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Implication of Laboratory Findings in Clinical Protocols for CAD-CAM Blocks Adhesion

Denis Bassi Lopes

Dissertação conducente ao Grau de Mestre em Medicina Dentária (Ciclo Integrado)

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Trabalho realizado sob a orientação de Prof. Dra. Maria João Calheiros-Lobo

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À minha amada esposa Sheila, companheira de uma vida toda, que jamais mediu esforços para me ajudar a superar cada obstáculo não importando a dificuldade. Sem ti nada disto seria possível, jamais poderei retribuir o suficiente.

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RESUMO

Introdução: Espera-se que protocolos que conseguem bons resultados nos testes laboratoriais *in vitro*, relativamente à adesão dos blocos CAD-CAM, provoquem impacto nos protocolos clínicos do profissional médico dentista no tratamento de seus pacientes, sempre que tais protocolos sejam aplicáveis à rotina clínica.

Objetivo: Analisar as implicações dos achados laboratoriais obtidos *in vitro* nos protocolos clínicos *in vivo* para a adesão eficiente de blocos de CAD-CAM, pela realização de uma revisão sistemática integrativa.

Materiais e Método: A pesquisa foi realizada nos bancos de dados PUBMED, EbscoHost e ScienceDirect, pela combinação dos termos na fórmula de busca [(CAD/CAM) E (adesivo OU adesão OU colagem OU cimentação) E (cerâmica OU bloco) E protocolo] publicados em inglês, com texto integral disponível e entre 01jan2015 e 31jul2021.

Resultados:

A pesquisa recuperou 508 artigos, mas apenas 39 foram selecionados de acordo com os critérios de inclusão, 37 estudos laboratoriais e 2 casos clínicos. Vita Enamic® (VITA) e IPS e.max® (Ivoclar) são os blocos CAD-CAM mais usados. Rely X® Ultimate Dual (3M) foi a resina de cimentação mais usada, e μSBS o teste de força adesiva mais usado.

Conclusões: Embora tenhamos padrões precisos de testes in vitro individuais, é necessário um maior nível de padronização entre os pesquisadores, a fim de promover maior fidelidade na reprodução de protocolos na prática cotidiana.

PALAVRAS-CHAVE: CAD/CAM, cerâmicas, blocos, adesão, cimentação, protocolo

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ABSTRACT

Introduction: It is expected that protocols that achieve good result in laboratory research *in vitro*, in relation to the adhesion protocols for CAD-CAM blocks, will have an impact on the clinical protocols of the dental professional in the treatment of their patients, whenever such protocols are applicable to the clinical routine.

Objective: To smooth out the implications of laboratory findings obtained in vitro in clinical protocols for efficient involvement of CAD-CAM blocks by conducting an integrative systematic review.

Materials and Method: The search was carried out in Pubmed, EbscoHost and ScienceDirect databases, by combining the terms in the search form[(CAD-CAM) AND (adhesive OR adhesion OR bonding OR cementation) AND (ceramics OR blocks) AND protocol], published in English, with full text available and between 01jan2015 and 31jul2021.

Results: The search retrieved 508 articles, but only 39 were selected according to the inclusion criteria, 37 laboratory studies and 2 clinical reports. Vita Enamic® (VITA) and IPS e. max® (Ivoclar) are the most used CAD-CAM blocks. Rely X® Ultimate Dual (3M) was the most used luting cement, and μSBS the most used bonding strength test.

Conclusions: Even though we have accurate standards of individual in vitro tests, a greater level of standardization among researchers is needed to promote greater fidelity in reproducing protocols in daily practice.

KEYWORDS: CAD-CAM, ceramics, blocks, adhesion, bonding, protocol

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ABBREVIATIONS AND ACRONYMS

µSBS – Micro shear bond strength
µTBS – Micro tensile bond strength
3D – Three-dimensional
CAD-CAM – Computer-aided design-Computer-aided manufacturing
d – days
h – hours
HF – Hydrofluoric acid
HSREB – Research Ethics Board for Health Sciences Research Involving Human Subjects
HV – Vickers Hardness
ISO – International Organization for Standardization
m – months
Mpa – megapascal unit
mV/cm² – millivolt per square centimetre
MZ – Monolithic zirconia materials
RCBs – Resin composite blocks
s – seconds

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1. INTRODUCTION

Computerized technologies such as Computer-aided design-Computer-aided manufacturing (CAD-CAM) are becoming a common practice in restorative dentistry nowadays, facilitating the manufacturing process of highly aesthetic indirect restorations.[1-5]

It allows 3D modelling, chair side milling of restorations[6] and single visit[1] restorations can be made with an excellent fit and mechanical properties.[7] CAM restorations are fabricated by industrial standardized methods, while laboratory-handmade restorations are fabricated and processed in dependence of the operator, what can cause a high level of variations. Comparing each other, the quality, the bond strength and the clinical longevity of these CAD-CAM restorations seem to have been increased over the years, having today in most of the cases a better performance.[8]

CAD-CAM blocks used for fabrication of indirect aesthetic restorations are mainly ceramics or composites.[1,6] Ceramics have long been the material of choice due to exceptional aesthetics, biocompatibility and high strength. However, conventional all-ceramics restorations are laborious to be fabricated and repaired, and suspicious of causing excessive wear of the opposing teeth. The continuous improvement of resin composites and adhesive dentistry led to the development of resin composite blocks (RCBs). The major advantages of RCBs compared to ceramics are easier fabrication, favourable properties as lower hardness and elastic modulus, and the possibility of direct intraoral fixing.[7]

Other materials have been developed using CAD-CAM technology with no need for additional aesthetic porcelain coating, such as monolithic zirconia materials (MZ).[9,10] These materials allow the offer of crowns with minimal thicknesses, 0.5 mm or even less, due to its hight degree of hardness (1387 HV). *In vitro* studies have shown that MZ crowns cause less wear damage to the antagonist tooth than older ceramic or ceramic-metallic restauration. However, worth mentioning that comparations between those studies cannot be reliable because the materials in question had different surface finishing and the methods to analyse the wear were different. Additionally, intraoral wear is a complex phenomenon that cannot be simulated easily in vitro, and the location of the restauration and the degree of parafunction habits can vary among patients.[10]

Composite resin bonding is an important step in the process of delivering indirect restorations, both ceramics or composites, that rely on adhesion and have direct effect in their longevity,[6] especially if it is needed to improve of the mechanical properties of the tooth-prothesis complex.[2] Successful adhesive bonding depends on the bond strength between the restoration and the material and may increase the intrinsic fracture resistance of each kind of material. Catastrophic, partial or chipping fractures are the most common failures found in the mouth due to function.[1,11] High retention, prevention of microleakage, and enhancement of marginal adaptation are the characteristics of a resilient and durable adhesive bond.[6] Recent bets on chemical modification of cementing resins with, for example, the introduction of antibacterial agents and multifunctional monomers, improved the adhesives bond strength to dentin, enhancing their long-term performance and protecting the toot-adhesive interface from microleakage.[3]

The literature is unclear regarding the surface treatment of the adhesive joint substrates, best luting cement, ceramic and dentine bonding agent to produce the highest bond strength, and a huge number of studies have been carried out, but still there is no consensus regarding the optimal protocol. [8,12] Resin composite, as a cement have been used for their advantageous mechanical and adhesive properties, in conventional metal crowns, fixed partial dentures, ceramic crowns and veneers, but also to repair fractured metal-ceramic, all-ceramics and composite restorations as a restorative material. Bond strength to ceramic material is influenced by the composition of the ceramic substrate and by mechanical and chemical interaction between substrate and the bonding agent.[8] The surface treatment method choice is important for the clinical utility of ceramic restorations and the selection of this method is dependent on the chemical and physical properties of the material.[13]

Mechanical and chemical mechanism of bonding are employed to enhance resin cement/glass-ceramic bonding, and silane can provide chemical adhesion to silica-containing ceramic substrates and acid etchants as hydrofluoric acid can dissolve part of the glassy phase facilitating mechanical interlocking with the resin cement.[13] Currently, combination of mechanical and chemical strategies is the most accepted procedure for enhancing resin cement/glass-ceramic bonding.[14] Nevertheless, in what concerns MZ, the consensus is not yet established.[13,15]

Various studies evaluated the effect of different pre-treatments on adhesion between restorative materials and dentin in laboratory studies,[2,8] but they have limitations in terms of clinical use. The large number of tested techniques are usually hardly comparable in the literature.[2]

Various factors can influence the quality of the bond, such as the intrinsic composition of the restorative material and luting agents, the type of surface treatment, and the physics characteristics of the mechanism of adhesion.[13,16]

For the clinician, the selection of the ideal surface treatment protocol and adequate luting agent for each material should be a major concern as it influences the long-term success of the restoration, technically conditioning the adhesion between indirect restorations and tooth.

2. OBJECTIVES

The aim of this integrative systematic review was to analyse the implications of laboratory findings obtained *in vitro* into the clinical protocols. Secondarily, we aimed to evaluate the *in vivo* efficacy of the adhesion of CAD-CAM blocks reported in the literature.

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3. MATERIALS AND METHOD

A bibliographic search was carried out in the databases PubMed, Sciencedirect and EBSCOhost, with the Keywords: "Adhesion"; "Adhesive"; "Protocol"; "System"; "Bonding"; "CAD". The search expression used was: (Adhesion OR Adhesive) AND (Protocol OR System) AND (Bonding) AND (CAD).

For inclusion the criteria were articles in English language, research papers, randomized clinical trials or clinical cases that addressed the theme of the study, publication in the last 6 years (01Jan2015 – 01Jul2021) and articles with accessible full-text. Systematic reviews, reviews, duplicated papers and papers published before 2015, were exclusion criteria. With this method of searching, a total of 508 articles were selected, and then a preliminary assessment of the work was carried out. 199 duplicated articles were withdrawn using the Zotero citation manager and 218 more articles were removed by title and abstract review, as shown in Figure 1.

After full reading 35 articles were excluded for not meeting the criteria.

Finally, 39 articles were selected and included in this review.

An addittional search was performed manually by pairing each keyword with the word CAD, to identify actual pertinent reviews, sistematic reviews related to the subject, or other studies indirectly related to the subject, to allow comparisions or to broaden the introduction and discussion seccions.

