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Tese

Métodos de envelhecimento da interface adesiva para testes de adesão à dentina

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“Se as coisas são inatingíveis... ora!
Não é motivo para não querê-las...
Que tristes os caminhos, se não fora
A presença distante das estrelas”

(MÁRIO QUINTANA)

Notas Preliminares

A presente tese foi redigida segundo o Manual de Normas para Dissertações, Teses e Trabalhos Científicos da Universidade Federal de Pelotas de 2013, adotando o Nível de Descrição em Capítulos Não Convencionais, descrito no referido manual:
<http://sisbi.ufpel.edu.br/?p=documentos&i=7> Acesso em: <20/12/18>.

O projeto de pesquisa referente à esta Tese, foi aprovado em 12 de fevereiro de 2016, pela Banca Examinadora composta pelas Professoras Doutoras Françoise Van de Sande, Marina da Rosa Kaizer e Gabriela Romaini Basso (suplente).

Resumo

BRAUNER, Katielle Valente. **Métodos de envelhecimento da interface adesiva para testes de adesão à dentina.** 2019. 118f. Tese (Doutorado em Odontologia) – Programa de Pós-Graduação em Odontologia. Universidade Federal de Pelotas, Pelotas, 2019.

O objetivo deste trabalho foi avaliar o efeito da degradação da interface resina-dentina, medida pela diminuição da resistência de união (RU) após diferentes métodos disponíveis para simulação de envelhecimento acelerado. O trabalho foi dividido em dois estudos: (1) uma revisão sistemática e meta-análise da literatura; e (2) um experimento *in vitro*. O primeiro estudo foi descrito de acordo com o PRISMA buscando avaliar se os diferentes métodos e protocolos de envelhecimento acelerado são efetivos na diminuição da resistência de união à dentina utilizando resina composta direta. Foi identificado que a ciclagem térmica teve efeito significativo na maioria dos protocolos utilizados para o envelhecimento da interface. Ciclagem mecânica e termomecânica, pressão pulpar, armazenamento de NaOCl e ciclagem térmica + armazenamento estático foram capazes de promover a diminuição da RU. O armazenamento em enzima só foi capaz de diminuir a RU em períodos de pelo menos 3 meses; e os protocolos de ciclagem de pH e desafio cariogênico avaliados não foram capazes de promover a diminuição da RU. Já o segundo estudo testou 5 das metodologias disponíveis em laboratório (termociclagem, ciclagem mecânica, ciclagem mecânica com Rub&Roll, desafio cariogênico e 5 semans de armazenamento em água) avaliando a resistência de uião à microtração. Para esse experimento foram utilizados dois tipos de adesivo (convencional e autocondicionante) e o grupo controle permaneceu em água (37ºC) por 24 horas. Foi observado que 14 dias de desafio cariogênico foram capazes de reduzir a RU do sistema adesivo convencional e a ciclagem mecânica do autocondicionante. Com esta tese podemos concluir que muitos métodos de envelhecimento acelerado podem ser efetivos na degradação da interface, porém diversos parâmetros devem ser considerados como tempo de envelhecimento, condições de armazenagem e material utilizado.

Palavras-chave: envelhecimento, dentina; resistência de união;

Abstract

BRAUNER, Katielle Valente. **Aging methods for dentin bond strength tests.** 2019. 118p. Thesis (PhD in Dentistry). Graduate Program in Dentistry. Federal University of Pelotas, Pelotas, 2019.

The aim of this study was to evaluate the effect of degradation of resin-dentin interface, measured by the decrease of the bond strength (BS) after different available methods for simulation of accelerated aging. The work was divided into two studies: (1) a systematic review and meta-analysis of the literature; and (2) an in vitro experiment. The first study was described according to PRISMA to investigate whether the different accelerated aging methods and protocols are effective in reducing bond strength to dentin using direct composite resin. It was identified that the thermal cycling had a significant effect in most of the protocols used for the aging of the interface. Mechanical and thermomechanical cycling, pulpal pressure, NaOCl storage and thermal cycling + static storage were able to promote the decrease of BS. Enzyme storage was only able to decrease the BS in periods of at least 3 months; and the pH cycling and cariogenic challenge protocols evaluated were not able to promote the decrease of the BS. The second study tested 5 of the available methodologies in the laboratory (thermal cycling, mechanical cycling, mechanical cycling with Rub & Roll, cariogenic challenge and 5 weeks of storage in water) and evaluated microtensile bond strength. Two types of adhesive were used for this experiment (etch-and-rinse and self-etch) and the control group remained in water (37 C) for 24 hours. It was observed that 14 days of cariogenic challenge were able to reduce the BS of the etch-and-rinse adhesive system and the mechanical cycling of the self-etch. With this thesis we can conclude that many methods of accelerated aging can be effective in the degradation of interface, however, many parameters should be considered as aging time, storage conditions and material used.

Key-words: aging, dentin, bond strength.

Sumário

1 Introdução

Fratura e cárie secundária são as maiores razões de falhas em uma restauração, o que torna sua longevidade, motivo de investigações em estudos de odontologia, principalmente por o sucesso/falha dessas restaurações dependerem de vários fatores relacionados ao paciente, idade, operador e material utilizado. Ainda assim, independentemente desses fatores, os eventos que ocorrem na cavidade bucal durante a função dentária promovem a contínua degradação ou envelhecimento dos materiais restauradores. Esse envelhecimento é um processo que pode levar ao surgimento de defeitos em restaurações tais como: manchamento superficial e marginal, aumento da porosidade superficial, degradação da interface adesiva e fraturas, tendo como consequência em certos casos a necessidade de substituição (DEMARCO et al., 2012, 2017; OPDAM et al., 2014).

Existem inúmeros eventos que ocorrem na cavidade bucal, geralmente combinando fatores físicos e químicos. Fatores físicos incluem as forças oclusais mastigatórias e os esforços repetitivos de expansão e contração associados a mudanças de temperatura no ambiente oral (AKIN et al., 2012; DE MUNCK et al., 2005). Já os fatores químicos desafiam as estruturas dentárias e materiais restauradores através da saliva, fluido dentinário, bebidas, alimentos e bactérias que atuam na superfície ou degradam fibrilas de colágeno desprotegidas e os componentes adesivos na interface dente-restauração (KHAMVERDI; REZAEI-SOUFI; ROSTAMZADEH, 2015; TASCHNER et al., 2014).

A simulação do envelhecimento na cavidade bucal é considerada essencial para avaliar materiais odontológicos em laboratório e avaliar a previsibilidade da adesão dentinária a longo prazo (SKOVRON et al., 2010). Na tentativa de simular os eventos que ocorrem clinicamente na cavidade bucal, várias metodologias têm sido utilizadas. O armazenamento de água é o procedimento mais utilizado para o envelhecimento das amostras em testes de durabilidade das interfaces de radesivos dentinários (SAURO et al., 2009; TOLEDANO et al., 2013; VIDAL et al., 2013), no entanto, a redução nos valores de resistência de união normalmente requer um período de 6 meses ou mais (GARBUI et al., 2012; SABOIA et al., 2009; SAURO et al., 2009).

Os ciclos térmicos e mecânicos são difundidos na literatura, geralmente realizados através de equipamentos específicos que simulam mudanças de temperatura e/ou eventos de carga ou mastigação (DANESHKAZEMI et al., 2015, 2013; ULKER et al., 2010). Embora comumente utilizados, não há consenso sobre qual é o melhor protocolo para envelhecer as interfaces adesivas. Além disso, a literatura apresenta vários outros métodos destinados a envelhecer essas interfaces, incluindo desafios químicos e cariogênicos através do armazenamento em saliva artificial, enzimas, hipoclorito de sódio e ciclagem de pH. Em outros casos, com o intuito de aproximar os estudos da realidade das condições desafiadoras do ambiente bucal, estudos *in situ* são realizados armazenando-se os espécimes em dispositivos intra-orais (HASS et al., 2016; SIMOES et al., 2014).

Outro problema das investigações in vitro em longo prazo sobre a ligação resina-dentina é que não apenas o método, mas também o protocolo de envelhecimento pode variar entre os estudos. Por exemplo, estudos usando ciclos térmicos para desafiar a interface adesiva podem usar de 100 a 100.000 ciclos térmicos e, portanto, uma comparação direta entre eles pode não ser viável (FUKUOKA et al., 2011; HARIRI et al., 2012; YOSHIHARA et al., 2015). Além disso, protocolos de ciclos térmicos mais longos também exporão as interfaces por mais tempo aos efeitos da degradação da água, portanto a influência das mudanças de temperatura pode ser superestimada. O mesmo cenário pode ser observado para outros métodos de envelhecimento.

Obter uma compreensão mais profunda sobre o mecanismo de adesão à dentina leva a resultados clínicos mais favoráveis, aumentando a durabilidade dos procedimentos preventivos e restauradores. Mas, quando se trata de envelhecimento acelerado, ainda existe uma lacuna em quais metodologias e protocolos são efetivos. Baseado nisso os objetivos da presente tese foram:

1. Revisar sistematicamente a literatura sobre o efeito da degradação da interface resina-dentina, medida pela diminuição da resistência de união após diferentes métodos disponíveis para simulação de envelhecimento acelerado.

2. Avaliar a resistência de união à microtração de um adesivo convencional e um autocondicionante após diferentes métodos de envelhecimento acelerado.

2 Capítulo 1

Title. Methods for aging dentin bonded interfaces: A systematic review and meta-analysis[1]

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Abrstract

Objectives. Many methods for simulating the aging of dentin-bond composites are commonly used in dentistry, but there is still a gap in which methods are actually capable of affecting bond strength. This systematic review aimed to evaluate the degradation effect of the resin-dentin interface, measured by decreasing bond strength (BS) after different in vitro and in situ methods available for simulation of accelerated aging of direct composite resin to dentin. Data. The database search for studies that made accelerated aging retrieved 11,001 eligible studies. After deduplication, 8,003 records were examined by the titles/abstracts; 7,806 studies were excluded and 197 articles were assessed for full-text reading. In total, 133 articles met inclusion criteria and were included in the study. Sources. The databases analyzed were MEDLINE/PubMed, ISI Web of Science, and Scopus. Study selection. Papers were selected if they presented an evaluation of (micro)tensile or (micro)shear bond strength to artificially age dentin bonded to composites. Groups were compared to non-aged bonded dentin interface. Only studies written in English were included. Studies or groups that performed only static aging were excluded. Conclusions. Thermal cycling had significative effect in most of protocols used for aging the interface. Mechanical and thermomechanical cycling, pulpal pressure, NaOCl storage and Thermal cycling + static storage were able to promote the decrease of BS. Enzyme storage was only able to decrease BS in periods of at least 3 months; and the evaluated pH cycling and cariogenic challenge protocols were not able to promote the decrease of BS.

Keywords: Aging; Bond Strength; Dentin; Composites; *in vitro*;

Highlights

Many methods to accelerated aging are commonly used.

Different methods of accelerated aging were able to promote the decrease of BS.

Thermal cycling was the most found method in studies that made accelerated aging.

1. Introduction

The resin-dentin interface in adhesive restorations is susceptible to failure over time [1]. There are numerous events that occur in the oral cavity, usually combining physical and chemical factors. Physical factors include the occlusal masticatory forces and repetitive expansion and contraction stresses associated with changes in temperature within the mouth [2,3]. Chemical factors challenge the dental structures and restorative materials through components in saliva, dentinal fluid, beverages, food and bacteria metabolites that act on the surfaces or degrading unprotected collagen fibrils and the adhesive components at the bonded interfaces [4,5].

The simulation of aging in the oral cavity is considered essential to evaluate dental materials in the laboratory and assess the predictability of the dentin bonding in the long term [6]. In an attempt to simulate the events that occur clinically in the oral cavity, several methodologies have been used. Thermal and mechanical cycling are widespread in the literature, usually performed through specific equipment that simulate temperature changes and/or loading or chewing events. Although commonly used, there is no consensus on which is the best protocol to age adhesive interfaces. In addition, the literature presents several other methods designed to age bonded interfaces, including chemical and cariogenic challenges through storage in artificial saliva, enzymes, sodium hypochlorite and pH cycling solution. In other cases, in an endeavor to bring the studies closer to the reality of the challenging conditions of the oral environment, in situ studies are carried out by storing the specimens in intraoral devices [7,8]

Another problem of long-term *in vitro* investigations on resin-dentin bonding is that not only the aging method but also the aging protocol may vary among studies. For instance, studies using thermal cycling to challenge the adhesive interface may use from 100 to 100,000 thermal cycles and, therefore, a direct comparison among them may not be feasible [9–11]. In addition, longer thermal cycling protocols will also expose the interfaces longer to water degradation effects, thus the influence of the temperature changes could be overestimated. The same scenario may be observed for other aging methods.

Obtaining a deeper understanding about the mechanism of adhesion to dentin can leads to more favorable clinical results, increasing the durability of restorative procedures. But when it comes to accelerated aging there is still a gap concerning which protocol to apply and for how long. Based on this, this systematic review aimed to evaluate the degradation effect of the resin-dentin interface, measured by decreasing bond strength (BS) after different *in vitro* and *in situ* methods available for simulation of accelerated aging.

2. Materials and Methods

This systematic review was carried out according to the guidelines of Cochrane Handbook for Systematic Reviews of Interventions [12] and followed the four-phase flow diagram based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [13]. To formulate the research question, the following PICOT was established: “Population”: direct resin composites bonded to dentin; Intervention: artificial aging of the bonded dentin interface; Comparison: non-aged bonded dentin interface; Outcome: BS to dentin; Type of study: *in vitro* or *in situ*. The research question was: Which accelerated aging methods are able to degrade the dentin BS?

