material, had the lowest bond strength and significantly lower SBS compared with Ufi Gel and Unifast, likely because of its high molecular weight monomers like acetoacetoxyethyl methacrylate (AAEMA) and 1,9-nonanediol dimethacrylate (1,9-NDMA), which may have impeded penetration and bond formation.^{35,44} Osathananda et al³⁵ reported that low molecular weight monomers promote better diffusion and penetration of reline materials into the denture base, enhancing bond strength through surface swelling and pore formation.

Bond strength is also influenced by the chemical composition, the adhesive properties of the reline materials, and the surface treatments applied.^{25,26} Because of their similar chemical properties, reline materials containing MMA generally exhibit better adhesion to PMMA denture bases compared with non-MMA materials.^{25,29} However, these studies did not account for thermocycling. In the present study, Unifast, an MMA material, had significantly lower SBS compared with Ufi Gel when bonded to heat-polymerized PMMA denture bases ($P < .001$). This reduced bond strength may result from increased water absorption and residual monomer release during thermocycling, weakening the bonded interface over time.^{10,11,32,33} Another contributing factor is the absence of adhesive components in Unifast, unlike Ufi Gel, which likely limited wetting, penetration, and bond formation.^{46,47} Adhesive components in Ufi Gel, like 2-HEMA, enhanced surface adaptation and chemical bonding by forming a stable interpenetrating polymer network, improving long-term bond durability, especially after thermocycling.^{35,45} Surface treatments,

such as airborne-particle abrasion or applying a monomer for 180 seconds before relining, have been reported to enhance bond strength by improving the surface morphology, increasing surface roughness, and micromechanical retention, which facilitates better bonding.^{33,45} However, surface treatments were not tested in this study to adhere to the manufacturer's recommendations and to avoid introducing additional variables that could have affected the bond strength outcomes. Further research is needed to explore how such treatments could impact the bond strength of different reline materials.

Failure types were analyzed using the SEM. In this study, although no significant differences in failure types were observed between the 2 types of denture bases ($P = .079$), CAD-CAM milled PMMA denture bases showed a higher frequency of cohesive and mixed failures, suggesting stronger internal bonding. In contrast, adhesive failures were predominantly observed with conventional heat-polymerized PMMA denture bases, indicating a weaker bond at the bonded interface. Weibull analysis further supported these observations, revealing that CAD-CAM milled PMMA combined with Ufi Gel not only had the highest characteristic bond strength but also demonstrated lower failure probability, indicating greater reliability. Conversely, Rebase II with conventional PMMA had lower bond strength and higher failure rates, identifying potential limitations in clinical durability. These findings underscore that bond strength and failure reliability should be considered when selecting reline materials for effective long-term outcomes.

Limitations of this study included that it simulated only 6 months of denture aging, which may not fully reflect the long-term impact on denture bases seen with extended use, potentially affecting bond strength. Moreover, it tested just 1 type of CAD-CAM milled PMMA and heat-polymerized PMMA resin along with a limited selection of reline materials. Future research should evaluate a wider range of materials and longer usage periods to gain a more comprehensive understanding of their performance and ensure optimal clinical outcomes.

CONCLUSIONS

Based on the findings of this in vitro study, the following conclusions were drawn:

1. CAD-CAM milled PMMA, especially when used with reline materials, provided better bonding and failure reliability compared with conventional heat-polymerized PMMA.
2. Among the tested materials, Ufi Gel had the highest bond strength and reliability for long-term

clinical success, with more cohesive and mixed failures, indicating stronger internal bonding. Unifast, while also effective, had slightly lower bond strength and a similar failure pattern.

- In contrast, Rebase II consistently had the weakest bond strength and a higher rate of adhesive failures, suggesting limitations in achieving durable relining outcomes.
- These findings emphasized the importance of selecting the appropriate relining materials for chairside relining procedures, as this choice significantly impacts denture retention, patient satisfaction, and clinical longevity.

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