Data extraction was performed, resumed in tables and the considered most pertinent information was displaied in comprehensive graphics, after application of the filters: type of CAD-CAM blocks used, luting material used in laboratory and *in vivo* tests, king of test used for bonding strength evaluation (μTBS or μSBS), type of surface treatment and coupling agent.

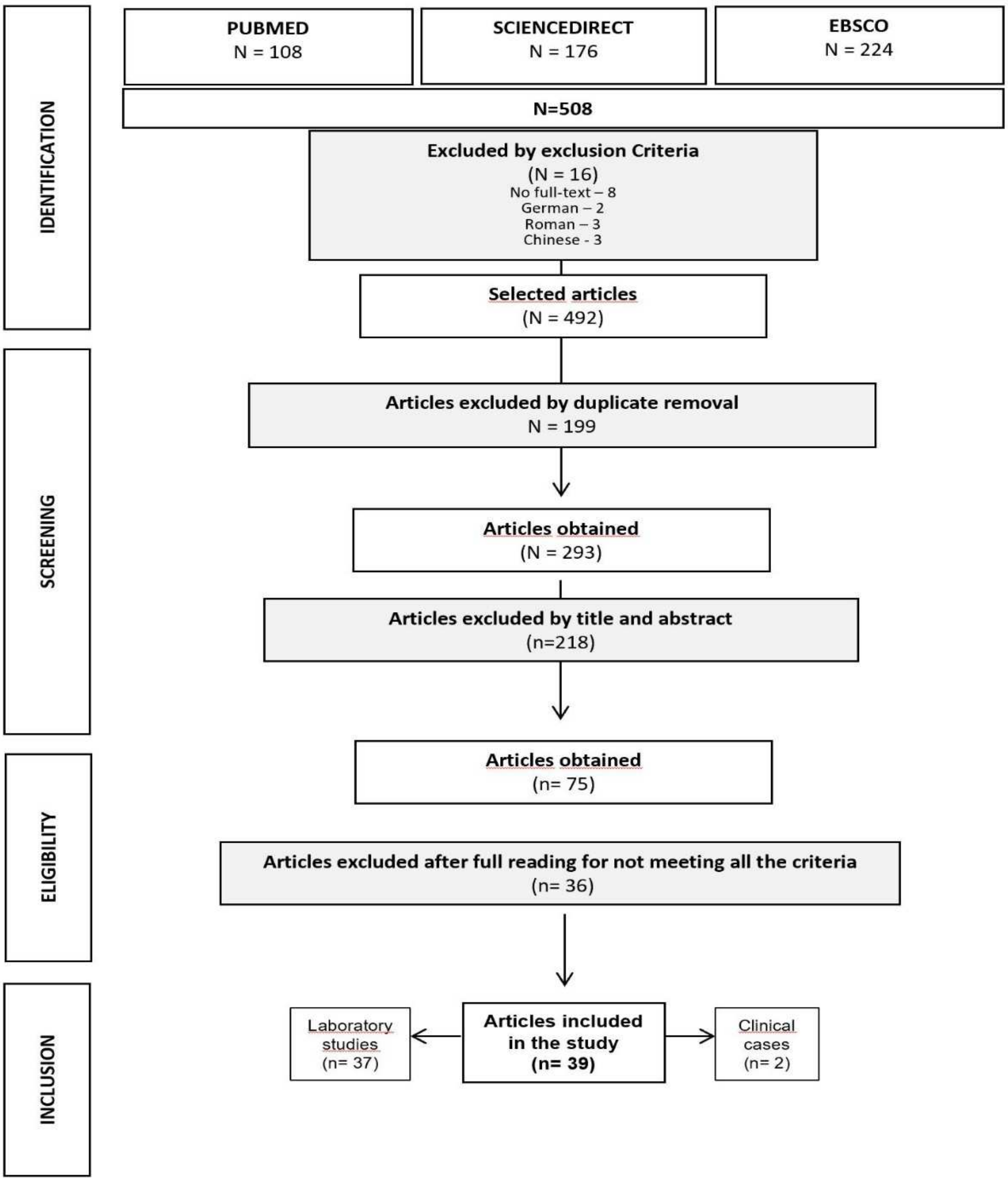

Figure 1 – Flowchart of the search strategy used in this study, according to PRISMA.

4. RESULTS

The search retrieved 508 articles, 108 articles found in the PubMed database, 176 in Sciencedirect and 224 in EBSCOhost, and after applying the inclusion and exclusion criteria, 39 were selected, from which 37 were laboratory studies[1,6,8,11,14,16-47] and 2 clinical reports[48,49]. The manual search retrieved 2 reviews,[4,5] 4 systematic reviews,[2,7,12,13] 3 systematic reviews with metanalysis,[3,9,10] 2 laboratorial studies[15,51] and 1 survey[50] that were used in the introduction and discussion sections.

Data extraction retrieved information displayed in Tables 1 to 5, and from the analysis of the data presented in the selected articles, filter by type of CAD-CAM blocks used (Figure 2), luting material used in laboratory and *in vivo* tests (Figure 3) and king of test used for bonding strength evaluation (μTBS or μSBS) (Figure 4).

There was a prevalence of use of Vita Enamic® (VITA Zahnfabrik) and IPS e. max® Cad (Ivoclar Vivadent) relatively to blocks from other manufacturers, followed by Vita Mark II® (VITA Zahnfabrik) and LAVA® Ultimate (3M ESPE). Without doubt the most luting cement used was Rely X® Ultimate Dual (3M ESPE).

The graphics resulting from the filters type of surface treatment and coupling agent can be seen in Figure 5 and 6.

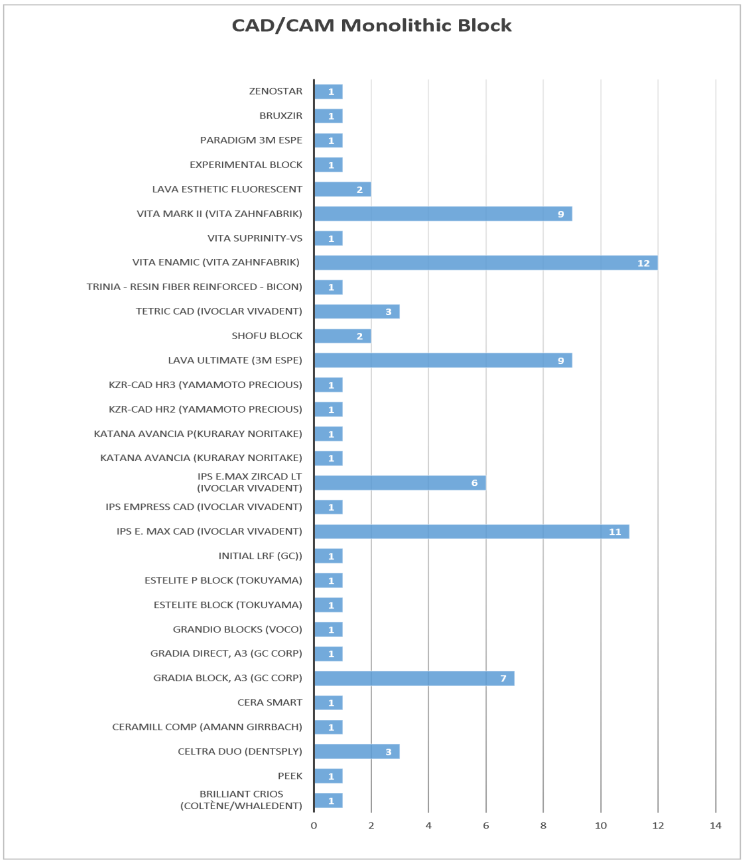

Figure 2 – CAD-CAM blocks found in the selected articles.

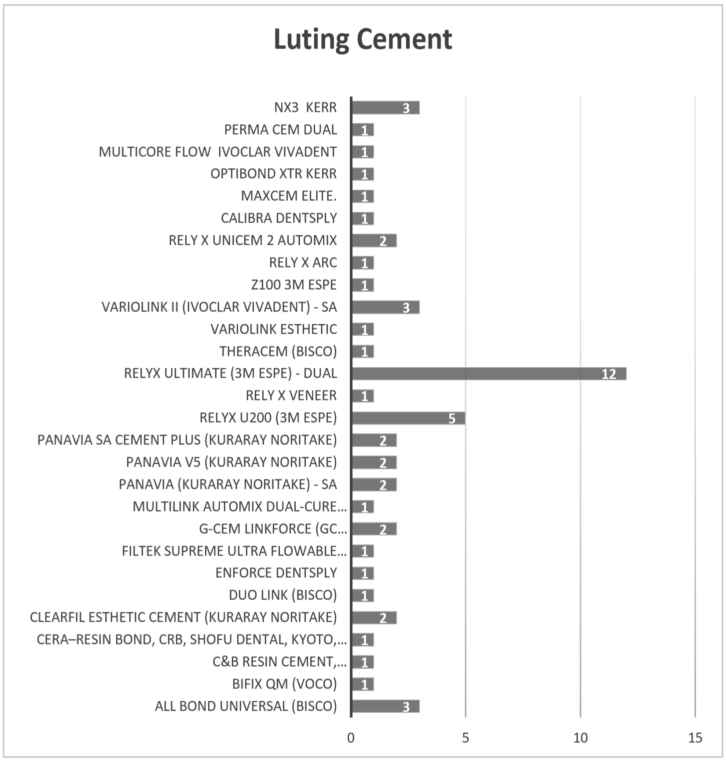

Figure 3 – Luting cements found in the selected articles.

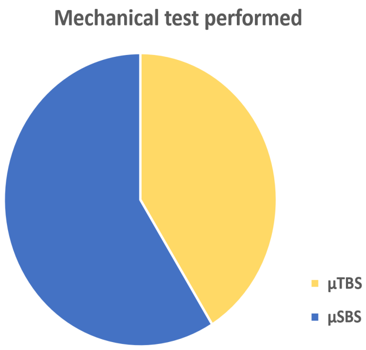

Figure 4 – Type of test that was found in the studies.

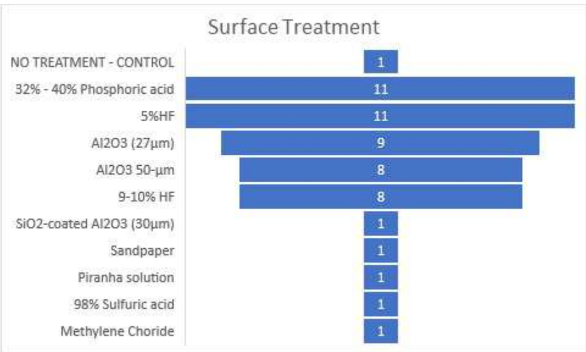

Figure 5 – Surface treatment used in the selected articles.