2.1. *Search Strategies*

Studies were identified through Medline/PubMed, Scopus, and Web of Science databases. The last search was carried out in November 2017 without date restrictions. The following search strategy was used in PubMed and adapted to the other databases: (aging*) AND (material* OR adhes*) AND (dentin*) AND (bond strength*) (Table 1). Literature search results were de-duplicated using EndNote X7 software (Thomson Reuters, New York, NY, USA).

2.2. *Study Selection*

Two independent reviewers initially screened the titles of all identified documents. The studies were analyzed according to the selection criteria described in Table 2. If the title indicated possible inclusion, the abstract was evaluated. After the abstracts were carefully appraised, manuscripts considered eligible (or in case of doubt) were selected for full-text reading. Discrepancies were resolved by discussion with a third reviewer. The references cited in the included papers were also checked to identify other potentially relevant articles.

2.3. *Data Collection*

A standardized outline was used for data extraction based on the characteristics of studies and groups tested: sample size, aging protocol, BS test, number of cycles or time of aging, material used, and conclusion. Dentin BS means and standard deviations were also extracted. The authors of the studies were contacted in case of missing or any unpublished data; these studies were only included if the authors provided the missing information. In case the authors did not reply and the data were presented in graphs, WEBPLOTDIGITIZER (version 3.10, http://arohatgi.info/WebPlotDigitizer/) was used for conversion of plots into numerical values.

2.4. *Assessment of Risk of Bias*

The risk of bias was assessed based on previous studies [14–16] and The Cochrane Collaboration's tool for assessing risk of bias [17]. The following parameters were considered: teeth randomization, materials used according to manufacturers' instructions, sample size calculation, and blinding of the operator of the testing machine. The reporting or not of each item was evaluated as high, low, or unclear risk of bias. Assessment of risk of bias was conducted using Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) by two researchers.

2.5. *Data Analysis*

Characteristics of the studies were summarized descriptively and a random effects meta-analysis was conducted to calculate pooled mean difference between the control and aging protocols. Analyses were initially carried out separately for self-etch and etch-and-rinse adhesives; however, as the adhesive systems presented similar results, the adhesives were not separated in the final analyses. As a *post hoc* decision, subgroups analyses were carried out to explore the influence of time and number of cycles in each aging method according to the included studies (Table 3). Multiple groups compared to a single control from the same study were analyzed according to the Cochrane guideline formula for combining groups [12] in order to obtain single values of sample size, mean and standard deviation. $P<0.05$ was considered statistically significant. Statistical heterogeneity was considered using I^2

test (>75% indicates high heterogeneity). The analyses were conducted using Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3. Results

3.1. *Search Strategy*

A total of 11,001 potentially relevant records were identified from all the databases, of which 2,998 were duplicates. No additional studies were identified as relevant after a search of the reference lists. Figure 1 shows a flowchart summarizing the article selection process according to the PRISMA Statement. After the title and abstract examination, 7,805 studies were excluded. From the 197 studies assessed in full, 64 studies were excluded because they did not meet the eligibility criteria or the study was not found. Details of articles selection and reasons for exclusions are also shown in Figure 1. A total of 133 studies fulfilled all of the selection criteria and were included in the quantitative and qualitative analysis.

3.2. *Risk of Bias of the Included Studies*

Concerning the quality assessment (Figure 2), most of the studies performed tooth randomization and used the materials according to the manufacturer's instructions. However, only two studies performed a sample size calculation [21,43]. and one study performed the BS test with a blind operator [135].

For all types of aging protocols, a qualitative analysis is presented (Tables 4 to 13).

3.3. *Thermocycling*

Figures 3 to 6 show the results of the meta-analysis of the studies that tested thermocycling. For this analyzes, 65 studies were evaluated and the results were divided into six subgroups. The only subgroup that did not show significant effect favoring this aging method was 501 to 3,000 cycles ($P = 0.45$). The global analysis favored the thermal cycling ($P < 0.00001$).

3.4. *Mechanical Cycling*

Figure 7 shows the results of the meta-analysis of the studies that tested mechanical cycling. For this analysis, 18 studies were evaluated and the results were divided into three subgroups. The effect size increased proportionally to the number of mechanical cycles, but all subgroup analyses favored the aging condition ($P < 0.00001$).

3.5. *Thermomechanical Cycling*

The third meta-analysis present results in Figure 8 of the studies that tested thermomechanical cycling, eleven studies were divided into three subgroup analysis. The effect size was bigger in the subgroup tested with more cycles. The global analyses favored the thermomechanical cycling ($P < 0.00001$).

3.6. *Static Storage and Thermocycling*

Figure 9 shows the only meta-analysis that evaluated the association of aging between thermocycling and storage in water or artificial saliva. For this analysis eight studies were evaluated and the obtained response favored this type of aging protocol ($P < 0.02$).

3.7. *Pulpal Pressure*

The subgroup analysis presented in Figure 10 evaluated pulpal pressure as an interface aging and seventeen studies were divided into three subgroups. All subgroups were satisfactory ($P < 0.00001$), but the one that had the biggest effect was the one that evaluated the BS after 1 week to 3 months under pulp pressure.

3.8. *NaOCl and Enzyme Storage*

Figures 11 and 12 represent NaOCl and enzyme storage, for these, seventeen studies with NaOCl and five with enzyme were analyzed separately. NaOCL storage presented significant results for the two subgroups tested and a decrease of BS in the groups tested with longer storage times. ($P < 0.00001$). On the other hand, studies that made enzyme storage were divided into three subgroups and the only one that presented favorable results to this method of aging was the storage for 12 weeks ($P < 0.00001$).

3.9. *Cariogenic Challenge and pH Cycling*

Figures 13 and 14 show meta-analysis of aging with cariogenic challenge and pH cycling, two and three studies were found respectively for each. For both groups there was no significant effect ($P = 0.14$) and ($P = 0.10$) respectively.

3.10. *In Situ*

Figure 15 shows the only meta-analysis that evaluated *in situ* studies. For this, two studies were found and results showed a significant reduction of BS (P <0.00001). The effect size was -9.58, 95% CI between -11.67 and -7.48 and I^2 = 29%.

4. Discussion

This review found several studies that used in vitro or in situ aging from the most elaborate to the simplest protocols to accelerate the degradation of the dentin-restoration interface. It was noted that there is no established standard for these types of evaluations because most studies consider different numbers of cycles, times, strength and temperature even using the same type of aging (eg mechanical cycling). For this reason, we tried to divide analyzes into subgroups, whenever possible, so that we could have the best possible evidence. Still, this is the first time almost all aging protocols are tested and results points toward a positive effect of almost all tested protocols, except for cariogenic challenge and Ph cycling.

An important issue to be discussed is that there was a high I^2 level. When we speak of heterogeneity in a meta-analysis, our intention is generally to understand the substantive implications of this heterogeneity in the findings. Although there is a common belief that the I^2 statistic provides this information, it does not, it is a kind of bridge between the observed effect and the actual effect and in fact it is the proportion of total variation in the point estimates that is attributable to between-study heterogeneity [142,143]. In this review, the included studies show a huge variation between methodologies, 98.5% of which are *in vitro*, which already tend to have methodological variations from study to study, and this is what the I^2 shows. However, when we analyze the results of different types of aging, they are able to show a global view, where we can see not only the methods of artificial aging that have been used over the years, but also whether they have been working or not.

The assessment by the bias risk instrument showed a high prevalence of unclear judgment, which indicates that problems in the reporting of studies may be an aggravating factor in the results. This factor may be related mainly to a lack of consensus guidelines or guidance on how to conduct and report studies in the in vitro dental literature, and this factor also seems to be related to the high heterogeneity found in the meta-analyzes.

Thermal cycling was undoubtedly the most used option for studies evaluating BS before and after accelerated aging. This method subjected the specimens to extreme temperatures to simulate intraoral conditions by generating repetitive contraction and expansion tensions between the dental substrate and the restoration [2]. This review evaluated 65 studies that performed thermal cycling, among them, were evaluated from 100 to 100,000 cycles. The subgroups were analyzed according to the number of cycles and the only subgroup that did not present difference when compared to the control was 500 - 3,000 cycles, the other 5 subgroups all decreased the BS after aging, including the subgroup that evaluated up to 500 cycles. Thermal cycles has been used for a long time and is therefore indicated in ISO standard TR 11405 (1994) suggesting 500 cycles as a suitable artificial aging test. In 1999 Gale and Darvell [144] established a relationship between 10,000 cycles of thermal cycling and a period of one year, which has been commonly used according to our findings.

The use of mechanical load cycling has been studied due to the potential capability of simulating mastication. Clinical studies showed that bonded interfaces are subject to some cyclic loading due parafunctional habits and masticatory function, and this can change with the size, position of the restoration and individual risk of the patient [145,146], and all influence of occlusal forces on the performance of restorations explains the relevance of this methodology. Our results have found a directly proportional correlation of the number of cycles versus interface degradation.

When it comes to studies on thermomechanical cycling that bind thermal cycles with mechanical or static aging in water with thermal cycling, it becomes more difficult to establish a protocol based on the predetermined studies, since they have a lot of methodological variety. For these, they were grouped in subgroups with the one that demonstrated more variation between the studies, in thermomechanical cycling the thermal cycles seemed to be more similar between the studies, since none used more than 1,000 cycles, reason why the subgroups were analyzed according to the mechanical cycles and the results corroborated with studies showing that the higher the number of cycles, the lower the adhesive resistance [31,84,95]. For studies that evaluated static aging + thermocycling, in all studies the specimens were submitted to 6 or 12 months of water and due to the low variability of cycles we chose to group all of them into a universal analysis which favored aging by associating the two methods. We could observe that the association of accelerated aging methods is a common practice and seeks to mimic different events that occur in the buccal environment [5,18].

Besides the impacts of the occlusal load and the impacts suffered by extreme temperatures, the dental structures are also influenced by chemical factors, such as pH oscillations and in addition biofilm accumulation and cariogenic challenge are conditions to which the oral environment is daily exposed [134,135]. The cariogenic challenge in both studies were carried out by intercalating culture medium with and without sucrose between 3 and 14 days. The pH cycling of the studies evaluated was done by alternating demineralising and remineralising immersions for 10 and 15 days [73,87,133]. Both analyzes have not been shown to be effective for the accelerated aging of the interface, however, few and short-term studies have been included in these analyzes, which impairs the result.

The use of an aqueous solution of sodium hypochlorite (NaOCl) as storage medium has been proposed as suitable for assessing bond durability and its relation with storage time has already been observed showing that the decrease was directly related to the storage period like in this review [116,120,147]. Dentin is a substrate composed of organic and inorganic components and its organic phase is represented by a structure rich in collagen, these structures are subject to degradation by proteolytic enzymes. This method has been used in many studies and the most used protocols are storage for three or five hours, both presenting drastic reductions of BS. Previous studies have shown BS reductions comparable to six-month storage in artificial saliva [78,126], which leads us to think that the use of an aqueous solution NaOCl as storage medium seems to be a very powerful model, able to promote fast adhesive interface degradation, however, this model may be considered too aggressive and less related to the natural events that occurs into the mouth when compared with the other ageing methods assessed. Additionally, enzymatic hydrolysis of adhesive resins by salivary enzymes is recognized as a plausible degradative mechanism. Enzymes that are activated in the low-pH environment of the mouth are responsible for the progressive breakdown of collagen matrices in resin-sparse regions at the bottom of bonding interfaces [130]. Storage in different enzyme types has been reported in different studies over the years and this review has identified that only the 3 months period seems to decrease dentin BS significantly.

Pulpal pressure creates difficulties and limitations for dentine sealing and restoration stability, the aim of this methodology is simulate the hydrostatic pressure that enhances water sorption leading to plasticization of polymer chains and increases collagen degradation [77,102]. Consequently, the BS was reduced for several bonding agents using this methodology [77,123]. In this review, three subgroups were analyzed: after 24h, after 3 months and after 6 months or more. Although all presented a statistically significant difference, the period that presented the biggest effect was the intermediate up to 3 months.

In situ models with cariogenic challenges are useful methods to age the resin–dentin interfaces [7,148]. However, as they depend on approval by a local Ethics Committee it requires much more time and costs, which makes in situ and in vivo studies more difficult than laboratory evaluations [2]. Only two studies were included in the meta-analysis, both of them aged the interface for 14 days and obtained favorable results for the degradation of the adhesive union after the experimental period [7,8].

Although water storage is the most popular method of artificial aging [96,123,134], it takes a long time to get results that can be obtained in days or weeks with other methods [78,120,123]. This review did not compare water storage but showed that different methods and protocols - from the easiest to hugely complex - can mimic events that occur in the mouth and bring challenging results to BS to dentin.

An important factor when it comes to microtensile is the conformation of the aged specimen, some studies age the entire block of the restoration and then section the samples on sticks; and others age the stick directly. Exposure of the entire block of restoration requires longer periods to identify the differences [149], although it may resemble a more realistic clinical situation in terms of hydrolytic degradation. On the other hand, the hydrolytic effect in smaller resin-dentin samples directly exposed to water can be obtained in shorter periods.[150–153] Some methods analyzed do not allow the direct aging of the toothpick as mechanical cycling and pulpal pressure, but when it is a question of thermal cycling, there is a lot of variation between studies when it comes to opting for direct or indirect aging.