Figure 6 - Coupling agents used in the selected articles.

Table 1- Resumed extraction data from the selected studies.

Author (year) and Article Title	Material	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement	Type of Test	Statistical Analysis	Results	Conclusions
Abdou et al (2021)[17] Bonding performance of dispersed filler resin composite CAD/CAM blocks with different surface treatment protocols.	Estelite Block (Tokuyama) Estelite P Block (Tokuyama) Katana Avancia (Kuraray) Katana Avancia P (Kuraray) KZR-CAD HR2 (Yamamoto) KZR-CAD HR3 (Yamamoto) Lava Ultimate (3M) Tetric CAD (Ivoclar)	HF 9.6%	Clearfil Ceramic Primer Plus (Kuraray) Clearfil Porcelain (Kuraray)	Universal Adhesive (UA) Clearfil tri-S Bond ND Quick (Kuraray)	Panavia V5 (Kuraray)	**µTBS Mpa** 24-h water storage Cross-head speed of 1 mm/min. SEM - 70× magnification (a) adhesive failure (≥80% of the failure within the adhesive or at the RCB-cement interface); (b) cohesive failure within the resin cement; (c) cohesive failure within the RCB, and (d) mixed failure (a+b).	Two-way ANOVA / Weibull analysis	Parametric Weibull regression model - significant effect of the RCB type, roughening protocol and chemical treatment on µTBS and the interactions between all of them ($p<0.001$). Combination of HF etching + UA without CP application may be the best choice for pretreatment of DF-RCBs.	For most DF-RCBs, the highest µTBS - HF+UA. UA application ≥ silanization, (silane is not crucial for DF-RCBs, especially after HF). Highest µTBS to PICN-RCB obtained with silanization. Roughening pretreatments increased the surface roughness and γc of all RCBs.
Cardenas et al (2017)[11] Effect of MDP-containing silane and adhesive used alone or in combination on the long-term bond strength and chemical Interaction with lithium disilicate ceramics.	IPS e. max CAD (Ivoclar)	N/A	Monobond Plus (Ivoclar) Monobond S (Ivoclar) Prime & Bond Elect (PBE)	Scotchbond Universal	RelyX Ultimate (3M) - DUAL Enforce Dentsply Scotchbond Universal Adhesive – SBU (3M)	**µSBS Mpa** Specimens stored in water (37°C for 24 h or 1 year) The failure pattern and µSBS were statistically evaluated ($\alpha = 0.05$) Specimens were examined for chemical interaction using Raman spectroscop.	Two-way ANOVA (groups vs time). Tukey's post-hoc test was applied with $\alpha = 0.05$. Student's t-test for independent samples was applied ($\alpha = 0.05$)	PBE adhesive alone - higher mean µSBS than both groups with silane (MSB or MB+) without PBE ($p < 0.001$) at 24 h. SBU adhesive or MBS silane alone, as well as MB+ associated with SBU - higher mean µSBS ($p < 0.001$) at 24 h. 1-year water storage - all groups showed a significant decrease in mean µSBS. In terms of chemical interaction, when silane (MSB or MB+) was applied, only a slight decrease of Si-O peaks occurred. Otherwise, when PBE or SBU adhesives were applied, methacrylate peaks were only observed in the SBU groups.	Best results in terms of bond strength after water storage with MDP containing silane + universal adhesive. Simplified bonding protocol that includes either a silane or a universal adhesive is not recommended.
Ceci et al (2015)[8] Effect of glycine pretreatment on the shear bond strength of a CAD/CAM resin nano ceramic material to dentin.	Lava Ultimate (3M)	35% phosphoric acid	Clinpro™ Prophy Powder (3M) Glicyne powder	Universal Adhesive Clearfil tri-S Bond ND Quick (Kuraray)	RelyX Ultimate (3M) - DUAL / Scotchbond Universal Adhesive – SBU 3M ESPE / Rely X Unicem 2 Automix	**µSBS Mpa** Specimens stressed in an occluso-gingival direction at a crosshead speed of 1 mm/min. Shear bond strength strength failure occurred by the bonding area.	Analysis of variance (ANOVA)	Glycine did not change the different bond strength demonstrated. Conventional resin composite cements used together with a self-etch adhesive reported the highest values. Glycine seems to increase the bond strength of self-adhesive resin cements	Glycine did not change the different bond strength of the various luting protocols tested. Conventional resin composite cements used together with a self-etch adhesive reported the highest values. Glycine seems to increase the bond strength of self-adhesive resin cements.
Demirel et al (2019)[19] Influence of different universal adhesives on the repair performance of hybrid CAD-CAM materials.	Cera Smart Lava Ultimate (3M) Shofu Block Vita Enamic (Vita)	Silica-coated Al_2O_3 - 30 µm (CoJet, 3M)	Porcelain Primer (Bisco) Adpter Single Bond-2	Single Bond Universal (3M)	All Bond Universal (Bisco) / Clearfill Universal	**µSBS Mpa** Bond strength was tested immediately after thermal cycling with a universal testing machine. A shear force was applied to the adhesive interface through a chisel-shaped loading device at a crosshead speed of 1 mm/min. Failure mode analysis with a stereomicroscope at ×25 magnification.	Analysis of variance (ANOVA)	The CAD-CAM block type and block-adhesive combination had significant effects on the bond strength values ($p < 0.05$). Significant differences were found between the following pairs of groups: VE/CO and VE/AB, CS/CO and CS/AB, VE/CU and CS/CU, and VE/ AB and CS/AB ($p < 0.05$)	µSBS values were affected by hybrid block type. All tested universal adhesive treatments can be used to the control treatment for repair, except the AB system on VE blocks (the VE/AB group). The µSBS values showed variation across different adhesive treatments on different hybrid CAD-CAM block types.
De Oliveira et al (2018)[18] Effect of aging and testing method on bond strength of CAD/CAM fiber-reinforced composite to dentin.	Trinia - RESIN FIBER REINFORCED - Bicon)	Al_2O_3 - 45-µm	All-bond 3 Bisco	Cera–Resin Bond CRB)(Shofu)	C&B resin cement, Bisco, Schaumburg, USA / Clearfil Esthetic Cement (Kuraray)	**µSBS Mpa** The shear test was performed immediately after removal of the specimen from the water. The sticks were stored in vials with distilled water (37◦C) for 24h. They were loaded in tension to failure at a crosshead speed of 0,75mm/min.	Weibull 2-parameters analysis	Weibull contour plots showed a significantly lower characteristic strength and Weibull modulus (m) for SC (= 6.9 MPa and m = 1.4) compared to TC (= 20.9 MPa and m = 4.5). Fatigued and thermocycled T groups presented significantly reduced characteristic strength (= 3.1 MPa and = 4.1 MPa, respectively) compared to TC. Weibull modulus was significantly reduced only for SC and TF groups compared TC. Failure predominantly occurred at the cement/FRC interface.	FRC bonded to dentin tested in shear compared to microtensile resulted in lower Weibull modulus and characteristic bond strength values when tested immediately. Aging through thermocycling or mechanical fatigue reduced the bond strength of samples tested in microtensile.
Dos Santos et al (2019)[20] Can universal adhesive systems bond to zirconia?	IPS e.max ZirCAD LT (Ivoclar)	Sandpaper	Z Prime Plus - Bisco / Scotchbond Universal 3M ESPE	N/A	All Bond Universal (Bisco) Single Bond Universal (3M) / Z350 XT 3M ESPE	**µSBS Mpa** Specimens designated for adhesive interface assessment were polished with sandpapers of increasingly fine grit sizes and cleaned in an ultrasonic cleaner. Specimens were subsequently mounted onto stubs with carbon adhesive tape and sputter-coated with gold, followed by SEM examination at magnifications ranging from 300×to 5000×.	F-test (ANOVA), Student's t-test, and Tukey's test	Bond strength was superior for grit-blasted zirconia. In specimens with this surface treatment, there were no significant differences between experimental groups. On SEM, blasted surfaces exhibited areas of micromechanical retention and adhesive interfaces exhibited areas of zirconia-adhesive interlocking.	Universal adhesive systems able to bond to zirconia. Grit-blasting of the zirconia surface proved essential to satisfactory bonding.
El-Damanhoury et al (2017)[21] Self-etching ceramic primer versus hydrofluoric acid etching: Etching efficacy and bonding performance.	IPS e.max ZirCAD LT (Ivoclar) Vita Enamic (Vita) Vita Mark II (Vita)	4.8% HF	Monobond Etch and prime / Monobond Plus (Ivoclar)	N/A	Multilink automix dual-cure luting resin cement	**µSBS Mpa** The samples were stored in distilled water at 37 ?C for 24 h and thermo-cycled (TC) between 5 and 55 ?C for 5000 cycles for SBS using a table-top ShearBond Strength Tester. The semicircular metal attachment of the machine applied shear forces at the resin-ceramic interface, running at a crosshead speed of 1.0 mm/min, till complete failure of the resin composite and debonding. The force required for failure was recorded in Newton and was divided by the surface area (mm^2) to calculate the SBS in MPa.	ANOVA and post hoc Bonferroni	Pretreatment with HFMP resulted in higher SBS and increased surface roughness in comparison to MEP and MP. Regardless the method of surface pretreatment, the mean SBS values of EM ceramic was significantly higher ($p < 0.05$) than those recorded for VM and VE, except when VE was treated with MEP, where the difference was statistically insignificant. Traces of fluoride ion were detected when MEP was used with VE and VM	Under limited conditions, using MEP resulted in comparable SBS results to HFMP; meanwhile HFMP remains the gold standard for pretreatment of glass ceramics for resin-luting cementation.
Elsaka et al (2020)[16] Effect of surface treatment and aging on bond strength of composite cement to novel CAD/CAM nanohybrid composite.	GRANDIO Blocks (VOCO) Lava Ultimate (3M) Vita Enamic (Vita)	Al_2O_3 50-µm	Silane - Ceramic Bond	N/A	Bifix QM (Voco)	**µTBS Mpa** Half sticks (n = 30) stored for 24 h in distilled water at 37°C (0 thermocycles). Other 30 sticks subjected to 5000 thermocycles in distilled water between 5°C and 55°C with a 5-s transfer time and a 30-s dwell time (5000 thermocycles). Microstick stressed under tensile force using a universal testing machine at a crosshead speed of 1 mm/min. The µTBS values were calculated in MPa by dividing the load at failure (N) by the bonded area (mm^2). Debonded specimens were examined using a stereomicroscope at 50X magnification to determine the mode of failure.	Two-way ANOVA - Tukey's test	The µTBS was significantly affected by the type of CAD/CAM material, type of treatment, and aging. Silane application significantly improved the µTBS ($p < 0.05$). The µTBS decreased significantly with aging (5000 thermocycles). BQ cement resulted in the highest µTBS to GR treated with TiF_4 2% wt/v + CB compared to the other groups ($p < 0.05$). Aged GR/BQ treated with TiF_4 2% wt/v + CB had the highest predicted µTBS (19 MPa)	TiF_4 2% wt/v followed by silane application enhanced the adhesion of GR/BQ and LU/BQ systems. On the other hand, HF surface treatment followed by silane application improved the adhesion of the VE/BQ system.

Table 2 - Resumed extraction data from the selected studies.

Author (year) and Article Title	Material	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement	Type of Test	Statistical Analysis	Results	Conclusions
Elsayed et al (2017)[22] Tensile bond strength of so-called Universal Primers and Universal Multimode Adhesives to zirconia and lithium disilicate ceramic.	IPS e. max CAD (Ivoclar) Zenostar	Al2O3 - 50-µm	Monobond Plus (Ivoclar) / Prime and Bond NT / Calibra Silane (Dentsply) / Duo Link	AllBond XTR Adhesive (Kerr) All Bond Universal (Bisco)	RelyX Ultimate (3M) - DUAL / Variolink Esthetic / OptiBond XTR Kerr / NX3 (Kerr)	**µTBS Mpa** Plexiglas tubes - diameter of 3.2 mm filled with a dual-curing composite, excess cement removal, air-blocking gel application. Light polymerization - 650 mW/cm2 2x 20 s each side + 90 s. Left for 10 min at room temperature + stored in 37°C water. Each bonding system n=24. Each n = 24 divided in n=8. Specimens (n = 8) stored either for 3 days initial time group) without thermal cycling (TC), 30 days - 7500 thermal cycles, or 150 days - 37,500 thermal cycles, ie, 7500 thermal cycles every 30 days. Thermocycling was performed between 5°C and 55°C with a dwell time of 3 s. Tensile bond strength (TBS) was tested at a crosshead speed of 2 mm/min.	Kruskal-Wallis test / Bonferroni-Holm correction for multiple testing	Initially, all bonding systems exhibited high TBS, but some showed a significant reduction after 30 and 150 days of storage. After 3, 30, and 150 days, Monobond Plus (silane and phosphate monomer) showed significantly higher bond strengths than the other universal primer and adhesive system	Lithium disilicate and zirconia ceramic bond strength were affected by the bonding system. Separate primer with silane and phosphate monomer provides more durable bonding than silanes incorporated in universal multimode adhesives.
Emsermann et al (2019)[23] Influence of pretreatment methods on the adhesion of composite and polymer infiltrated ceramic CAD-CAM blocks.	Brilliant Crios (Coltène/Whaledent) Gradia Block, A3 (GC) Lava Ultimate (3M) Vita Enamic (Vita)	Al2O3 - 30-µm Al2O3 50-µm HF 5%	Silane primer G-Multi Primer / One coat 7 Universal / Scotchbond Universal 3M ESPE / Ultradent Silane / Vitasil Silane (VITA)	One Coat 7 (Coltène)	DuoCem (Coltène/Whaledent) / G-Cem LinkForce (GC Europe) / RelyX U200 (3M) / RelyX Ultimate (3M) - DUAL	**µSBS** After surface pretreatment, a hollow cylinder of clear acrylic with an internal diameter of 2.9 mm and a height of 4 mm was attached to the surface using a custom-made bonding jig. The bolt was loaded with 1 kg with the help of the bonding jig to spread the resin luting material evenly on the substrate surface without entrapping air. The resin luting material was light cured from three different sides for 20 s at 1200 mW/cm2. Specimens were removed from the bonding jig, placed in demineralized water at 37°C, and stored for 6 months under these conditions.	R software (version 3.1.2., R Core Team, R Foundation for Statis-tical Computing; Vienna, Austria)	Low bond strengths were obtained without pretreatment (Brilliant Crios 3.01 ± 0.54 MPa, Cerasmart 2.66 ± 0.47 MPa, Lava Ultimate 1.76 ± 0.26 MPa, VITA Enamic 2.83 ± 0.63 MPa). Grit blasting achieved high bond strengths across all materials (Brilliant Crios 5.17 ± 0.77 MPa, Cerasmart 4.27 ± 0.50 MPa, Lava Ultimate 3.98 ± 0.54 MPa, VITA Enamic 4.97 ± 0.90 MPa). Silane application tended to decrease bond strengths on CAD- CAM composite resins. Following the manufacturers' specifications achieved the highest bond strengths for all materials except Cerasmart (Brilliant Crios 5.75 ± 0.91 MPa, Cerasmart 2.82 ± 0.28 MPa, Lava Ultimate 6.63 ± 0.97 MPa, VITA Enamic 7.09 ± 0.77 MPa).	Grit blasting and the application of a suitable material primer is a useful pretreatment for the bonding of CAD-CAM composite resins.
Frankenberger et al (2015)[24] Adhesive luting of new CAD-CAM materials.	Celtra Duo (Dentsply) IPS e. max CAD (Ivoclar) Lava Ultimate (3M) Vita Enamic (Vita)	Al2O3 50-µm HF 5%	Prime & Bond XP + SCA /	Prime & Bond XP + SCA	Rely X Unicem 2 Automix / Calibra Dentsply	**µTBS Mpa** The same (or approximated) percentage of the 100 final specimens per group received 0 MPa as a final µ-TBS result. The µ-TBS sticks were then fractured according to a well-suited protocol, with a crosshead speed of 0.5 mm/min.	Kolmogorov-Smirnov test), nonparametric tests were used (Wil-coxon matched-pairs signed-ranks test, Mann-Whitney test)	Bonding performance of recent CAD/CAM materials was clearly influenced by the pretreatment method. Significantly higher µ-TBS values were recorded for the ceramic materials compared to the hybrid materials . Among the hybrid materials, Enamic exhibited higher bond strengths than Lava Ultimate.	When pretreated as recommended by the manufacturers, recent tooth-colored CAD/CAM materials show an encouraging bonding performance for adhesive luting.
Ilie et al (2019)[25] Shear bond strength vs interfacial fracture toughness - Adherence to CAD/CAM blocks.	Tetric CAD (Ivoclar)	35% phosphoric acid	Adhese Universal	Universal Adhesive Clearfil tri-S Bond ND Quick (Kuraray)	Variolink Esthetic	**µSBS Mpa** Microshear bond test and interfacial fracture toughness (IKIC)	ANOVA and Scheffé modified t-tests (= 0.05).	SBS results showed a significant difference between the 60 grit group and the other groups. Thermocycling led to a significant decrease in SBS in all groups. After thermocycling, there was a significant difference between the 60 and the 600 grit groups. All KIC samples fractured adhesively at the RCB surface. KIC of the RCLA was significantly higher than IKIC of all groups.	The results endorse the use of fracture mechanics methodology for the characterization of adherence. The results also suggest that adherence to CAD/CAM RCB may be limited by the strength of the RCB adhesive interface.
Ishii et al (2017)[26] Bonding state of metal-free CAD/CAM onlay restoration after cyclic loading with and without immediate dentin sealing.	Lava Ultimate (3M) Vita Enamic (Vita) Vita Mark II (Vita)	32% Phosphoric acid	Scotchbond Universal 3M ESPE	Universal Adhesive Clearfil tri-S Bond ND Quick (Kuraray) / scotch bond universal	RelyX Ultimate (3M) - DUAL	**µTBS Mpa** All restored specimens were stored in 37°C water for 24 h. The specimens were subjected to cyclic load stress. Each restored specimen was sectioned intermittently and vertically. Four standardized beam-shaped test pieces were trimmed and obtained from each restored specimen. The microtensile bond strength was measured at 1.0 mm/min crosshead speed.	Student's t-test. Kruskal-Wallis test / Bonferroni	No pretesting failure was observed. Based on these results, the CAD/CAM restoration with either of the popular resin composite blocks was significantly superior to the restoration with a feldspathic ceramic block in terms of intra-cavity bond strength, regardless of IDS.	IDS improves the internal bond strength and the bond reliability of metal-free CAD/CAM onlay restorations. The resin composite block seems to be more effective than a typical glass-ceramic block for achieving both high bond strength and excellent bond reliability
Kalavacharla et al (2015)[27] Influence of etching protocol and silane treatment with a Universal Adhesive on lithium disilicate bond strength.	IPS e. max CAD (Ivoclar)	5%HF 10% HF acid	Rely X ceramic primer	Scotchbond Universal Adhesive	Z100 3M ESPE / Rely X Unicem 2 Automix	**µSBS** The specimens were thermocycled for 10,000 cycles (58C-508C/15 s dwell time). Specimens were loaded until failure using a universal testing machine at a crosshead speed of 1 mm/min. The peak failure load was used to calculate the shear bond strength. Scanning electron mi croscopy images were taken of representative e.max specimens from each group	two-way analysis of variance (ANOVA)	Silane treatment provided higher shear bond strength regardless of the use or concentration of the HF etchant. Shear bond strength values for each etch time were significantly different and could be divided into significantly different groups based on silane treatment.	Both HF and silane treatment significantly improved the bond strength be tween resin and lithium disilicate when usedwith a universal adhesive.
Kassem et al (2020)[28] Marginal gap and fracture resistance of CAD/CAM ceramill COMP and cerasmart endocrowns for restoring endodontically treated molars bonded with two adhesive protocols: an in vitro study.	Ceramill COMP (Amann Girrbach) Cera Smart	35% phosphoric acid	Ceramic Primer 2	No bonding agent was required after the application of ceramic primer II according to manufacturer's recommendation	RelyX Ultimate (3M) - DUAL	**µ-TBS Mpa** From these results, it can be noted that the treatment type did afect the µ-TBS of silanized surfaces at diferent water-storage periods. The Wm and PF10 values of DR specimens, which are typical indicators of bonding reliability, were similar to or significantly greater than the values of CO specimens, regardless of the water-storage period. Especially in the 3 m group, the µ-TBS values of UV and VL specimens were significantly greater than those of CO specimens.	No statistical analysis	The marginal gap results were statistically insignificant across the material and bonding protocol groups before thermo-mechanical aging. Thermo-mechanical aging significantly reduced the marginal gap distance for Ceramill COMP endocrowns cemented using the total-etch protocol (p ¼ 0.002). No statistically significant difference was recorded for the fracture resistance in either the material or bonding protocol groups (p 0.05)	Both materials and bond ing protocols can, therefore, be used in the posterior region providing conservative treatment, adequate marginal gap and fracture resistance.