Due to the large number of included studies and their heterogeneities, analyzes between methods were not performed, but taken together, the results of this review show that several aging methodologies are able to promote the degradation of the adhesive dentin-resin interface, and still is not possible to point out a single best method for this purpose. The overall results show that the choice of aging parameters is important considering what challenges are wanted to be brought to the interface. Considering the capability of methods to degrade the adhesive interface, researchers can select faster and efficient methods to simulate aging in in vitro research.

5. Conclusions

Within the limitations of this review it was possible to observe:

Thermal cycling was unable to decrease BS when used when used with less than 3.1 cycles;

Thermal cycling combined with storage, mechanical and thermomechanical cycling, pulpal pressure, storage in NaOCl were able to promote the decrease of BS;

In situ studies were able to promote the decrease of BS;

Enzyme storage was only able to promote the decrease of BS in periods of at least 3 months;

The evaluated pH cycling and cariogenic challenge protocols were not able to promote the decrease of BS.

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Figures

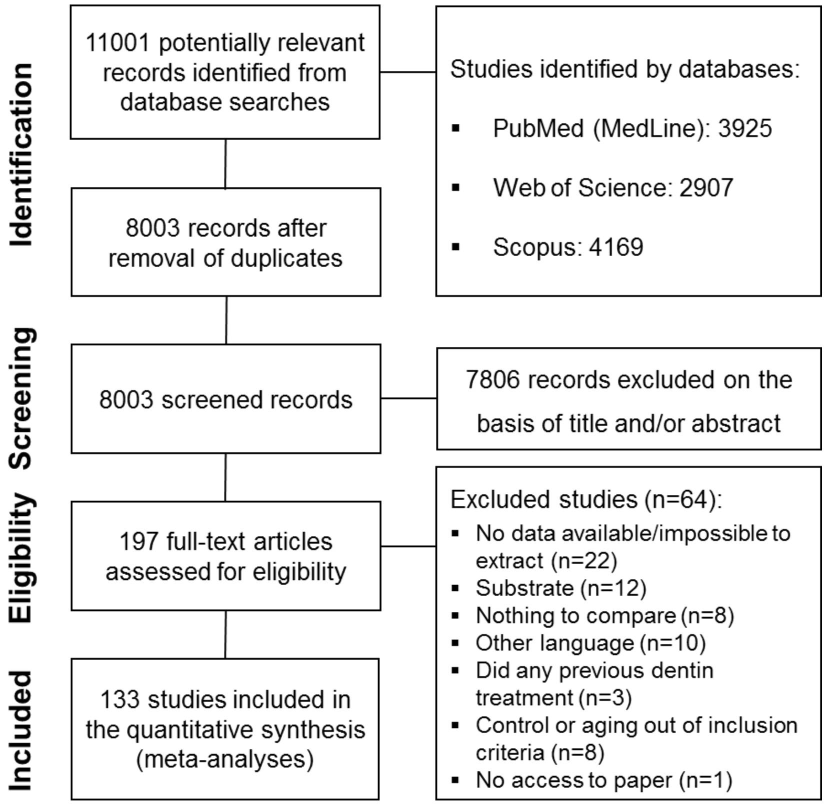


Figure 1. Search flow (as described in the PRISMA statement)

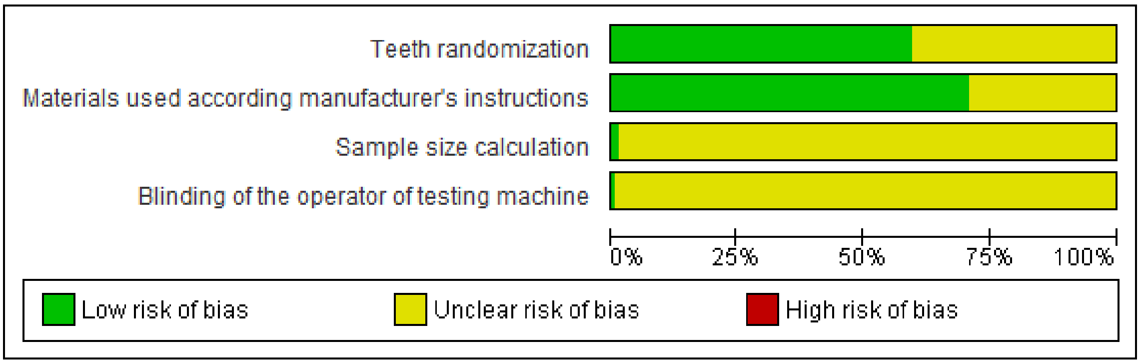


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Study or Subgroup	Control Mean	Control SD	Control Total	Experimental Mean	Experimental SD	Experimental Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 > 501 cycles								
Amaral et al. (2008)	29.3	7.2	100	25.6	7.4	100	0.6%	3.70 [1.68, 5.72]
Hariri et al. (2012)	43.1	7.4	16	41.25	16.02	32	0.5%	1.85 [-4.78, 8.48]
Hasegawa et al. (1995)	17.6	3.7	15	14.95	6.52	30	0.6%	2.65 [-0.34, 5.64]
Korkmaz et al. (2010)	14.8	5.95	12	15.36	6	12	0.5%	-0.56 [-5.34, 4.22]
Korkmaz et al. (2010)	11.08	4.97	12	11.01	4.56	12	0.5%	0.07 [-3.75, 3.89]
Lino Carracho et al. (1991)	11.6	2.7	10	14.8	9.73	20	0.5%	-3.20 [-7.78, 1.38]
Lino Carracho et al. (1991)	8	3.9	10	2.9	4.16	20	0.6%	5.10 [2.07, 8.13]
Lino Carracho et al. (1991)	11.4	2.8	10	8.5	7.11	20	0.5%	2.90 [-0.67, 6.47]
Retief et al. (1990)	5.8	2.9	15	6.1	3.2	15	0.6%	-0.30 [-2.49, 1.89]
Retief et al. (1990)	8	4	15	5.7	4.7	15	0.5%	2.30 [-0.82, 5.42]
Retief et al. (1990)	6.6	3	15	7.9	2.7	15	0.6%	-1.30 [-3.34, 0.74]
Rüttermann et al. (2013)	11.1	4.9	10	15.8	5.7	10	0.5%	-4.70 [-9.36, -0.04]
Rüttermann et al. (2013)	11.7	5.6	10	15.4	6.8	10	0.5%	-3.70 [-9.16, 1.76]
Shakya et al. (2015)	21.5	7.68	15	20.66	7.62	15	0.5%	0.84 [-4.63, 6.31]
Shakya et al. (2015)	23.69	8.51	15	21.01	8.64	15	0.5%	2.68 [-3.46, 8.82]
Shakya et al. (2015)	26.04	7.49	15	21.43	7.69	15	0.5%	4.61 [-0.82, 10.04]
Subtotal (95% CI)			**295**			**356**	**8.4%**	**0.97 [-0.46, 2.39]**
Heterogeneity: Tau² = 4.49; Chi² = 37.47, df = 15 (P = 0.001); I² = 60%								
Test for overall effect: Z = 1.33 (P = 0.18)								
2.2.2 501 - 3k cycles								
Amaral et al. (2008)	29.3	7.2	100	21	11.1	100	0.6%	8.30 [5.71, 10.89]
Berry, E. A. and J. M. Powers (1994)	9.6	4.7	5	11.1	3.4	5	0.5%	-1.50 [-6.58, 3.58]
Berry, E. A. and J. M. Powers (1994)	14.2	3.6	5	13.9	4.7	5	0.5%	0.30 [-4.89, 5.49]
Brueckner et al. (2017)	11.6	3.5	10	5.4	3.7	10	0.5%	6.20 [3.04, 9.36]
Charlton, D. G. and B. K. Moore (1991)	7	2.79	10	17.73	3.84	10	0.6%	-10.73 [-13.67, -7.79]
Charlton, D. G. and B. K. Moore (1991)	2.81	1.28	10	8.21	2.23	10	0.6%	-5.40 [-6.99, -3.81]
Daneshkazemi et al. (2015)	29.4	2.9	12	26.6	2.5	12	0.6%	2.80 [0.63, 4.97]
Donmez et al. (2015)	29.5	9.9	15	26.5	5.3	15	0.5%	3.00 [-2.68, 8.68]
Donmez et al. (2015)	21.3	5.2	15	31.5	6.8	15	0.5%	-10.20 [-14.53, -5.87]
Fritz et al. (1997)	14.9	2.6	10	13.7	1.2	10	0.6%	1.20 [-0.57, 2.97]
Hariri et al. (2012)	43.1	7.4	16	33.8	5.9	16	0.5%	9.30 [4.66, 13.94]
Khoroushi, M. and E. Rafiei (2013)	10.93	5.28	12	12.76	10.74	12	0.5%	-1.83 [-8.60, 4.94]
Khoroushi, M. and E. Rafiei (2013)	28.42	12.86	12	37.63	14.35	12	0.4%	-9.21 [-20.11, 1.69]
Nakata et al. (2007)	27.75	8.79	16	27.01	20.03	48	0.5%	0.74 [-6.38, 7.86]
Nakata et al. (2007)	23.1	13.97	16	18.56	33.23	48	0.3%	4.54 [-7.09, 16.17]
Nikaido et al. (2002) b	37.4	9.4	17	42.1	7.7	18	0.5%	-4.70 [-10.41, 1.01]
Omar et al. (2007)	21.4	7.6	25	18.3	7.11	25	0.5%	3.10 [-0.98, 7.18]
Omar et al. (2007)	22.2	4.6	25	15.7	5.5	25	0.6%	6.50 [3.69, 9.31]
Omar et al. (2007)	24.3	5.7	25	22.3	6.7	25	0.5%	2.00 [-1.45, 5.45]
Xie et al. (2002)	36	24	35	31	16	35	0.4%	5.00 [-4.56, 14.56]
Xie et al. (2002)	51	25	35	40	18	35	0.4%	11.00 [0.79, 21.21]
Subtotal (95% CI)			**426**			**491**	**10.4%**	**0.89 [-1.84, 3.61]**
Heterogeneity: Tau² = 32.89; Chi² = 230.97, df = 20 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 0.64 (P = 0.52)								

Mean Difference
IV, Random, 95% CI

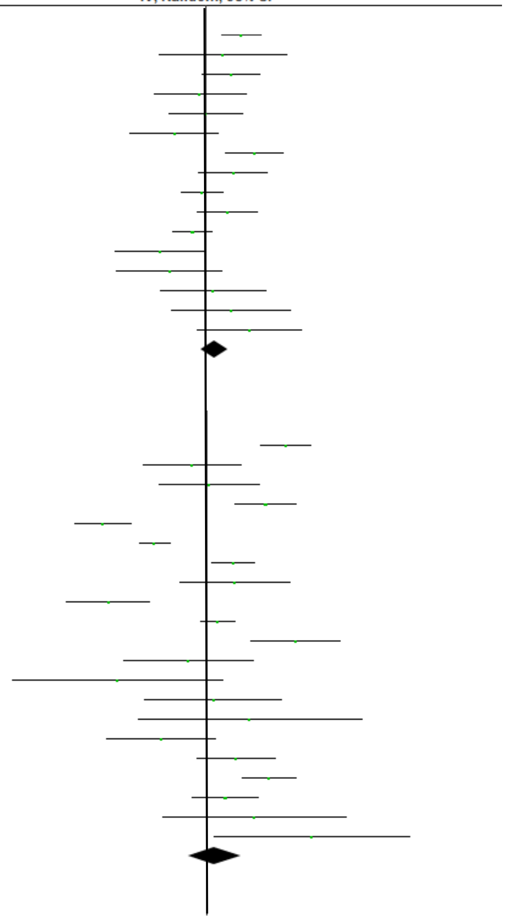


Figure 3. Meta-analysis considering the subgrups: up 500 and 501 to 3k cycles of thermal cycling.