Table 3 - Resumed extraction data from the selected studies.

Author (year) and Article Title	Material	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement	Type of Test	Statistical Analysis	Results	Conclusions
Komoto et al (2021)[40] The efect of additional photochemical treatments on the bonding of silanized CAD/CAM ceramic restorations after water-storage.	Vita Mark II (Vita)	N/A	Rely X ceramic primer / Ceremic Primer 2 / Scotchbond Universal 3M ESPE	Scotchbond Universal Adhesive	Filtek Supreme Ultra Flowable Restorative (3M) / RelyX U200 (3M) / Rely X Unicem 2 Automix	**µTBS Mpa** Restored specimens were stored in 37 °C water for 24. The specimens were divided into three groups based on the water-storage period: 1d (one day), 1m (one month), and 3m (three months). The µ-TBS values were measured at a crosshead speed of 1.0 mm/min	Kruskal–Wallis and Steel–Dwass test. Weibull	The micro-tensile bond strength of UV specimens were signifcantly greater than those of control group. Specimens and were similar to those of (dry heating additional treatment) specimens. Both Weibull modulus and Weibull stress at 10% failure probabilities values of the UV and VL specimens were signifcantly greater than those of control specimens regardless of the water storage period.	These fndings reveal that additional photochemical treatments had efect to improve the bond strength and bonding reliability of the CAD/CAM restorations, when compared to CO and DR conditions.
Liebermann et al (2018)[29] Impact of recently developed Universal Adhesives on tensile bond strength to computer-aided design/manufacturing ceramics.	Celtra Duo (Dentsply) Initial LRF (GC)) Vita Mark II (Vita)	9% HF	Monobond Etch and prime / Silane primer G-Multi Primer / One coat 7 Universal / Scotchbond Universal 3M ESPE / Prime bond Active	All-Bond Universal / Clearfil Universal Bond / G-Multi Primer / iBond Universal / One Coat 7 Universal / Prime&Bond Active / Scotchbond Universal	All Bond Universal (Bisco) / Scotchbond Universal Adhesive – SBU 3M / Clearfill Universal	**µTBS Mpa** All specimens were stored for 24 hours at 37°C in distilled water in an incubator and then subjected to thermal cycling. The measurement of TBS was carried out with a universal testing machine. The required tensile force was determined using a 500-N load cell. The calculation of tensile strength was analyzed using the following equation: TBS (MPa) = fracture load (N)/ bonding area (mm2)	Kolmogorov-Smirnov, Kruskal-Wallis, Mann-Whitney U, and Spear man-Rho tests (a=0.05)	ABU, MEP, and MBP obtained the significantly highest TBS, while CUB, IBU, and OCO resulted in the lowest, regardless of the CAD/CAM ceramic. SBU showed varying TBS results depending on the CAD/CAM ceramic used. ABU, MEP, and MBP showed no impact of CAD/CAM ceramic on TBS values. ABU, GMP, MEP, and MBP showed predominantly cohesive failure types in luting composite, while CUB and OCU demonstrated adhesive failure types.	ABU, MBP, and MEP showed the highest TBS results. MBP and MEP presented similar stability outcomes concerning TBS values. Not all universal systems can be used for each glass ceramic. The use of universal adhesives combined with ceramic primers or activators is technique sensitive.
Lümkemann (2020)[43] Effect of Cleaning Protocol on Bond Strength between Resin Composite Cement and Three Different CAD/CAM Materials	IPS e. max CAD (Ivoclar) IPS e.max ZirCAD LT (Ivoclar) Tetric CAD (Ivoclar)	37% phosphoric acid 5%HF	Monobond Plus (Ivoclar) / Adhese Universal	Adhese Universal	Variolink Esthetic	**TBS Mpa** Fracture patterns analyzed - light microscope at 20×. Fracture type definition: (A) adhesive: no residuals of cement on specimen surface, (B) cohesive: adhering residuals of cement on specimen surface, (C) mixed: adhering residuals of cement on specimen surface combined with fractures in specimen substrate. Storage in distilled water at 37°C for 24 h. Aging for 20,000 cycles split between two water baths with distilled water (dwell time 30 s) at a temperature of 5°C and 55°C . After 20,000 cycles of thermo-cycling, all specimens were dried in ambient air for 2 h before being subjected to TBS measurements.	Kolmogorov–Smirnov test, 1- and 2-way ANOVA with post-hoc Scheffé and partial eta-squared (ηP2). The Kruskal–Wallis and Mann–Whitney U tests.	The type of material showed an impact on the tensile bond strength (p < 0.001; ηP2 = 0.156) while the cleaning protocol did not affect the results (p > 0.766). Zirconia with highest tensile bond strength, followed by lithium disilicate ceramic (p < 0.001). CAD/CAM composite with overall lowest bond strength results (p < 0.003). No statistic differences in tensile bond strength were found in dependence of the cleaning protocol (p > 0.824), though an increased variance can be observed within lithium disilicate ceramic for cleaning with ethanol, universal cleaning paste, and distilled water, when compared with phosphoric acid or phosphoric acid + ethanol.	The impact of the chosen cleaning method seems to play a subordinate role in obtaining a durable bond strength to resin composite cement as long as the clinician complies with the bonding protocol of the respective restorative material and handles the bonding materials correctly.
Monteiro et al (2020)[30] Effect of surface treatment on the retention of zirconia crowns to tooth structure after aging	Lava Esthetic Fluorescent	Al2O3 - 27µm	Scotchbond Universal 3M ESPE	Scotchbond Universal (3M)	RelyX Ultimate (3M) - DUAL	**µSBS Mpa** After 24 hours of distilled water storage in room temperature (22°C), NA specimens were tested and aged specimens were submitted to artificial aging by mechanical loading, followed by thermal cycling combined with pH cycling. Mechanical loading was applied with a 6 mm diameter stain less steel tip for 240 000 cycles at 60 mm/min with a vertical load of 0-50 N and a temperature of 35°C. For thermal and pH cycling, an acidic (pH 3.62) and a basic (pH 7.8) solution were prepared with distilled water, citric acid, and sodium phosphate solution. The acidic solution was poured into the 5C chamber and the basic solution into the 55°C chamber. Ten thousand cycles were performed (30 seconds immersion time and 15 seconds dwell time).	(ANOVA) and Tukey test (P < .05)	Aging decreased the retention strength in control specimens (P < .001). Sur face treatment improved the retention strength of aged specimens (P < .001), with similar results between alumina and tribochemical silica coating	The chemical interaction between the universal bonding system and zirconia's surface was not sufficient to withstand artificial aging. Tribochemical silica coating did not promote additional retention in comparison to alumina blasting.
Murata et al (2018)[31] Effect of immediate dentin sealing applications on bonding of CAD/CAM ceramic onlay restoration	Vita Mark II (Vita)	Al2O3 - 27µm 40% phosphoric acid	Scotchbond Universal 3M ESPE Single Bond Universal (3M) Clearfil Ceramic Primer Plus (Kuraray)	Universal Adhesive Clearfil tri-S Bond ND Quick (Kuraray)	Panavia V5 (Kuraray)	**µTBS** Cyclic loading stress with the opposing object in place at 157 N for 90 cycles/min and for 3×105 cycles in total, performed in 37°C water. After the cyclic loading, each restored specimen was sectioned using a water-cooled microtome. The µ-TBS of each test specimen was measured at a crosshead speed of 1.0 mm/min using a universal testing machine.	(ANOVA) test and Tukey's	IDS application improved not only the µ-TBS, but also the bonding reliability and durability of the CAD/CAM restoration. In particular, the S restoration exhibited the highest-performance as regards both robust bond strength and stable bonding	IDS application was found to affect the resin cement layer thickness of an MODP CAD/CAM ceramic onlay restoration. IDS application had an influence on the Wm value of the CAD/CAM restoration. The S restoration exhibited the highest-performance in terms of bonding reliability based on the Wm value. IDS application also affected the PF10 and PF90 values of the CAD/CAM restoration. The stress values of the three IDS restorations at both the PF10 and PF90 levels were greater than those of the N restoration
Murilo Gómez et al (2017)[14] Short- and Long-Term Bond Strength Between Resin Cement and Glass-Ceramic Using a Silane Containing Universal Adhesive	IPS e.max ZirCAD LT (Ivoclar)	10% HF acid	Clearfil Ceramic Primer Plus (Kuraray)	Scotchbond universal (3M)	RelyX Ultimate (3M) - DUAL	**µSBS** After each storage time, specimens were dried and attached to a holding device using cyanoacrylate cement, and placed on the platen of a universal testing machine to perform micro shear bond testing (SBS). An uplifting shear load was applied to the extreme base of each resin cement cylinder at a crosshead speed of 0.5 mm/min through the aid of a thin wire (0.20-mm diameter) placed strictly parallel to and in contact with the adhesion area on the substrate. Using the cross-sectional area of each specimen, the resulting bond strength was calculated and expressed in MPa, after which a group mean was computed (n=18).	two-way analysis of variance and the Tukey post hoc test (a=0.05)	IDS application was found to affect the resin cement layer thickness of an MODP CAD/CAM ceramic onlay restoration. The IDS application was also found to have an influence on the Wm value of the CAD/CAM restoration. The S restoration exhibited the highest-performance in terms of bonding reliability based on the Wm value, which is defined as the reliability required to achieve the specific µ-TBS value for a restoration. The IDS application also affected the PF10 and PF90 values of the CAD/CAM restoration. Further, the stress values of the three IDS restorations at both the PF10 and PF90 levels were significantly greater than those of the N restoration specimens.	Conventional silane followed by an adhesive system application improved ceramic/resin cement bond strength after water aging. Application of separate silane and adhesive components and a silane-containing, universal adhesive demonstrated the least decrease in microshear bond strength after long-term water storage. The conventional silane and the HF–only controls showed reduced bond strength from 24 hours to six months of water storage, while silane, followed by adhesive application, the universal adhesive, and the universal ceramic primer, did not change during that time period.
Nejat et al (2018)[32] Retention of CAD-CAM resin composite crowns following different bonding protocols	Experimental block	Al2O3 50-µm 5%HF	N/A	OptiBond XTR Kerr	Maxcem elite.	**µSBS Mpa** Crowns were fatigued for 100,000 cycles at 100 N in water and debonded in tension (1 mm/minute)	three-way ANOVA	Surface treatment, silane and adhesive applications independently affect retention force (p < 0.05). Alumina airborne abrasion surface treatment, silane and adhesive applications all improve retention strength. The highest mean retention strength values were recorded when the crowns were alumina particle abraded and coated with adhesive.	A durable bond between resin composite crowns and tooth structure provides both improved retention but also improves the strength of the resin composite crown
Peumans et al (2016)[6] Bonding Effectiveness of Luting Composites to Different CAD/CAM Materials	Celtra Duo (Dentsply) IPS e. max CAD (Ivoclar) IPS Empress CAD (Ivoclar) Vita Enamic (Vita) Vita Mark II (Vita)	Al2O3 - 27µm CoJet - SiO2-coated Al2O3 - 30µm HF <5%	Monobond Plus (Ivoclar)	Heliobond (Ivoclar)	Clearfil Esthetic Cement (Kuraray) Panavia (Kuraray) - SA	**µTBS** Mode of failure/fracture Light microscopy - 50X	Significance level of α=0.05 Statistical software package (R 3.1.1, R Foundation for Statistical Computing; Vienna, Austria)	Surface treatment significantly influenced the bonding performance of the six CAD-CAM. Luting cement significantly influenced bond strength for Celtra Duo and Lava Ultimate. Chemical surface treatments resulted in the highest bond strengths. Lava Ultimate-highest bond strengths with hydrofluoric acid, silane and hydrofluoric acid + silane. Failure analysis showed a relation between bond strength and failure type. Adhesive failures percentage was higher for CAD-CAM materials with higher flexural strength (Celtra Duo, IPS e.max CAD, and Lava Ultimate).	Bond strength to CAD/CAM materials is influenced by surface treatment and luting composite. Individualization of CAD/CAM material/luting composite for optimal bonding protocol. Effect of aging needs deep examination.

Table 4 - Resumed extraction data from the selected studies.

Author (year) and Article Title	Material	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement	Type of Test	Statistical Analysis	Results	Conclusions
Sakraana (2017)[41]- Effect of chemical etching solutions versus air abrasion on the adhesion of self-adhesive resin cement to IPS e.max ZirCAD with and without aging	IPS e.max ZirCAD LT (Ivoclar)	Al2O3 - 50-µm Methylene Choride	Monobond Plus (Ivoclar)	Monobond Plus (Ivoclar)	RelyX Ultimate (3M) - DUAL	**µTBS** Specimens stored in distilled water at 37ºC/24 h, randomly divided into two subgroups. Half sticks subjected to an MTBS test without aging/half subjected to x6000 thermocycles (5 to 55 ± 2ºC; dwelling time in each bath: 20 s; transfer time: 5 s) prior to testing. The bonding area of each stick specimen was measured before the tests using a digital caliper (Starrett) with an accuracy of 100 µm. The tensile force was applied at a crosshead speed of 0.5 mm/min until debonding in the universal testing machine.	two-way ANOVA and Tukey's tests (D = 0.05)	Each conditioned zirconia block was bonded to its cor responding resin composite block us ing self-adhesive resin cement (RelyX Unicem Aplicap, 3M ESPE) under a load of 300 g.	Chemical etching of zirconia may have potential use as a substi tute for air abrasion as a surface conditioning method for zirconia.
Passia et al (2015)[33] Tensile bond strength of different universal adhesive systems to lithium disilicate ceramic	IPS e.max ZirCAD LT (Ivoclar)	5%HF	Monobond Plus (Ivoclar) Scotchbond Universal (3M) Duo-Link	Scotchbond Universal (3M) Monobond Plus (Ivoclar)	Multilink automix dual-cure luting resin cement / RelyX Ultimate (3M) - DUAL / OptiBond XTR Kerr / MultiCore Flow (Ivoclar) / NX3 (Kerr)	**µTBS Mpa** Evaluated in a universal testing machine at a crosshead speedof 2 mm per minute. Attached an alignment jig to the load cell and crosshead by means of upper and lower chains. TBS was calculated by dividing the force in newtons, by the bonding area in square millimeters.	Kruskal-Wallis and Wilcoxon tests with a Bonferroni-Holm correction for multiple testing	Initially, all adhesive systems exhibited considerable TBS, but some showed a significant reduction after 30 days of storage. After 3, 30, and 150 days, the Monobond Plus and Multilink Automix (Ivoclar) silane containing adhesive system showed significantly higher bond strengths to lithium disilicate ceramic than did the other universal adhesive systems.	The bond strength to lithium disilicate ceramic is affected significantly by the adhesive bonding system used.
Rigos et al (2018)[34] Effect of Immediate Dentin Sealing on the Bond Strength of Monolithic Zirconia to Human Dentin	BruxZir	Al2O3 - 27µm	Monobond Plus (Ivoclar)	Monobond Plus (Ivoclar)	Panavia F2.0 / Perma Cem Dual	**µSBS Mpa** Bonded specimens were water-stored (378C, 24hours) and subjected to SBS testing (50-kgF load cell, 1 mm/min). Fracture type was evalu ated with stereomicroscopy. Data (MPa) were statistically analyzed using three-way analysis of variance (a=0.05).	Shapiro Wilk test / Levene test / Cochran test / Dixon Q-test / Grubbs test	All factors significantly affected SBS values (p,0.001). Dentin conditioning method presented the greatest effect. Mean SBS values ranged from 12.603 MPa (PER-APA-DDS) to 40.704 MPa (PER-TBC-IDS). Based on the fracture type, adhesive failures at the luting agent–zirconia interface were the least common.	Bonding strategies for monolithic zirconia restorations could potentially benefit from IDS, regardless of the adhesive luting agent system used.
Roperto et al (2016)[35] Effect of different adhesive strategies on microtensile bond strength of computer aided design/computer aided manufacturing blocks bonded to dentin	Vita Mark II (Vita) BruxZir	5%HF 34% phosphoric acid Al2O3 50-µm	Monobond Plus (Ivoclar)	Monobond Plus (Ivoclar)	Clearfil Esthetic Cement (Kuraray) / Smart Cem 2 / Panavia F2.0 / Calibra Dentsply / Primer and Bond NT (Dentsply)	**µTBS Mpa** Bonded specimens were stored in 100% humidity for 24h at 37°C, and then sectioned with a slow-speed diamond saw to obtain 1 mm × 1 mm × 6 mm microsticks. Microtensile testing was then conducted using a microtensile tester. µTBS values were expressed in MPa.	ANOVA with post hoc (Tukey) test at the 5% significance level	Mean values and standard deviations of µTBS (MPa) were 17.68 (±2.71) for GI/ceramic; 17.62 (±3.99) for GI/composite; 13.61 (±6.92) for GII/composite; 12.22 (±4.24) for GII/ceramic; 7.47 (±2.29) for GIII/composite; and 6.48 (±3.10) for GIII/ceramic; ANOVA indicated significant differences among the adhesive modality and block interaction (P < 0.05), and no significant differences among blocks only, except between GI and GII/ceramic. Bond strength of GIII was consistently lower (P < 0.05) than GI and GII groups, regardless the block used.	Cementation of CAD/CAM restorations, either composite or ceramic, can be significantly affected by different adhesive strategies used.
Shinohara et al (2017)[36] Effects of tributylborane-activated adhesive and two silane agents on bonding computer-aided design and manufacturing (CAD-CAM) resin composite	Gradia Block, A3 (GC) Gradia Direct, A3 (GC)	40% phosphoric acid	GC Ceramic Primer Scotchbond Universal (3M)	N/A	N/A	**µSBS Mpa** The veneered specimens were subjected to thermocycling between 4 and 60°C for 10,000 cycles	Tukey–Kramer HSD test (a = 0.05, n = 8 / Two-way ANOVA	MT/SC (38.7 MPa) exhibited the highest mean bond strengths, followed by MT/GC (30.4 MPa), SC (27.9 MPa), and MT/Cont (25.7 MPa), while Cont (12.9 MPa) and GC (12.3 MPa) resulted in the lowest bond strengths	The combined use of the MMA-TBB liquid and the silane agent (MT/SC or MT/GC) improved the bond strength.
Şişmanoğlu et al (2020)[1] Microshear bond strength of contemporary selfadhesive resin cements to CAD/CAM restorative materials: effect of surface treatment and aging.	Cera Smart Lava Ultimate (3M) Tetric CAD (Ivoclar) Vita Enamic (Vita) Vita Mark II (Vita)	9% HF	Clearfil Ceramic Primer Plus (Kuraray)	Scotchbond Universal Adhesive (3M) Methyl methacrylate 95.6 wt %	Panavia SA Cement Plus (Kuraray) RelyX U200 (3M) TheraCem (Bisco)	**µSBS Mpa** Immediate µSBS testing and µSBS testing after thermal cycling (5000 thermal cycles between 5 C and 55 C with a 30-second dwell). Shear force - 0.5 mm/min. Load at failure/area of the adhesive interface. Stereomicroscope at 30X magnification. The failure modes were categorized as adhesive failure (failure at the CAD/ CAM block-SARC interface), cohesive failure (failure within the CAD/CAM block), mixed failure, and pretesting failure.	Mean µSBS and ± standard deviations 4-way ANOVA	µSBS The findings revealed that silane application yielded higher µSBS values (P<.05). All surface treatments were showed a significant increase in µSBS values compared to the control (P<.05). For FHC and RNC, the most influential treatments were AIO and TSC (P<.05)	Bond strength - µSBS influenced by the CAD/CAM material type, resin cement type, surface treatment, and aging. Sandblasting more effective - resin nano-ceramics (CS, LU, and HC), HF etching better - hybrid-ceramic (VE) + feldspar ceramic (VM). CoJet sandblasting - slightly more durable.
Siqueira et al (2019)[44] Effect of Self-Etching Primer Associated to Hydrofluoric acid or Silane on Bonding to Lithium Disilicate	IPS e. max CAD (Ivoclar)	5%HF	Monobond Etch and prime (Ivoclar) Monobond Plus (Ivoclar)	Monobond Plus, Ivoclar-Vivadent/ Excite® F DSD Ivoclar-Vivadent	Variolink II (Ivoclar) - SA	**µSBS Mpa** Cylinder-shaped specimens (0.8 mmø x 0.5 mm), were stored in water (37 °C for 24h or 1 year). For evaluation of chemical interactions by Raman Spectroscopy, the DL specimens were divided into 3 groups (n=4): 1) no treatment (DL); 2) HF + SI; and 3) MEP For evaluation of the ceramic surface conditioning pattern after the SEM treatments, the DL specimens were divided into 3 groups (n=3): 1) DL; 2) HF; 3) MEP; and 4) HF + MEP.	2-way ANOVA and Tukey's test; α=0.05	No difference was observed significant in immediate µSBS between groups (p=0.73), but after 1 year of storage of the samples in water, reduced µSBS (p>0.0001). HF or HF + MEP produced greater dissolution of the vitreous matrix than did use of MEP alone. After the application of SI and MEP, there was a reduction of siloxane bonds, suggesting the coupling of the silane layer on the surface of the DL	The ceramic self-etching primer can be an alternative to the traditional ceramic treatment, when compared to the traditional treatment, were statistically similar. The association of hydrofluoric acid or silane with a self-etching ceramic primer did not add any benefits.
Spitznagel et al (2016)[37] Adhesive Bonding to Hybrid Materials: An Overview of Materials and Recommendations	Cera Smart Shofu Block Vita Enamic (Vita) Lava Esthetic Fluorescent	Al2O3 30-µm Al2O3 50-µm 5%HF	Ceramic Primer 2	Silane + composite cement	N/A	N/A	N/A	N/A	Hybrid ceramics should be pretreated with HF acid and silane should be applied prior to cementation; CAD/CAM composite resins with a resin matrix should be subjected to air-particle abrasion and application of a universal bonding agent; and (3) all hybrid materials should be luted adhesively with either light-curing or dual-curing resin cements.