2.2.3 3.1 - 5k cycles

Baracco et al. (2013)	32.3	2.8	46	24.1	3.3	37	0.6%	8.20 [6.86, 9.54]
Baracco et al. (2013)	33	4.3	47	21.2	2.5	39	0.6%	11.80 [10.34, 13.26]
Baracco et al. (2013)	17.9	3.4	39	16.6	1.7	28	0.6%	1.30 [0.06, 2.54]
Baracco et al. (2013)	14.8	1.7	39	11.1	2.5	29	0.6%	3.70 [2.65, 4.75]
Baracco et al. (2013)	31.7	2.8	49	21.5	3.4	35	0.6%	10.20 [8.83, 11.57]
Baracco et al. (2013)	34.9	3.9	46	31.9	3.7	43	0.6%	3.00 [1.42, 4.58]
Baracco et al. (2013)	24.2	3.3	45	16.1	3	35	0.6%	8.10 [6.72, 9.48]
Bumrungruan, C. and R. Sakoolnamarka (2016)	24.4	6.21	30	23.9	7.14	30	0.5%	0.50 [-2.89, 3.89]
Bumrungruan, C. and R. Sakoolnamarka (2016)	32.2	8.94	30	31.8	6.8	30	0.5%	0.40 [-3.62, 4.42]
Chiang et al. (2013)	30.3	12.4	12	17	6.8	12	0.4%	13.30 [5.30, 21.30]
Deng et al. (2013)	36.7	3.7	15	22.6	4.9	15	0.5%	14.10 [10.99, 17.21]
Deng et al. (2013)	32.2	3.5	15	26.4	3.9	15	0.5%	5.80 [3.15, 8.45]
El-Damanhoury, H. M. and M. Gaintantzopoulou(2015)	48.4	8	32	33.32	7.2	32	0.5%	15.08 [11.35, 18.81]
El-Damanhoury, H. M. and M. Gaintantzopoulou(2015)	43.6	6.2	32	36.64	6.6	32	0.5%	6.96 [3.82, 10.10]
El-Damanhoury, H. M. and M. Gaintantzopoulou(2015)	25.9	5.5	32	20.17	3.8	32	0.5%	5.73 [3.41, 8.05]
El-Damanhoury, H. M. and M. Gaintantzopoulou(2015)	26.8	4.2	32	21.12	4.5	32	0.5%	5.68 [3.55, 7.81]
El-Damanhoury, H. M. and M. Gaintantzopoulou(2015)	58.2	10.1	32	43.6	8.4	32	0.5%	14.60 [10.05, 19.15]
El-Damanhoury, H. M. and M. Gaintantzopoulou(2015)	39.6	7.1	32	33.79	3.8	32	0.5%	5.81 [3.02, 8.60]
Feitosa et al. (2012) b	47.1	3.4	22	46.9	4.4	22	0.5%	0.20 [-2.12, 2.52]
Feitosa et al. (2012) b	40.8	4.3	22	41.1	4.5	22	0.5%	-0.30 [-2.90, 2.30]
Guan et al. (2016)	58.9	14.2	20	64.7	13.1	20	0.4%	-5.80 [-14.27, 2.67]
Guan et al. (2016)	64.3	15.6	20	68.1	11.2	20	0.4%	-3.80 [-12.22, 4.62]
Guan et al. (2016)	67.3	16.7	20	71	7.3	20	0.4%	-3.70 [-11.69, 4.29]
Gunaydin et al. (2016)	27.1	0.96	15	12.96	0.49	15	0.6%	14.14 [13.59, 14.69]
Gunaydin et al. (2016)	35.4	2.26	15	17.97	1.31	15	0.6%	17.43 [16.11, 18.75]
Gunaydin et al. (2016)	30.2	1.2	15	14.36	1.16	15	0.6%	15.84 [15.00, 16.68]
Gunaydin et al. (2016)	36.1	2.5	15	17.6	1.7	15	0.6%	18.50 [16.97, 20.03]
Han et al. (2014)	45.9	14.5	20	40.4	11.5	14	0.4%	5.50 [-3.26, 14.26]
Matsui et al. (2015)	68.8	12.6	35	66.3	12.5	35	0.5%	2.50 [-3.38, 8.38]
Matsui et al. (2015)	84.5	10.1	35	59.8	10	35	0.5%	24.70 [19.99, 29.41]
Nikaido et al. (2002) b	37.4	9.4	17	42.1	7.7	18	0.5%	-4.70 [-10.41, 1.01]
Oilo, G. and S. Olsson (1990)	1.36	1.04	10	0.05	0.07	10	0.6%	1.31 [0.66, 1.96]
Oilo, G. and S. Olsson (1990)	3.29	1.29	10	0.37	0.71	10	0.6%	2.92 [2.01, 3.83]
Oilo, G. and S. Olsson (1990)	3.72	2.15	10	2.81	2.05	10	0.6%	0.91 [-0.93, 2.75]
Oilo, G. and S. Olsson (1990)	3.31	1.27	10	1.26	0.63	10	0.6%	2.05 [1.17, 2.93]
Omar et al. (2007)	24.3	5.7	25	22.3	6.7	25	0.5%	2.00 [-1.45, 5.45]
Omar et al. (2007)	22.2	4.6	25	15.7	5.5	25	0.5%	6.50 [3.69, 9.31]
Omar et al. (2007)	21.4	7.6	25	18.3	7.11	25	0.5%	3.10 [-0.98, 7.18]
Price et al. (2003)	16.92	2.01	20	17.2	2.05	20	0.6%	-0.28 [-1.54, 0.98]
Price et al. (2003)	6.73	2.02	20	12.68	2	20	0.6%	-5.95 [-7.20, -4.70]
Sampaio et al. (2011)	19.3	9.3	21	19.7	10	26	0.5%	-0.40 [-5.93, 5.13]
Wagner et al. (2014)	36.7	14.5	33	26.1	9.7	34	0.5%	10.60 [4.68, 16.52]
Wagner et al. (2014)	37.9	14	104	36.6	18.7	41	0.5%	1.30 [-5.02, 7.62]
Wagner et al. (2014)	38.5	14.8	28	25.2	9.2	22	0.5%	13.30 [6.60, 20.00]
Wagner et al. (2014)	52.6	12.7	35	44.7	12.7	30	0.5%	7.90 [1.71, 14.09]
Wagner et al. (2014)	44	21.9	35	48.3	13.85	18	0.4%	-4.30 [-13.97, 5.37]
Wang et al. (2017)	57.7	9.75	15	50.71	9.33	15	0.5%	6.99 [0.16, 13.82]
Wang et al. (2017)	37.2	5.79	15	36.48	7.24	15	0.5%	0.72 [-3.97, 5.41]
Wang et al. (2017)	37.1	6.51	15	27.66	8.48	15	0.5%	9.44 [4.03, 14.85]
Wang et al. (2017)	54.3	8.6	15	51.1	8.25	15	0.5%	3.20 [-2.83, 9.23]
Yu et al. (2017)	33.4	6.4	80	20.8	2.2	80	0.6%	12.60 [11.12, 14.08]
Zhang et al. (2014)	37.69	4.24	50	18.95	7.43	50	0.5%	18.74 [16.37, 21.11]
Zhang et al. (2014)	51.09	8.01	50	30.58	7.23	50	0.5%	20.51 [17.52, 23.50]
Zhang et al. (2014)	39.92	8.72	50	30.89	6.72	50	0.5%	9.03 [5.98, 12.08]
Zhang et al. (2014)	54.05	6.06	50	37.06	5.17	50	0.5%	16.99 [14.78, 19.20]
Subtotal (95% CI)			**1627**			**1472**	**28.3%**	**6.64 [4.72, 8.55]**

Heterogeneity: Tau² = 47.95; Chi² = 3399.47, df = 54 (P < 0.00001); I² = 98%
Test for overall effect: Z = 6.80 (P < 0.00001)

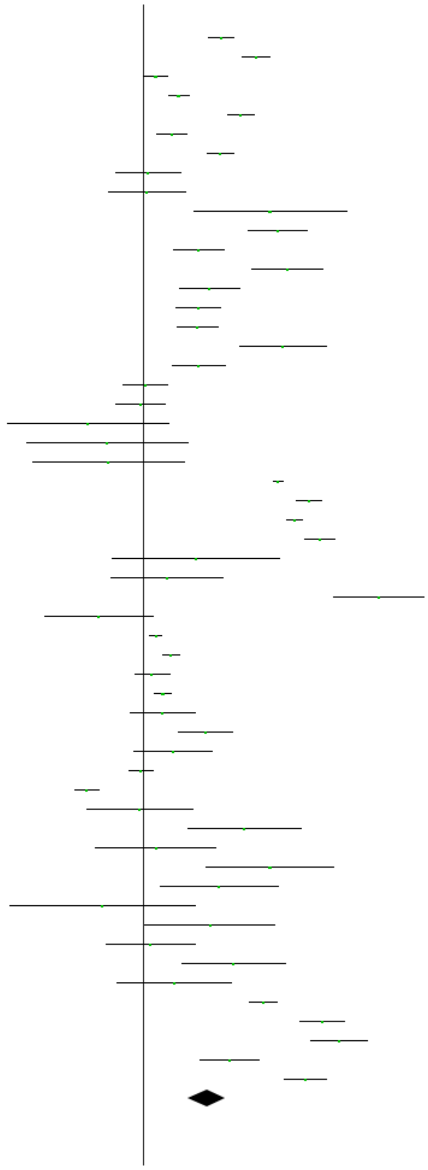


Figure 4. Meta-analysis considering the subgroup of 3,1 up to 5k cycles of thermal cycling.

2.2.4 5.1 - 10k cycles								
Akin et al. (2012)	23.6	3.04	20	24.12	3.51	20	0.7%	-0.52 [-2.56, 1.52]
Akin et al. (2012)	20.3	3.24	20	22	3.23	20	0.8%	-1.70 [-3.71, 0.31]
Akin et al. (2012)	20.4	4.49	20	23.16	2.65	20	0.6%	-2.76 [-5.04, -0.48]
Benetti et al. (2007)	20.4	6.6	8	21	4.3	8	0.1%	-0.60 [-6.06, 4.86]
Benetti et al. (2007)	22.2	5.5	8	22.7	6.1	8	0.1%	-0.50 [-6.19, 5.19]
Benetti et al. (2007)	19.2	4.4	8	24.8	6.3	8	0.1%	-5.60 [-10.92, -0.28]
Benetti et al. (2007)	22	2.8	8	23.3	4.4	8	0.2%	-1.30 [-4.91, 2.31]
Benetti et al. (2007)	25.5	4.4	8	22.3	6.3	8	0.1%	3.20 [-2.12, 8.52]
Benetti et al. (2007)	26.2	4.3	8	26.2	7.9	8	0.1%	0.00 [-6.23, 6.23]
Benetti et al. (2007)	24.4	4	8	29.8	5.7	8	0.1%	-5.40 [-10.23, -0.57]
Benetti et al. (2007)	22.8	2.6	8	27.5	7.4	8	0.1%	-4.70 [-10.14, 0.74]
Chang, Y. E. and D. H. Shin (2010)	29.4	3.4	16	19.1	2.5	16	0.7%	10.30 [8.23, 12.37]
Chen et al. (2015)	50.1	6.8	40	47.8	9.5	40	0.2%	2.30 [-1.32, 5.92]
Chen et al. (2015)	56.3	10.2	40	54.1	10.6	40	0.1%	2.20 [-2.36, 6.76]
Chen et al. (2015)	48.2	9.7	40	38.4	10.1	40	0.2%	9.80 [5.46, 14.14]
Chen et al. (2015)	48	7.4	40	44.1	9.6	40	0.2%	3.90 [0.14, 7.66]
Chen et al. (2015)	59.9	11.8	40	55.8	11.9	40	0.1%	4.10 [-1.09, 9.29]
Daneshmehr et al. (2013)	18.7	4.4	16	7.3	3.9	16	0.4%	11.40 [8.52, 14.28]
Daneshmehr et al. (2013)	14.8	4.5	16	6.5	4.5	16	0.3%	8.30 [5.18, 11.42]
Daneshmehr et al. (2013)	18.9	5.5	16	10.6	3.9	16	0.3%	8.30 [5.00, 11.60]
Deng et al. (2014)	41.9	4.2	45	24.8	3.7	45	1.2%	17.10 [15.46, 18.74]
Deng et al. (2014)	39.5	5.1	45	22.3	4.1	45	0.8%	17.20 [15.29, 19.11]
El-Deeb et al. (2016)	34.2	4.5	28	16.6	4.7	28	0.5%	17.60 [15.19, 20.01]
El-Deeb et al. (2016)	29.3	5.3	28	14.9	4.8	28	0.4%	14.40 [11.75, 17.05]
El-Deeb et al. (2016)	32.7	6.4	28	15.9	4.3	28	0.4%	16.80 [13.94, 19.66]
Gan et al. (2017)	20.8	6.4	50	15.1	5.8	50	0.5%	5.70 [3.31, 8.09]
Guan et al. (2016)	64.3	15.6	20	79.2	12	20	0.0%	-14.90 [-23.53, -6.27]
Guan et al. (2016)	58.9	14.2	20	49.6	9.9	20	0.1%	9.30 [1.71, 16.89]
Guan et al. (2016)	67.3	16.7	20	71.3	20.6	20	0.0%	-4.00 [-15.62, 7.62]
Guo et al. (2017)	30.3	8.1	30	22.9	5.5	30	0.3%	7.40 [3.90, 10.90]
Hariri et al. (2012)	43.1	7.4	16	31.9	5.4	16	0.2%	11.20 [6.71, 15.69]
Inoue et al. (2005)	44.7	13.2	17	39	16.1	12	0.0%	5.70 [-5.36, 16.76]
Inoue et al. (2005)	37.9	5.9	12	35.9	10.4	15	0.1%	2.00 [-4.23, 8.23]
Inoue et al. (2005)	40.8	7.9	12	43.3	9.3	14	0.1%	-2.50 [-9.11, 4.11]
Irmak et al. (2017)	28.3	6.88	42	36.36	6.42	42	0.4%	-8.06 [-10.91, -5.21]
Irmak et al. (2017)	28.8	6.47	42	35.69	7.42	42	0.3%	-6.89 [-9.87, -3.91]
Irmak et al. (2017)	25.8	6.24	42	33.92	6.99	42	0.4%	-8.12 [-10.95, -5.29]
Irmak et al. (2017)	25.3	5.57	42	32.33	7.65	42	0.4%	-7.03 [-9.89, -4.17]
Irmak et al. (2017)	25.2	5.05	42	21.23	5.81	42	0.6%	3.97 [1.64, 6.30]
Irmak et al. (2017)	26.1	4.16	42	22.41	5.76	42	0.7%	3.69 [1.54, 5.84]
Kim, Y. H. and D. H. Shin (2012)	19.8	2.4	7	13.37	2.37	7	0.5%	6.43 [3.93, 8.93]
Kim, Y. H. and D. H. Shin (2012)	19.2	2.8	7	12.3	2.5	7	0.4%	6.90 [4.12, 9.68]
Lohbauer et al. (2008)	67.6	26.5	20	50.2	20.3	20	0.0%	17.40 [2.77, 32.03]
Lohbauer et al. (2008)	92.7	31.8	20	90.9	26.6	20	0.0%	1.80 [-16.37, 19.97]
Matsui et al. (2015)	68.8	12.6	35	66.3	12.5	35	0.1%	2.50 [-3.38, 8.38]
Matsui et al. (2015)	84.5	10	35	54.5	16.7	35	0.1%	30.00 [23.55, 36.45]
Ozel-Bektas et al. (2011)	29.4	1.76	20	30.26	4.19	20	0.8%	-0.86 [-2.85, 1.13]
Ozel-Bektas et al. (2011)	29.6	4.21	20	25.91	2.58	20	0.7%	3.69 [1.53, 5.85]
Ozel-Bektas et al. (2011)	34.5	4.2	20	33.8	3.1	20	0.6%	0.70 [-1.59, 2.99]
Sangwichit et al. (2016)	43.4	3.4	13	30.7	9.8	13	0.1%	12.70 [7.06, 18.34]
Sangwichit et al. (2016)	29.1	4.99	13	22.85	7.62	13	0.1%	6.25 [1.30, 11.20]
Sangwichit et al. (2016)	34.2	3.98	13	31.98	5.75	13	0.2%	2.22 [-1.58, 6.02]
Sangwichit et al. (2016)	32.5	5.6	13	25.8	5	13	0.2%	6.70 [2.62, 10.78]
Sangwichit et al. (2016)	46.7	5.3	13	32.2	7.8	13	0.1%	14.50 [9.37, 19.63]
Sangwichit et al. (2016)	39.7	8.4	13	30.7	5.8	13	0.1%	9.00 [3.45, 14.55]
Sangwichit et al. (2016)	17	5.68	13	16.16	5.27	13	0.2%	0.84 [-3.37, 5.05]
Sangwichit et al. (2016)	40.5	8.01	13	36.34	4.87	13	0.1%	4.16 [-0.94, 9.26]
Smisson et al. (2005)	8.2	4.6	15	8.7	4.8	15	0.3%	-0.50 [-3.86, 2.86]
Tezvergil et al. (2003)	11.72	3.21	10	15.12	5.53	10	0.2%	-3.40 [-7.36, 0.56]
Tezvergil et al. (2005)	11.25	3.5	20	15.37	6	20	0.3%	-4.12 [-7.16, -1.08]
Yang et al. (2016)	34.1	5.5	50	25	4.6	50	0.8%	9.10 [7.11, 11.09]
Zanatta et al. (2017)	56	33.5	10	65.8	30.2	10	0.0%	-9.80 [-37.75, 18.15]
Zanatta et al. (2017)	61.5	34.4	10	68	24.4	10	0.0%	-6.50 [-32.64, 19.64]
Zhou et al. (2015)	28.4	4.4	35	21.54	3.4	35	0.9%	6.86 [5.02, 8.70]
Zhou et al. (2015)	27.4	2.8	35	20.56	2.4	35	2.1%	6.84 [5.62, 8.06]
Zhou et al. (2015)	37.1	3.5	35	29	4.4	35	0.9%	8.10 [6.24, 9.96]
Zhuge et al. (2017)	63.4	5.3	13	50.3	7.9	13	0.1%	13.10 [7.93, 18.27]
Zhuge et al. (2017)	45.1	4.5	13	26.8	5.2	13	0.2%	18.30 [14.56, 22.04]
Zhuge et al. (2017)	87.2	14.3	13	54.8	10	13	0.0%	32.40 [22.91, 41.89]
Zhuge et al. (2017)	93.4	9.6	13	62	5.1	13	0.1%	31.40 [25.49, 37.31]
Ülker et al. (2010)	35.8	9.28	20	36.88	9.07	20	0.1%	-1.08 [-6.77, 4.61]
Ülker et al. (2010)	21.7	9.49	20	15.05	5.66	20	0.1%	6.65 [1.81, 11.49]
Ülker et al. (2010)	27.2	7.79	20	24.38	7.31	20	0.1%	2.82 [-1.86, 7.50]
Ülker et al. (2010)	28.8	6.04	20	25.63	6.64	20	0.2%	3.17 [-0.76, 7.10]
Ülker et al. (2010)	22.9	4.81	20	20.29	6.35	20	0.3%	2.61 [-0.88, 6.10]
Ülker et al. (2010)	26.4	9.57	20	23.16	5.69	20	0.1%	3.24 [-1.64, 8.12]
Ülker et al. (2010)	38.2	5.75	20	34.4	4.95	20	0.3%	3.80 [0.47, 7.13]
Ülker et al. (2010)	42.3	8.52	20	39.57	7.43	20	0.1%	2.73 [-2.22, 7.68]
Subtotal (95% CI)			**1731**			**1731**	**24.6%**	**5.54 [5.18, 5.89]**

Heterogeneity: Chi² = 1576.78, df = 77 (P < 0.00001); I² = 95%

Test for overall effect: Z = 30.57 (P < 0.00001)

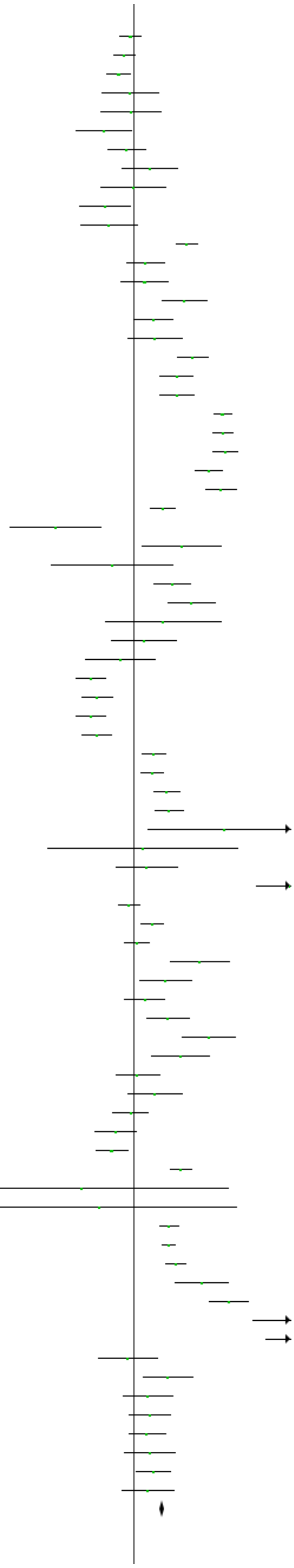


Figure 5. Meta-analysis considering the subgroup of 5,1 up to 10k cycles of thermal cycling.

2.2.6 15k - 100k cycles								
De Munck et al. (2005)	23.8	8.3	12	23.1	7.5	12	0.5%	0.70 [-5.63, 7.03]
De Munck et al. (2005)	14.7	11.9	12	12.6	3.8	12	0.4%	2.10 [-4.97, 9.17]
De Munck et al. (2005)	20	3.6	12	18.3	9.8	12	0.5%	1.70 [-4.21, 7.61]
Fukuoka et al. (2011)	29.9	8	18	13.6	3.4	15	0.5%	16.30 [12.22, 20.38]
Fukuoka et al. (2011)	36.4	7.7	14	5.4	3.1	19	0.5%	31.00 [26.73, 35.27]
Fukuoka et al. (2011)	44.4	13.6	12	20.2	4.6	18	0.4%	24.20 [16.22, 32.18]
Inoue et al. (2005)	40.8	7.9	12	42.8	10.7	15	0.4%	-2.00 [-9.02, 5.02]
Inoue et al. (2005)	40.8	7.9	12	43.7	13.9	15	0.4%	-2.90 [-11.23, 5.43]
Inoue et al. (2005)	40.8	7.9	12	40.2	7.4	14	0.5%	0.60 [-5.32, 6.52]
Inoue et al. (2005)	40.8	7.9	12	35.3	7.5	11	0.5%	5.50 [-0.79, 11.79]
Inoue et al. (2005)	37.9	5.9	12	40.6	10.8	14	0.5%	-2.70 [-9.27, 3.87]
Inoue et al. (2005)	37.9	5.9	12	35.9	8.9	15	0.5%	2.00 [-3.61, 7.61]
Inoue et al. (2005)	37.9	5.9	12	40	15.5	12	0.4%	-2.10 [-11.48, 7.28]
Inoue et al. (2005)	37.9	5.9	12	22.5	7.7	14	0.5%	15.40 [10.16, 20.64]
Inoue et al. (2005)	44.7	13.2	17	33.8	9.2	15	0.4%	10.90 [3.09, 18.71]
Inoue et al. (2005)	44.7	13.2	17	32.2	10.2	13	0.4%	12.50 [4.13, 20.87]
Inoue et al. (2005)	44.7	13.2	17	31	10.9	12	0.4%	13.70 [4.90, 22.50]
Inoue et al. (2005)	44.7	13.2	17	23.2	7.6	14	0.4%	21.50 [14.07, 28.93]
Karadas, M. and I. Caglar (2017)	9.9	2.9	15	3.31	2.5	15	0.5%	6.59 [4.65, 8.53]
Karadas, M. and I. Caglar (2017)	23.11	5.7	15	29.8	9.3	15	0.5%	-6.69 [-12.21, -1.17]
Karadas, M. and I. Caglar (2017)	33.48	8.1	15	37.13	8.1	15	0.5%	-3.65 [-9.45, 2.15]
Karadas, M. and I. Caglar (2017)	17.42	4.1	15	8.68	4.1	15	0.5%	8.74 [5.81, 11.67]
Mine et al. (2012)	0	0	20	0.1	0.4	20		Not estimable
Mine et al. (2012)	26.2	9.2	20	27.5	9.2	20	0.5%	-1.30 [-7.00, 4.40]
Mine et al. (2012)	13.7	12.1	20	8.3	10.3	20	0.4%	5.40 [-1.56, 12.36]
Mine et al. (2012)	16.3	16.9	20	20.3	13.6	20	0.4%	-4.00 [-13.51, 5.51]
Perdigao et al. (2011)	38.2	21.2	122	18.9	21.8	117	0.5%	19.30 [13.85, 24.75]
Perdigao et al. (2011)	53.9	16.2	105	57.6	20.1	89	0.5%	-3.70 [-8.90, 1.50]
Perdigao et al. (2011)	54.3	13.6	81	54.1	15.8	94	0.5%	0.20 [-4.16, 4.56]
Saboia et al. (2009)	49.8	7	75	28.9	8.6	75	0.5%	20.90 [18.39, 23.41]
Yoshihara et al. (2015)	10.8	3.9	24	4.3	4.7	21	0.5%	6.50 [3.96, 9.04]
Yoshihara et al. (2015)	10.3	5.1	26	3.1	3.2	22	0.5%	7.20 [4.83, 9.57]
Yoshihara et al. (2015)	17.4	7.8	22	16.1	5.5	22	0.5%	1.30 [-2.69, 5.29]
Subtotal (95% CI)			**839**			**832**	**15.1%**	**6.52 [3.42, 9.62]**
Heterogeneity: Tau² = 70.38; Chi² = 443.21, df = 31 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 4.13 (P < 0.0001)								
Total (95% CI)			**4918**			**4882**	**100.0%**	**4.92 [3.89, 5.96]**
Heterogeneity: Tau² = 49.86; Chi² = 6238.95, df = 201 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 9.31 (P < 0.00001)								
Test for subgroup differences: Chi² = 32.44, df = 4 (P < 0.00001), I² = 87.7%								

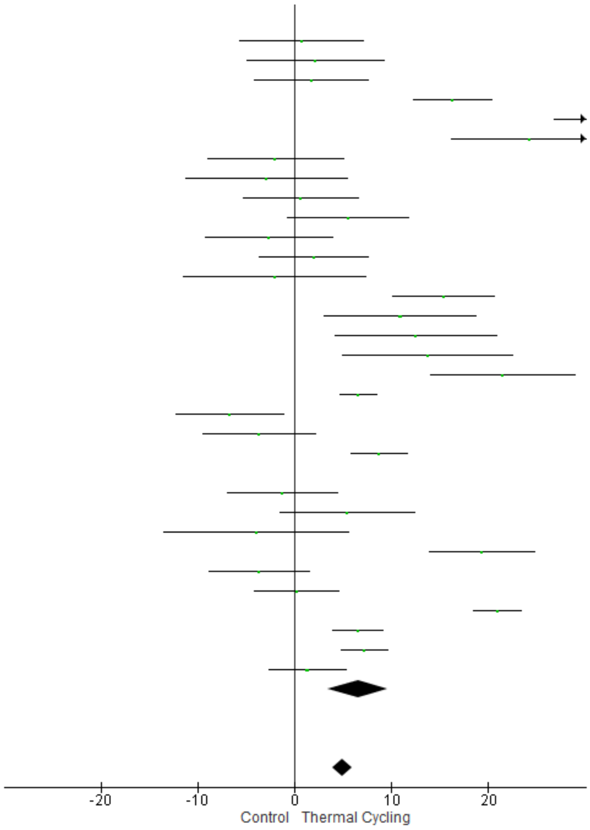


Figure 6. Meta-analysis considering the subgrups: 15k to 100k cycles of thermal cycling.