Table 5 - Resumed extraction data from the selected studies.

Author (year) and Article Title	Material	Surface Treatment	Coupling Agent	Adhesive System	Luting Cement	Type of Test	Statistical Analysis	Results	Conclusions
Silthampitag et al (2016)[45] Effect of surface pretreatments on resin composite bonding to PEEK	PEEK	Al2O3 - 27µm 98% sulfuric acid Piranha solution	Heliobond (Ivoclar)	HelioBond (Ivoclar)	Z350 XT 3M ESPE	**µSBS Mpa** The SBS test was performed using a universal testing machine at a crosshead speed of 1 mm/min until the resin composite cylinder came off. The failure force in newtons was recorded and divided the force with bond surface area (mm2) resulting in megapascals (MPa).	Two-way ANOVA / Tukey's comaprisons.	SEM demonstrated porosities and pitting from chemical etching, which suggested a significant influence on the adhesion between PEEK and resin materials	The SBS of resin composite on PEEK in the 98% sulfuric acid with Heliobond® was statistically greater than those of the other groups. Adhesion between PEEK and resin materials appears to be micromechanical locking from penetration of bonding agent along the pits. Surface topography seems to affect the adhesion more than surface roughness.
Tekçe et al (2017)[38] Microtensile Bond Strength of CAD/CAM Resin Blocks to Dual-Cure Adhesive Cement: The Effect of Different Sandblasting Procedures	Cera Smart Lava Ultimate (3M) Vita Enamic (Vita)	Al2O3 - 27µm Al2O3 - 50-µm	Silane primer G-Multi Primer	N/A	G-Cem LinkForce (GC)	**µTBS Mpa** The beams were attached to a modified device for µTBS testing and were subjected to a tensile force in a universal testing machine at a 0.5 mm/min crosshead speed. The tensile load was applied until specimen failure. The failure modes were evaluated at 40x magnification using a stereomicroscope. The failure modes were classified as cohesive failure within the resin block and adhesive failure at the inteface.	Kruskal-Wallis One-way ANOVA and Dunn's Post Hoc Test (p < 0.05).	Group 1 exhibited significantly lower µTBS than the other groups (p < 0.05). The highest bond strength values were obtained from group 4 (p > 0.05). For LAVA, µTBS values of specimens that were sandblasted with 50-µm Al2O3 powder were significantly higher than 30-µm-SiO2 and 27-µm Al2O3 (p < 0.05).	The sand particles investigated (27-µm Al2O3, 30-µm SiO2, or 50-µm Al2O3) did not significantly affect µTBS results of CAD/CAM blocks for Cerasmart and VITA, although the results changed significantly for LAVA. The ideal bond protocol for CAD/CAM blocks is specific to the material used.
Trindade et al (2016)[39] Ceramic Inlays: Effect of Mechanical Cycling and Ceramic Type on Restoration-dentin Bond Strength	IPS e. max CAD (Ivoclar) Vita Mark II (Vita)	35% phosphoric acid 10% HF acid	Rely X ceramic primer Adpter Single Bond-2 Single Bond Universal (3M)	Rely X ceramic primer (3M) Adpter Single Bond-2 Single Bond Universal (3M)	Rely X ARC	**µTBS Mpa** Specimens were fixed with cyanoacrylate to a metal base. Both bonded interfaces from each microbar were submitted to the MTBS test. MTBS test - each microbar was bonded to a stainless-steel tensile testing device using a light-polymerized adhesive resin and was submitted to the MTBS loading.	Student t-test / Tukey test (a=0.05).	The adhe sive failure mode at the ceramic/cement inter face was the most frequent. Vita Mark II showed the highest value of average rough ness. IPS e.max Press and Vita Mark II ceram ics presented the lowest contact angles.	Different ceramic inlay restorations can promote different adhesion, with the highest bond strength mean values obtained with the Vitamark II ceramic groups, with and without mechanical cycling. Vitamark II showed the highest surface roughness and the lowest contact angle values. The study showed that the mechanical cycling did not significantly degrade the bond strength between dentin and ceramic restoration.
Ustun et al (2020)[42] Effect of different cement systems and aging on the bond strength of chairside CAD-CAM ceramics	Cera Smart Vita Enamic (Vita) Vita Suprinity-VS	37% phosphoric acid 5%HF	Single Bond Universal (3M) Ultradent Porcelain Silane	Single Bond Universal (3M)	RelyX U200 (3M) RelyX Ultimate (3M) - DUAL	**µSBS Mpa** Half of the specimens were thermally aged in a 5°C to 55°C water bath for 5000 cycles with 30 seconds in distilled water and a transfer time of 5 seconds, representing approximately 6 months of clinical use. Each specimen was held with the fixture of the universal testing machine and loaded at 0.5 mm/min until fracture when the maximum force was recorded (N) by the machine. The shear bond strength (S) values (MPa) were calculated by using the formula S=L/A, where L is the load at failure (N) and A is the adhesive area (mm2) measured.	3-way analysis of variance (ANOVA)	The highest bond strength value was found in the nonthermal aged VS-TE and the lowest in the thermal aged VE-TE. Significant interaction was found between TE and SE cemented ceramics (P<.001). For specimens cemented with the SA system, significant interaction was found among ceramics with thermal aged specimens (P<.001). Thermal aging significantly decreased the mean bond strength (P<.05).	Differences in bond strength were observed in chairside CAD-CAM ceramics when cemented with TE, SE, and SA systems. Additionally, thermal aging significantly reduced the bond strength values of all the ceramic materials.
Wu et al (2018)[40] Effect of tribochemical silica coating or multipurpose products on bonding performance of a CAD/CAM resin-based material	Lava Ultimate (3M)	Al2O3 - 27µm Al2O3 - 50-µm	Porcelain Primer - Bisco Silane (No specification)	N/A	Rely X Veneer Rely X Unicem 2 Automix	**µSBS Mpa** Micro-shear bond strength (µ-SBS) was measured after 24-h water storage or ageing with 10,000 thermocycles plus additional 90-d water storage. Surface morphology was observed by using a scanning electron microscope.	Three way analysis of variance (ANOVA) followed by Tukey's post-hoc LSD test	µ-SBS was significantly affected by bond strategies and ageing. Ageing by thermocycling and water storage significantly decreased µ-SBS. µ-SBS values derived by use of a universal adhesive or self-adhesive resin cement alone were no lower than the values derived by use of a silane coupling agent alone. Pre-silanization further enhanced the bonding improvement of universal adhesive or self-adhesive resin cement. Tribochemical silicacoating failed to provide higher µ-SBS compared with alumina air abrasion. XRD detected nomonoclinic zirconia phase after alumina air abrasion or tribochemical silica coating.	Combination of presilanization and universal adhesives improve resin bonding of nanocomposite ceramics. Tribochemical silica coating is not superior to alumina air abrasion for pretreated nanocomposite ceramics
Yazigi et al (2017)[47] Influence of various bonding techniques on the fracture strength of thin CAD/CAM-fabricated occlusal glass-ceramic veneers	IPS e. max CAD (Ivoclar)	37% phosphoric acid	Adhese Universal	Adhese Universal (Ivoclar)	Variolink Esthetic	**µSBS Mpa** Half of the specimens of each subgroup were subjected to thermo- dynamic loading in a chewing simulator with 1,200,000 cycles at 10 kg load. The other half and the surviving specimens were subjected to quasi-static loading until failure.	Shapiro-Wilk test / Three-way ANOVA / Tukey's post-hoc	All specimens except one survived the artificial aging. A significantly higher fracture strength of restorations (p≤0.001) was obtained when immediate dentin sealing was followed regardless of the etching method with values ranging from a minimum of 1,122±336 N to a maximum of 1,853±333 N. Neither the pre-cementation treatment nor the artificial aging had a statistical significant effect on the fracture strength	Premolar occlusal veneers fabricated from lithium disilicate ceramic and adhesively bonded to dentin demonstrated fracture resistance exceeding the recommended values for restoring posterior teeth. Following the immediate dentin sealing protocol can have a beneficial effect on the fracture resistance of the occlusal veneers. Moreover, it can be concluded that selective etching of the enamel was as effective as total-etching.
Archibald (2017)[48] Retrospective clinical evaluation of ceramic onlays placed by dental students	IPS e. max CAD (Ivoclar)	10% HF 35% phosphoric acid	Monobond S	Multilink Primer Scotchbond Universal	Variolink II (Ivoclar)	Thirty-seven onlays were evaluated clinically. Data were statistically analyzed using the Cox proportional hazards model . Survival probability was calculated using the Kaplan-Meier algorithm.	Cox proportional hazards model to compare tooth type and failures and the Fisher exact and McNemar tests to compare the USPHS criteria for significant differences (a=.05)	Five onlays were considered to be failures and needed replacement. According to the Kaplan-Meier analysis, the estimated survival rate was 96.3% after 2 years and 91.5% at 4 years. All 5 of the failures occurred on molars (13.5%) and none on premolars (P=.025). A statistically significant difference was found for marginal discoloration between onlays placed within 0 to 3 years and 3 to 6 years (P<.05) but no differences between any other criteria	Ceramic onlays placed by dental students demonstrated acceptable long-term clinical performance.
Ernst (2016)[49] Innovative adhesive luting protocol	IPS e. max CAD (Ivoclar)	5% HF	Monobond Etch & Prime	Adhese Universal	Variolink Esthetic DC	Aesthetic evaluation of anterior crowns after cimentation	N/A	The tremendous improvement in the appearance of the front teeth, which was achieved with the all-ceramic restorations on tooth 11 and 21.	It remains to be seen if external studies can confirm the effectiveness of the product in establishing na adhesive bond on ceramics other than those from Ivoclar Vivadent