Study or Subgroup	Control Mean	Control SD	Control Total	Experimental Mean	Experimental SD	Experimental Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 > 101k cycles								
Aguilera et al. (2012)	10.74	3.7	27	13.52	7.6	27	2.1%	-2.78 [-5.97, 0.41]
Aguilera et al. (2012)	29.29	10.1	27	32.98	8.1	27	2.0%	-3.69 [-8.57, 1.19]
Aguilera et al. (2012)	29.4	11.5	27	25	7.2	27	2.0%	4.40 [-0.72, 9.52]
Belli et al. (2009)	19.8	3.86	17	16.67	2.15	17	2.2%	3.13 [1.03, 5.23]
Belli et al. (2009)	22.72	3.92	17	11.92	2.52	17	2.2%	10.80 [8.58, 13.02]
Belli et al. (2009)	27.65	4.28	17	19.46	3.87	17	2.2%	8.19 [5.45, 10.93]
Belli et al. (2009)	40.9	3.5	17	31.2	2.5	17	2.2%	9.70 [7.66, 11.74]
Belli et al. (2009)	33.22	5.55	17	22.91	1.89	17	2.2%	10.31 [7.52, 13.10]
Daneshkazemi et al. (2015)	29.4	2.9	12	22.66	3.94	24	2.2%	6.74 [4.46, 9.02]
Daneshkazemi, et al. (2013)	35.4	2.3	12	29.78	4.17	24	2.2%	5.62 [3.50, 7.74]
Deng et al. (2016)	22.9	3.08	16	17.14	2.55	16	2.2%	5.76 [3.80, 7.72]
Farias et al. (2016)	35.27	13.6	45	12.77	5	45	2.1%	22.50 [18.27, 26.73]
Farias et al. (2016)	53.27	4.2	45	64.27	4.1	45	2.2%	-11.00 [-12.71, -9.29]
Farias et al. (2016)	56.27	7.8	45	51.07	4.4	45	2.2%	5.20 [2.58, 7.82]
Farias et al. (2016)	43.77	7.2	45	49.77	14.3	45	2.0%	-6.00 [-10.68, -1.32]
Farias et al. (2016)	46.97	7.9	45	52.67	10.1	45	2.1%	-5.70 [-9.45, -1.95]
Farias et al. (2016)	37.57	8.7	45	41	9.8	45	2.1%	-3.43 [-7.26, 0.40]
Marquezan et al. (2010)	27	8.9	45	27	8.2	45	2.1%	0.00 [-3.54, 3.54]
Monticelli et al. (2007)	15.36	4.8	0	14.6	31.6	0		Not estimable
Nikaido et al. (2002) b	37.4	9.4	17	41.7	8.2	19	1.9%	-4.30 [-10.09, 1.49]
Osorio et al. (2005) b	45.7	8.3	30	40.6	6.3	30	2.1%	5.10 [1.37, 8.83]
Toledano et al. (2006) b	46.07	12.1	37	30.61	5.3	37	2.1%	15.46 [11.20, 19.72]
Toledano et al. (2006) b	29.1	4.7	37	11.7	3.2	37	2.2%	17.40 [15.57, 19.23]
Toledano et al. (2006) b	43.3	11.1	37	28.3	8.4	37	2.0%	15.00 [10.51, 19.49]
Toledano et al. (2006) b	16.99	7.7	37	0	0	37		Not estimable
Toledano et al. (2006) b	29.8	4.5	37	25.2	7.9	37	2.2%	4.60 [1.67, 7.53]
Toledano et al. (2017)	23.49	2.99	18	20.96	3.36	18	2.2%	2.53 [0.45, 4.61]
Ülker et al. (2010)	27.2	7.8	20	20.9	6.2	20	2.1%	6.30 [1.93, 10.67]
Ülker et al. (2010)	38.2	5.8	20	27.5	5	20	2.1%	10.70 [7.34, 14.06]
Ülker et al. (2010)	22.9	4.8	20	15.6	3.7	20	2.2%	7.30 [4.64, 9.96]
Ülker et al. (2010)	35.8	9.3	20	25.7	5.4	20	2.0%	10.10 [5.39, 14.81]
Ülker et al. (2010)	28.8	6	20	18.9	6.1	20	2.1%	9.90 [6.15, 13.65]
Ülker et al. (2010)	42.3	8.5	20	34.1	9.8	20	2.0%	8.20 [2.51, 13.89]
Ülker et al. (2010)	21.7	9.5	20	13.3	4.4	20	2.0%	8.40 [3.81, 12.99]
Ülker et al. (2010)	26.4	9.6	20	18.8	6.3	20	2.0%	7.60 [2.57, 12.63]
Subtotal (95% CI)			**931**			**957**	**69.6%**	**5.59 [2.96, 8.22]**
Heterogeneity: $Tau^2 = 56.10$; $Chi^2 = 847.03$, df = 32 ($P < 0.00001$); $I^2 = 96\%$								
Test for overall effect: Z = 4.16 ($P < 0.0001$)								
1.3.2 101 - 250k cycles								
Bravis et al. (2012)	37.5	17.78	28	20.25	7.11	22	1.8%	17.25 [10.03, 24.47]
Bravis et al. (2012)	23.8	6.4	28	22.9	7.4	15	2.1%	0.90 [-3.53, 5.33]
Feitosa et al. (2012) b	47.1	3.4	22	40.7	3.1	22	2.2%	6.40 [4.48, 8.32]
Feitosa et al. (2012) b	40.8	4.3	22	32.5	4.5	22	2.2%	8.30 [5.70, 10.90]
Montagner et al. (2016)	34	12.2	60	25	14.2	60	2.0%	9.00 [4.26, 13.74]
Montagner et al. (2016)	37.4	14	60	24.4	26.6	58	1.8%	13.00 [5.29, 20.71]
Subtotal (95% CI)			**220**			**199**	**12.0%**	**8.16 [5.00, 11.33]**
Heterogeneity: $Tau^2 = 10.11$; $Chi^2 = 19.28$, df = 5 ($P = 0.002$); $I^2 = 74\%$								
Test for overall effect: Z = 5.06 ($P < 0.00001$)								
1.3.3 251 - 750k cycles								
Daneshkazemi et al. (2015)	29.37	2.89	12	13.56	1.23	12	2.2%	15.81 [14.03, 17.59]
Daneshkazemi, et al. (2013)	35.4	2.3	12	18.13	1.72	12	2.2%	17.27 [15.65, 18.89]
Kawai et al. (2016)	23.45	11.8	21	19.02	7.97	21	1.9%	4.43 [-1.66, 10.52]
Kawai et al. (2016)	25.05	11.55	21	15.25	7.25	21	1.9%	9.80 [3.97, 15.63]
Kawai et al. (2016)	23.55	10.6	21	15.12	6.57	21	2.0%	8.43 [3.10, 13.76]
Montagner et al. (2016)	37.4	14	60	21.51	18.72	113	2.0%	15.89 [10.94, 20.84]
Montagner et al. (2016)	34	12.2	60	23.7	18.79	120	2.0%	10.30 [5.74, 14.86]
Montagner et al. (2017)	32.4	14	63	20.3	12.3	67	2.0%	12.10 [7.56, 16.64]
Montagner et al. (2017)	36.2	15.6	62	13.2	11.4	72	2.0%	23.00 [18.31, 27.69]
Subtotal (95% CI)			**332**			**459**	**18.4%**	**13.50 [10.68, 16.32]**
Heterogeneity: $Tau^2 = 13.54$; $Chi^2 = 44.76$, df = 8 ($P < 0.00001$); $I^2 = 82\%$								
Test for overall effect: Z = 9.38 ($P < 0.00001$)								
Total (95% CI)			**1483**			**1615**	**100.0%**	**7.37 [5.15, 9.59]**
Heterogeneity: $Tau^2 = 57.59$; $Chi^2 = 1216.64$, df = 47 ($P < 0.00001$); $I^2 = 96\%$								
Test for overall effect: Z = 6.50 ($P < 0.00001$)								
Test for subgroup differences: $Chi^2 = 16.47$, df = 2 ($P = 0.0003$), $I^2 = 87.9\%$								

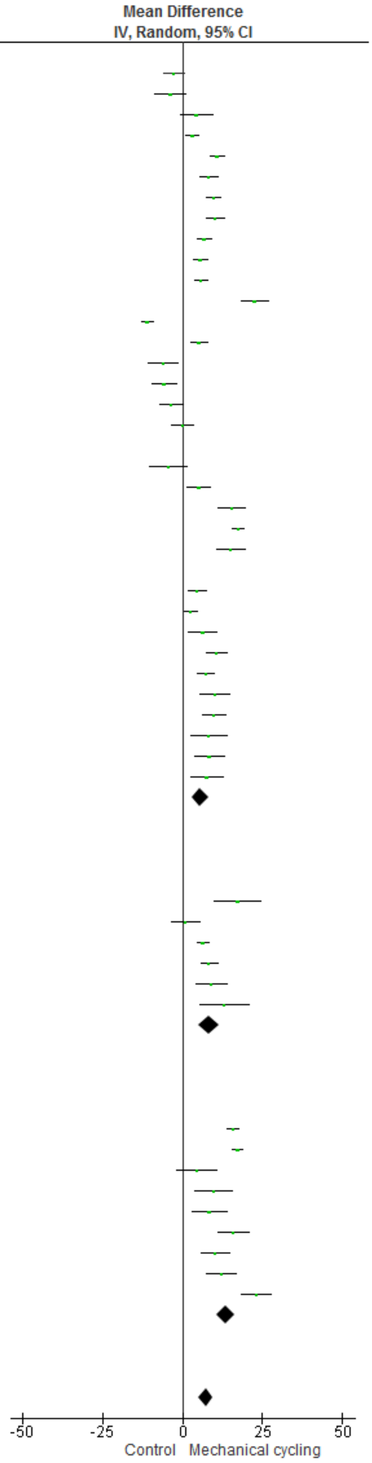
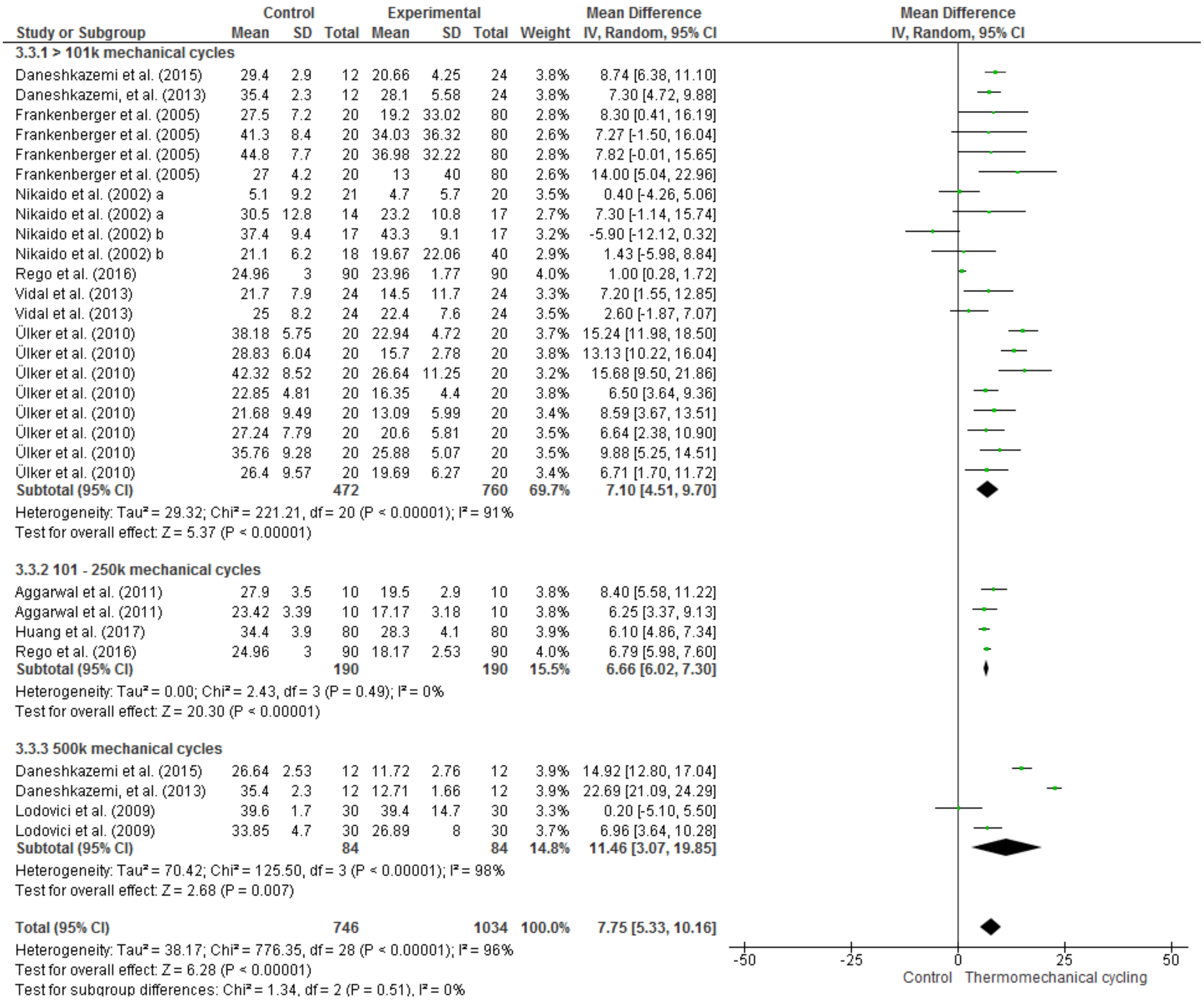


Figure 7. Metanalysis considering mechanical cycling. The analyzes were separated into three subgroups all favoring aging through mechanical cycles.



Study or Subgroup	Control Mean	Control SD	Control Total	Experimental Mean	Experimental SD	Experimental Total	Weight	Mean Difference IV, Random, 95% CI
3.3.1 > 101k mechanical cycles								
Daneshkazemi et al. (2015)	29.4	2.9	12	20.66	4.25	24	3.8%	8.74 [6.38, 11.10]
Daneshkazemi, et al. (2013)	35.4	2.3	12	28.1	5.58	24	3.8%	7.30 [4.72, 9.88]
Frankenberger et al. (2005)	27.5	7.2	20	19.2	33.02	80	2.8%	8.30 [0.41, 16.19]
Frankenberger et al. (2005)	41.3	8.4	20	34.03	36.32	80	2.6%	7.27 [-1.50, 16.04]
Frankenberger et al. (2005)	44.8	7.7	20	36.98	32.22	80	2.8%	7.82 [-0.01, 15.65]
Frankenberger et al. (2005)	27	4.2	20	13	40	80	2.6%	14.00 [5.04, 22.96]
Nikaido et al. (2002) a	5.1	9.2	21	4.7	5.7	20	3.5%	0.40 [-4.26, 5.06]
Nikaido et al. (2002) a	30.5	12.8	14	23.2	10.8	17	2.7%	7.30 [-1.14, 15.74]
Nikaido et al. (2002) b	37.4	9.4	17	43.3	9.1	17	3.2%	-5.90 [-12.12, 0.32]
Nikaido et al. (2002) b	21.1	6.2	18	19.67	22.06	40	2.9%	1.43 [-5.98, 8.84]
Rego et al. (2016)	24.96	3	90	23.96	1.77	90	4.0%	1.00 [0.28, 1.72]
Vidal et al. (2013)	21.7	7.9	24	14.5	11.7	24	3.3%	7.20 [1.55, 12.85]
Vidal et al. (2013)	25	8.2	24	22.4	7.6	24	3.5%	2.60 [-1.87, 7.07]
Ülker et al. (2010)	38.18	5.75	20	22.94	4.72	20	3.7%	15.24 [11.98, 18.50]
Ülker et al. (2010)	28.83	6.04	20	15.7	2.78	20	3.8%	13.13 [10.22, 16.04]
Ülker et al. (2010)	42.32	8.52	20	26.64	11.25	20	3.2%	15.68 [9.50, 21.86]
Ülker et al. (2010)	22.85	4.81	20	16.35	4.4	20	3.8%	6.50 [3.64, 9.36]
Ülker et al. (2010)	21.68	9.49	20	13.09	5.99	20	3.4%	8.59 [3.67, 13.51]
Ülker et al. (2010)	27.24	7.79	20	20.6	5.81	20	3.5%	6.64 [2.38, 10.90]
Ülker et al. (2010)	35.76	9.28	20	25.88	5.07	20	3.5%	9.88 [5.25, 14.51]
Ülker et al. (2010)	26.4	9.57	20	19.69	6.27	20	3.4%	6.71 [1.70, 11.72]
Subtotal (95% CI)			**472**			**760**	**69.7%**	**7.10 [4.51, 9.70]**
Heterogeneity: Tau² = 29.32; Chi² = 221.21, df = 20 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 5.37 (P < 0.00001)								
3.3.2 101 - 250k mechanical cycles								
Aggarwal et al. (2011)	27.9	3.5	10	19.5	2.9	10	3.8%	8.40 [5.58, 11.22]
Aggarwal et al. (2011)	23.42	3.39	10	17.17	3.18	10	3.8%	6.25 [3.37, 9.13]
Huang et al. (2017)	34.4	3.9	80	28.3	4.1	80	3.9%	6.10 [4.86, 7.34]
Rego et al. (2016)	24.96	3	90	18.17	2.53	90	4.0%	6.79 [5.98, 7.60]
Subtotal (95% CI)			**190**			**190**	**15.5%**	**6.66 [6.02, 7.30]**
Heterogeneity: Tau² = 0.00; Chi² = 2.43, df = 3 (P = 0.49); I² = 0%								
Test for overall effect: Z = 20.30 (P < 0.00001)								
3.3.3 500k mechanical cycles								
Daneshkazemi et al. (2015)	26.64	2.53	12	11.72	2.76	12	3.9%	14.92 [12.80, 17.04]
Daneshkazemi, et al. (2013)	35.4	2.3	12	12.71	1.66	12	3.9%	22.69 [21.09, 24.29]
Lodovici et al. (2009)	39.6	1.7	30	39.4	14.7	30	3.3%	0.20 [-5.10, 5.50]
Lodovici et al. (2009)	33.85	4.7	30	26.89	8	30	3.7%	6.96 [3.64, 10.28]
Subtotal (95% CI)			**84**			**84**	**14.8%**	**11.46 [3.07, 19.85]**
Heterogeneity: Tau² = 70.42; Chi² = 125.50, df = 3 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 2.68 (P = 0.007)								
Total (95% CI)			**746**			**1034**	**100.0%**	**7.75 [5.33, 10.16]**
Heterogeneity: Tau² = 38.17; Chi² = 776.35, df = 28 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 6.28 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.34, df = 2 (P = 0.51), I² = 0%								

Figure 8. Meta-analysis considering thermomechanical cycling. The analyzes were separated into three subgroups divided by mechanical cycles. All subgroups favored aging through thermomechanical cycles.

Study or Subgroup	Control Mean	Control SD	Control Total	Experimental Mean	Experimental SD	Experimental Total	Weight	Mean Difference IV, Random, 95% CI
Amaral et al. (2008)	29.3	7.2	100	18.7	12.3	100	7.8%	10.60 [7.81, 13.39]
Duarte Jr et al. (2009)	61.8	38.7	52	54.8	38.4	45	2.2%	7.00 [-8.38, 22.38]
Duarte Jr et al. (2009)	4.4	5.1	33	0	0	40		Not estimable
Ebrahimi et al. (2017)	60.39	18.91	10	71.03	21.75	10	1.8%	-10.64 [-28.50, 7.22]
Ebrahimi et al. (2017)	63.01	23.75	10	23.15	11.02	10	2.1%	39.86 [23.63, 56.09]
Galafassi et al. (2013)	43.2	15	40	41.17	12.95	40	5.9%	2.03 [-4.11, 8.17]
Galafassi et al. (2013)	34.34	12.46	40	42.76	15.43	40	5.9%	-8.42 [-14.57, -2.27]
Galafassi et al. (2013)	27.09	15.67	40	35.31	18.86	40	5.1%	-8.22 [-15.82, -0.62]
Galafassi et al. (2014)	27.89	10.1	80	22.5	13.3	80	7.4%	5.39 [1.73, 9.05]
Khamverdi et al. (2015)	23.42	2.08	12	22.1	2.74	12	8.2%	1.32 [-0.63, 3.27]
Khamverdi et al. (2015)	29.58	4.07	12	25.9	2.75	12	7.8%	3.68 [0.90, 6.46]
Mousavinasab et al. (2009)	34	5.58	8	33.25	6.11	8	6.1%	0.75 [-4.98, 6.48]
Mousavinasab et al. (2009)	40.78	4.08	8	42.25	6.08	8	6.5%	-1.47 [-6.54, 3.60]
Mousavinasab et al. (2009)	25.62	5.75	8	14.75	6.34	8	6.0%	10.87 [4.94, 16.80]
Mousavinasab et al. (2009)	11.75	4.68	8	11.12	6.75	8	6.2%	0.63 [-5.06, 6.32]
Mousavinasab et al. (2009)	33.25	5.8	8	31.5	7.65	8	5.6%	1.75 [-4.90, 8.40]
Shafiei et al. (2013)	21.28	3.61	10	14.94	2.97	10	7.8%	6.34 [3.44, 9.24]
Shafiei et al. (2013)	24.48	3.95	10	19.74	3.32	10	7.6%	4.74 [1.54, 7.94]
Total (95% CI)			**489**			**489**	**100.0%**	**3.22 [0.55, 5.89]**

Heterogeneity: Tau² = 21.67; Chi² = 92.03, df = 16 (P < 0.00001); I² = 83%
Test for overall effect: Z = 2.36 (P = 0.02)

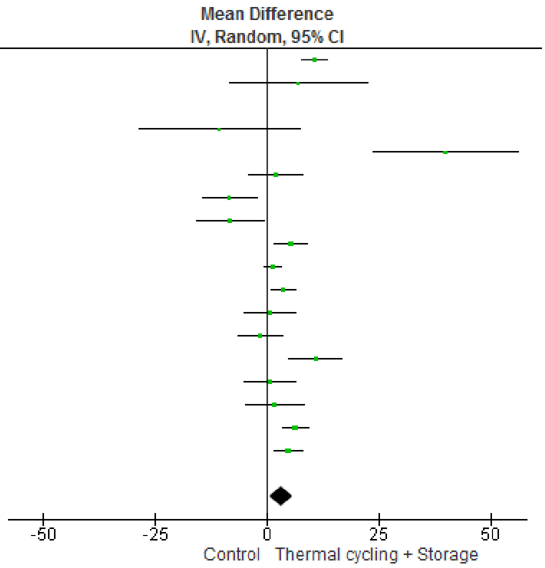


Figure 9. Mata-analysis considering the association of thermal cycling and storage as an aging method. The union of the methods showed favorable results as a way of aging the interface.