5. DISCUSSION

Limiting this research to publications from the last 6 years was due with the intention of seeking laboratory results of materials potentially in use in contemporary clinical practice. However, the bias of the results should not have occurred, since on this subject, in the last 20 years, 70% of the articles were published within the chosen period.

In this systematic review, we found several types of protocols that aim to establish an adequate, efficient, and reliable way from the point of view of the longevity of prosthetic rehabilitation, for the adhesion of the different types of milled CAD-CAM blocks to dental structures in cases of indirect restorations. These protocols aim, above all, to offer solutions for the clinicians so that they can achieve with their patients a restorative treatment that is functionally and aesthetically satisfactory for as long as possible, as the innovations brought by the CAD CAM process has greatly facilitated indirect restorations with a high degree of esthetic demand and when well executed, they are satisfactorily long-lasting since the adhesive systems used achieve a stable union between the milled material and the tooth in a relatively practical and fast way, as demonstrated by the two clinical trials presented here.[11,17,22,26,28,46,48,49]

We should also highlight, as a success factor for this type of restoration, the low production cost when compared to traditional methods of manual ceramic application.[13] In other words, there are numerous factors that seem very evident when we talk about the success of indirect restorations with CAD-CAM blocks.[22] This review, however, brings out one of the dissonant factors regarding this issue, which is the apparent lack of systematization between the different in vitro protocols found in the articles accessible to be analyzed.

A careful analysis of the tests, whether *in vitro* or *in vivo*, highlights the lack of parallelism between the protocols used by the different authors, which makes it difficult for the clinician to identify a reliable process that can be reproducible in daily practice.

It is also important to refer that the process of choosing the union system for different restorative materials often presents itself as a complicated issue for clinicians.

According to Klosa et al. (2016)[50] a quiz taken in German dentists showed that a high number of professionals employed inappropriate bonding methods. This indicates the potential benefit of simplifying bonding processes as well as establishing clear and evidence based criteria.[22]

We can certainly find a level of agreement among the reviewed authors regarding the importance of using appropriate cements as well as the judicious use of surface conditioners and bonding agents to obtain durable restorations.[12,16,24,26]

However, the universe of options both in terms of laboratory protocols and the diversity of materials available for CAD-CAM restorations, such as blocks, cements, bonding agents and surface conditioners is vast.[23] Equally varied is the number of types of tests that assess strength,[25] as well as protocols that simulate aging and bonding failure. What we do know for sure, is that we still don't have a clear answer as to which type of ceramic and adhesive system has the highest bond strength values for clinical use,[42] which absolutely does not mean that we do not have good materials and good analysis protocols at our disposal, it is just not yet possible to say precisely which are the best. Such a variety of materials often plays a counterproductive role in a research of this nature as it is impossible to test all of them at the same time, so it is very common to see researchers going in the diametrically opposite direction, that is, testing only one type of material. This choice obviously presents itself as a limitation, as even though a dual-cure resin cement is considered the gold standard for adhesive luting, each of the different brands has important differences in their properties.[27,29,44]

The most evident limitation regarding these studies is the fact that most of the articles, 37 of them, were *in vitro* studies in detriment of only 2 *in vivo* studies where both used pressed all-ceramic IPS e.max® crowns or IPS e.max CAD ® as restorative blocks. Variolink® Esthetic, Variolink II ®Ivoclar (Vivadent AG) and RelyX Ultimate (3M ESPE) was chosen as luting material corroborating the trend of choice of such materials by researchers, either *in vitro* or *in vivo* tests.[48,49] We know, for example, that it is very common for specimens in laboratory tests to be kept in water, which does not fully reproduce the dynamics of the oral cavity environment in terms of temperature variations, saliva bath, occlusal loads or eventual parafunctional habits.[28,29,38,42,51]

Furthermore, in vivo studies often entail risks for both professionals and volunteers, who undergo these studies. Such dreaded risks have stimulated the advancement of research guidelines involving human subjects such as the Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) of the Western University, Ontario, Canada[48] or the Ethic Committee for Humans Studies from Bauru School of Dentistry at University of São Paulo, Brazil,[18] a fact that can act as a demotivation for the pursue of randomised clinical trials, the probable reason for our finding of only to studies.

Addressing the issue of lack of parallelism between studies involving the CAD-CAM blocks in their specific points, we can mention the tests that assess the bond strength.

The most common tests used by researchers are the tensile bond strength (TBS) and shear bond strength (SBS) tests. Such tests are specifically used when we have specimens with bonded areas between 7 to 28 mm^2, numbers that represent relatively large areas for intraoral dimensions.[1] However, when analysing the articles that bring cohesive strength tests in this review, it is much more common to find the so-called micro-shear and micro-tensile tests due to limitations related to cohesive failures in areas larger than 2 mm^2.[1] Smaller areas have a lower coefficient of variation when compared to other types of tests[11,18,46]. As shown in Figure 4, this review found a slight trend towards greater use of μSBS tests to the detriment of μTBS. Of the articles researched, only one of them used both types and test.[18] All others used only μSBS[1,8,11,14,18-21,23,25,27,32,34,36,40,42,44,47] or only μTBS tests[6,17,29,43].

Although both types of tests meet the International Organization for Standardization (ISO) guidelines, the choice of doing only tensile and compression tests or tests that assess the bond strength at the interface between the block and the tooth or even both types of tests together sound more like a researcher's preference over a universal analysis standard.[46]

When analysing the studies, some authors tried to simulated aging and materials fatigue by submitting the specimens to thermocycling. We found a disparity related to the amount of thermocycling between the articles, which ranged from 5.000[19,21] to 240.000[30] cycles, but also had variation of temperature and moisture conditions for the same type of test.

As discussed above, in vitro tests involving CAD-CAM blocks try to reproduce the conditions found both in the oral cavity, but also try to reproduce the resources available for the clinician. The materials used as cements, bonding agents, surface conditioners and light curing agents tend to be the same found in any dental office around the world. However, the way these resources are used in *in vitro* assays varies considerably.

When approaching light curing protocols, we found important differences in the articles of this systematic review both in terms of the light wavelength used and curing time adopted, as we have articles that advocate a wavelength of 1220mW/cm^2,[23,29,44] some use 1000 mW/cm^2, [6,8,19] and others 650 mW/cm^2,[22] As for the polymerization time, it can vary from 20s[8] to 400s,[6] what means approximately 7 minutes. Such variations can certainly cause confusion among clinicians, not to mention the impracticality of polymerizing a single restoration for 7 minutes in a patient with multiple teeth to be restored and the potential pulpal lesion by heating.[52]

To reproduce in a minimally similar way the conditions found in the oral cavity, the tests conducted in the articles adopted the water-storage of the specimens at 37ºC for some period, but in turn do not meet standard criteria. The water-storage periods varied a lot, ranging from 24h[22,46] to 6 months,[14] Therefore, we have a convergence regarding objective parameters such as the average body (oral) temperature, but the divergence is evident when adopting subjective parameters such as the time.

Regarding the specific focus of this systematic review, we can see, in Figure s 2 and 3, that despite having a wide variety of materials available, researchers tend to privilege some materials over others. In relation to CAD-CAM blocks, the most used materials are the IPS e. max® (Ivoclar Vivadent), Vita Enamic® (Vita - Zahnfrabik) and Lava® Ultimate (3M ESPE). Among the luting materials, Rely X® Ultimate Dual (3M ESPE) stands out as the most used of them.[1,6,8,11,14,16,19,21-24,26,27,29-31,33,37,38,41,42,47,49] As frequently the laboratorial studies are sponsored, we cannot discharge the hypothesis that the preferred materials were, in some extent, conditioned by the access to sponsorship or were chosen in view of the dental clinicians' preferences.

6. CONCLUSIONS

Based on the findings of this systematic review, we concluded that:

1) The lack of standardization in laboratory studies is evident, and several aspects related to materials testing and technical resources are usually complex and sometimes contradictory to allow the clinicians to have maximum assurance that they are following a conduct that is scientifically accurate.

2) There is a real commitment of researchers to find the best way to test materials and develop methods that can serve as parameters, so that clinicians can carry out restorative rehabilitation with CAD-CAM blocks, a technology that undoubtfully is increasing mechanical performance and intraoral durability.

3) *In vitro* studies cannot accurately reproduce the entire dynamics of intraoral conditions.

4) It is desirable a unification of the test parameters, at least of those that could be reproduced in the daily clinic as trusty as possible.

5) Randomized clinical trials or well documented clinical cases concerning this subject are almost inexistent, probably reflecting the rapidly emerging materials, a fact that didn't allow the inference of direct application of laboratory findings in clinical practice.

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7. CLINICAL CONSIDERATIONS

The relevance of this systematic review is within the scope of the importance of unifying the scientific parameters that test the characteristics of the materials used by the clinician daily. Such standardization gives professionals the security of using materials to the fullest of their restorative capabilities, leading to even longer lasting, aesthetic and functional treatments.

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