Study or Subgroup	Control Mean	Control SD	Control Total	Pulpal Pressure Mean	Pulpal Pressure SD	Pulpal Pressure Total	Weight	Mean Difference IV, Random, 95% CI
8.3.1 24h								
Abdalla et al. (2008)	37	5.5	20	36	4.6	20	1.7%	1.00 [-2.14, 4.14]
Abdalla et al. (2008)	39	4.3	20	38	3.9	20	1.8%	1.00 [-1.54, 3.54]
Abdalla et al. (2008)	36	5.2	20	34	3.3	20	1.8%	2.00 [-0.70, 4.70]
Abdalla et al. (2008)	38	4.7	20	39	4.5	20	1.7%	-1.00 [-3.85, 1.85]
Abdalla et al. (2008)	41	6.2	20	39	4.8	20	1.7%	2.00 [-1.44, 5.44]
Feitosa et al. (2013)	25.6	3.3	45	21.8	8	90	1.8%	3.80 [1.89, 5.71]
Feitosa et al. (2013)	28.9	4.2	45	27.3	8.8	90	1.8%	1.60 [-0.59, 3.79]
Feitosa et al. (2013)	38.9	4.6	45	28.3	6.6	90	1.8%	10.60 [8.69, 12.51]
Feitosa et al. (2014)	41.4	3.9	30	34.7	4.5	30	1.8%	6.70 [4.57, 8.83]
Feitosa et al. (2014)	31.2	5.6	30	29.9	3	30	1.8%	1.30 [-0.97, 3.57]
Feitosa et al. (2014)	52.1	4.2	30	42.2	3.4	30	1.8%	9.90 [7.97, 11.83]
Hosaka et al. (2007) a	40.4	10	13	37.8	8.3	13	1.5%	2.60 [-4.46, 9.66]
Hosaka et al. (2007) a	35.3	3.8	13	22	3.7	13	1.7%	13.30 [10.42, 16.18]
Hosaka et al. (2007) a	44.2	8.6	13	40	7.4	13	1.5%	4.20 [-1.97, 10.37]
Hosaka et al. (2007) a	40.7	6.7	13	32.9	9.5	13	1.5%	7.80 [1.48, 14.12]
Hosaka et al. (2007) b	36.7	2	17	22	2.1	16	1.8%	14.70 [13.30, 16.10]
Hosaka et al. (2007) b	34.1	1.9	17	29.3	1.8	17	1.8%	4.80 [3.56, 6.04]
Prati et al. (1991)	9.5	1.5	8	11.4	1.2	8	1.8%	-1.90 [-3.23, -0.57]
Prati et al. (1991)	12.9	3.9	10	8.8	3	6	1.7%	4.10 [0.69, 7.51]
Tao et al. (1991)	8.1	1.1	10	5.4	1	10	1.8%	2.70 [1.78, 3.62]
Tao et al. (1991)	8.8	1.3	10	6.9	0.8	10	1.8%	1.90 [0.95, 2.85]
Subtotal (95% CI)			**449**			**579**	**36.4%**	**4.44 [2.35, 6.53]**
Heterogeneity: Tau² = 21.54; Chi² = 490.29, df = 20 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 4.16 (P < 0.0001)								
8.3.2 1 week to 3 months								
Feitosa et al. (2012) b	47.1	3.4	22	46.7	6.6	44	1.8%	0.40 [-2.01, 2.81]
Feitosa et al. (2012) b	40.8	4.3	22	34	7.8	44	1.7%	6.80 [3.88, 9.72]
Hosaka et al. (2007) b	36.7	2	17	16.4	3.8	29	1.8%	20.30 [18.62, 21.98]
Hosaka et al. (2007) b	34.1	1.9	17	20.7	6.4	32	1.8%	13.40 [11.01, 15.79]
Nakajima et al. (2006)	47.3	10.3	16	33.6	16.2	24	1.4%	13.70 [5.49, 21.91]
Subtotal (95% CI)			**94**			**173**	**8.4%**	**10.85 [2.63, 19.07]**
Heterogeneity: Tau² = 83.66; Chi² = 194.65, df = 4 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 2.59 (P = 0.010)								
8.3.3 6 months, 1 and 2 years								
Abdalla et al. (2008)	41	6.2	20	30	5.2	20	1.7%	11.00 [7.45, 14.55]
Abdalla et al. (2008)	37	5.5	20	29	3.7	20	1.7%	8.00 [5.09, 10.91]
Abdalla et al. (2008)	39	4.3	20	35	4.2	20	1.8%	4.00 [1.37, 6.63]
Abdalla et al. (2008)	38	4.7	20	35	4.6	20	1.7%	3.00 [0.12, 5.88]
Abdalla et al. (2008)	36	5.2	20	25	3.9	20	1.7%	11.00 [8.15, 13.85]
Abuna et al. (2016)	23.5	3.5	100	4.5	3.1	100	1.8%	19.00 [18.08, 19.92]
Abuna et al. (2016)	35.1	5.2	100	38.7	4	100	1.8%	-3.60 [-4.89, -2.31]
Abuna et al. (2016)	32.9	2.7	100	28.2	5.7	100	1.8%	4.70 [3.46, 5.94]
Abuna et al. (2016)	48	5.7	100	24.1	2.9	100	1.8%	23.90 [22.65, 25.15]
Abuna et al. (2016)	19.8	3.4	100	14.6	2.3	100	1.8%	5.20 [4.40, 6.00]
Belli et al. (2010)	10.1	6.5	30	8.4	6.2	30	1.7%	1.70 [-1.51, 4.91]
Belli et al. (2010)	44.1	19.9	30	43.7	20	30	1.2%	0.40 [-9.70, 10.50]
Belli et al. (2010)	10.4	9.4	30	8	9.8	30	1.6%	2.40 [-2.46, 7.26]
Belli et al. (2010)	27.3	15.6	30	31.7	22.6	30	1.2%	-4.40 [-14.23, 5.43]
Belli et al. (2010)	22.3	10	30	22.9	13.6	30	1.5%	-0.60 [-6.64, 5.44]
Belli et al. (2010)	5.7	3.1	30	5.1	9.4	30	1.7%	0.60 [-2.94, 4.14]
El-Deeb et al. (2015)	30.7	5.2	24	13	2.6	24	1.8%	17.70 [15.37, 20.03]
El-Deeb et al. (2015)	39.9	9.1	24	29.4	3.9	24	1.7%	10.50 [6.54, 14.46]
El-Deeb et al. (2015)	25.7	3.4	24	12.1	3.3	24	1.8%	13.60 [11.70, 15.50]
El-Deeb, et al. (2013)	15.78	3.9	24	14.84	1.9	24	1.8%	0.94 [-0.80, 2.68]
El-Deeb, et al. (2013)	34.87	4.9	24	20.69	3.1	24	1.8%	14.18 [11.86, 16.50]
El-Deeb, et al. (2013)	38.11	5.1	24	22.67	1.8	24	1.8%	15.44 [13.28, 17.60]
El-Deeb, et al. (2013)	16.22	4.9	24	15.6	1.7	24	1.8%	0.62 [-1.46, 2.70]
Feitosa et al. (2012) a	44.75	3.27	40	43.2	9	80	1.8%	1.55 [-0.67, 3.77]
Feitosa et al. (2012) a	42.04	3.1	40	32.6	5.3	80	1.8%	9.44 [7.93, 10.95]
Feitosa et al. (2012) a	47.2	5.72	40	36.6	6.5	80	1.8%	10.60 [8.33, 12.87]
Gotti et al. (2015)	48.3	6.6	60	51.1	5.1	60	1.8%	-2.80 [-4.91, -0.69]
Gotti et al. (2015)	63.7	4.8	68	50.6	6.2	56	1.8%	13.10 [11.12, 15.08]
Gotti et al. (2015)	69	4.1	60	69.2	4.8	60	1.8%	-0.20 [-1.80, 1.40]
Mobarak (2011)	24.33	5.1	20	9.46	3.4	20	1.8%	14.87 [12.18, 17.56]
Nagi (2015)	16.1	5.2	24	13	5.6	24	1.7%	3.10 [0.04, 6.16]
Nagi (2015)	20.75	7.1	24	13.6	6.1	24	1.7%	7.15 [3.41, 10.89]
Subtotal (95% CI)			**1324**			**1432**	**55.1%**	**6.94 [4.01, 9.86]**
Heterogeneity: Tau² = 68.31; Chi² = 2216.41, df = 31 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 4.64 (P < 0.00001)								
Total (95% CI)			**1867**			**2184**	**100.0%**	**6.37 [4.43, 8.32]**
Heterogeneity: Tau² = 54.21; Chi² = 3289.47, df = 57 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 6.42 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.54, df = 2 (P = 0.17), I² = 43.4%								

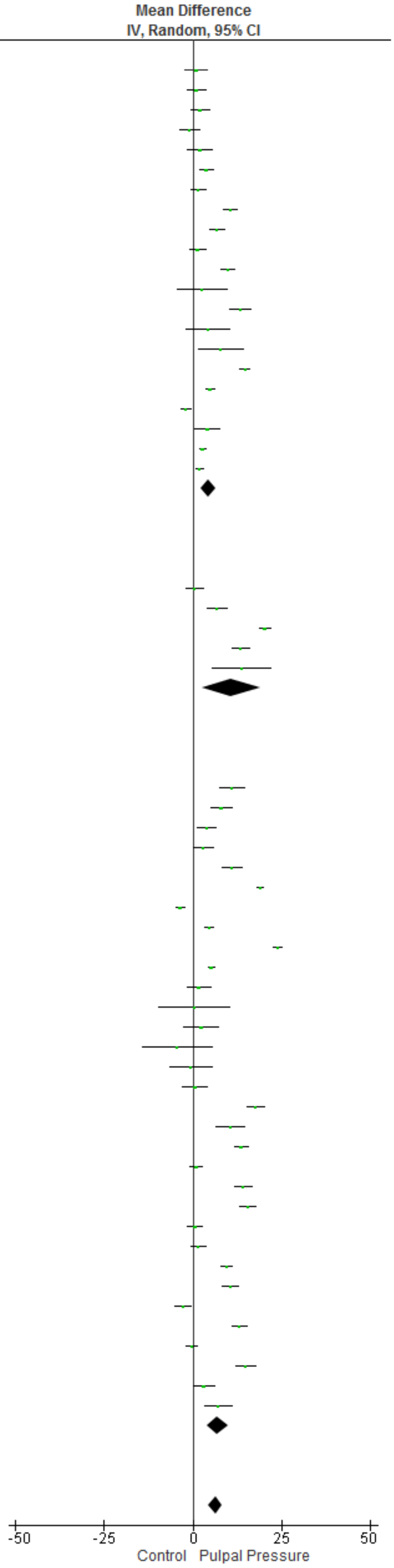


Figure 10. Mata-analysis considering pulpal pressure. All subgroups favored aging through pulpal pressure.

Study or Subgroup	Control Mean	Control SD	Control Total	NaOCl storage Mean	NaOCl storage SD	NaOCl storage Total	Weight	Mean Difference IV, Random, 95% CI
7.2.1 1-3 hours								
Apolonio et al. (2015)	39.9	12.7	49	24.4	9.9	47	2.4%	15.50 [10.96, 20.04]
Apolonio et al. (2015)	27	6.8	52	16.1	3.7	57	2.5%	10.90 [8.82, 12.98]
Apolonio et al. (2015)	26.6	8.3	52	11.7	4.2	42	2.5%	14.90 [12.31, 17.49]
Apolonio et al. (2015)	13.2	3.1	45	4.9	2.4	44	2.5%	8.30 [7.15, 9.45]
Barros et al. (2013)	44.7	2.7	32	14.4	2	36	2.5%	30.30 [29.16, 31.44]
Barros et al. (2013)	33.9	5.8	31	22.8	5	33	2.5%	11.10 [8.44, 13.76]
De Munck et al. (2007)	15.9	7.2	10	7.4	2.5	11	2.4%	8.50 [3.80, 13.20]
De Munck et al. (2007)	10.5	5.4	10	2.8	1.7	9	2.5%	7.70 [4.17, 11.23]
Deng et al. (2014)	39.5	5.1	45	19.1	3.3	45	2.5%	20.40 [18.63, 22.17]
Deng et al. (2014)	41.9	4.2	45	19.5	4.1	45	2.5%	22.40 [20.69, 24.11]
Gan et al. (2017)	20.8	6.4	50	16.1	4.7	50	2.5%	4.70 [2.50, 6.90]
Garbui et al. (2012)	54.9	8.3	100	30.2	7.8	193	2.5%	24.70 [22.74, 26.66]
Kim et al. (2011)	32.91	5.23	20	19.12	6.18	20	2.5%	13.79 [10.24, 17.34]
Li et al. (2012)	27.2	6.9	40	14	3.7	40	2.5%	13.20 [10.77, 15.63]
Li et al. (2012)	32.4	8.3	40	15.3	4.2	40	2.5%	17.10 [14.22, 19.98]
Li et al. (2012)	27.8	6.8	40	13.5	3.5	40	2.5%	14.30 [11.93, 16.67]
Saboia et al. (2009)	49.8	7	0	18.95	13.54	150		Not estimable
Sauro et al. (2009)	60.2	13.3	30	41.8	14.3	30	2.3%	18.40 [11.41, 25.39]
Sauro et al. (2009)	58.2	12.4	30	32.8	9.8	30	2.4%	25.40 [19.74, 31.06]
Yoshida et al. (2004)	50.8	11.13	12	15.48	4.84	12	2.3%	35.32 [28.45, 42.19]
Yoshida et al. (2004)	80.8	21.29	12	33.38	12.09	12	1.8%	47.42 [33.57, 61.27]
Subtotal (95% CI)			**745**			**986**	**48.8%**	**17.58 [13.50, 21.66]**
Heterogeneity: $Tau^2 = 82.02$; $Chi^2 = 1136.09$, df = 19 ($P < 0.00001$); $I^2 = 98\%$								
Test for overall effect: Z = 8.44 ($P < 0.00001$)								
7.2.2 4-6 hours								
Aguilera et al. (2012)	29.29	10.1	27	13.43	5.6	27	2.4%	15.86 [11.50, 20.22]
Aguilera et al. (2012)	29.4	11.5	27	10.7	6.3	27	2.4%	18.70 [13.75, 23.65]
Aguilera et al. (2012)	10.74	3.7	27	0	0	27		Not estimable
Erhardt et al. (2011)	48.5	6.7	30	19.5	3.8	30	2.5%	29.00 [26.24, 31.76]
Erhardt et al. (2011)	42	6.1	30	21.6	3.6	30	2.5%	20.40 [17.87, 22.93]
Garbui et al. (2012)	54.9	8.3	100	14	2.3	83	2.5%	40.90 [39.20, 42.60]
Monticelli et al. (2007)	15.36	4.8	40	6.5	3.4	40	2.5%	8.86 [7.04, 10.68]
Osorio et al. (2005) a	43.3	11.1	30	16.2	4.7	30	2.4%	27.10 [22.79, 31.41]
Osorio et al. (2005) a	45.3	9.9	30	23.5	4.4	30	2.5%	21.80 [17.92, 25.68]
Osorio et al. (2005) b	45.7	8.3	30	10.9	3	30	2.5%	34.80 [31.64, 37.96]
Taschner et al. (2012)	26.9	6.2	69	18.7	3.2	48	2.5%	8.20 [6.48, 9.92]
Taschner et al. (2012)	17.6	4.3	61	8.6	3.8	28	2.5%	9.00 [7.23, 10.77]
Taschner et al. (2014)	19	12.8	66	2.2	1.4	25	2.5%	16.80 [13.66, 19.94]
Taschner et al. (2014)	48	14.2	50	6.4	3.6	40	2.5%	41.60 [37.51, 45.69]
Taschner et al. (2014)	52.3	16.7	43	11	4.8	32	2.4%	41.30 [36.04, 46.56]
Taschner et al. (2014)	44.2	15	49	2.3	2.3	27	2.4%	41.90 [37.61, 46.19]
Toledano et al. (2006) a	44.79	10.1	40	23.53	4	40	2.5%	21.26 [17.89, 24.63]
Toledano et al. (2006) a	30	5.5	40	20.6	5.8	40	2.5%	9.40 [6.92, 11.88]
Toledano et al. (2006) a	42.8	9.1	40	16.2	4.9	40	2.5%	26.60 [23.40, 29.80]
Toledano et al. (2006) a	30.1	5.7	40	13.3	2	40	2.5%	16.80 [14.93, 18.67]
Toledano et al. (2006) a	15.01	6.5	40	0	0	40		Not estimable
Yoshida et al. (2004)	50.8	11.13	12	8.47	7.32	24	2.3%	42.33 [35.39, 49.27]
Yoshida et al. (2004)	80.8	21.29	12	30.72	21.5	24	1.7%	50.08 [35.28, 64.88]
Subtotal (95% CI)			**933**			**802**	**51.2%**	**25.45 [19.94, 30.96]**
Heterogeneity: $Tau^2 = 160.74$; $Chi^2 = 1619.61$, df = 20 ($P < 0.00001$); $I^2 = 99\%$								
Test for overall effect: Z = 9.05 ($P < 0.00001$)								
Total (95% CI)			**1678**			**1788**	**100.0%**	**21.60 [18.29, 24.92]**
Heterogeneity: $Tau^2 = 111.91$; $Chi^2 = 2809.57$, df = 40 ($P < 0.00001$); $I^2 = 99\%$								
Test for overall effect: Z = 12.79 ($P < 0.00001$)								
Test for subgroup differences: $Chi^2 = 5.06$, df = 1 (P = 0.02), $I^2 = 80.2\%$								

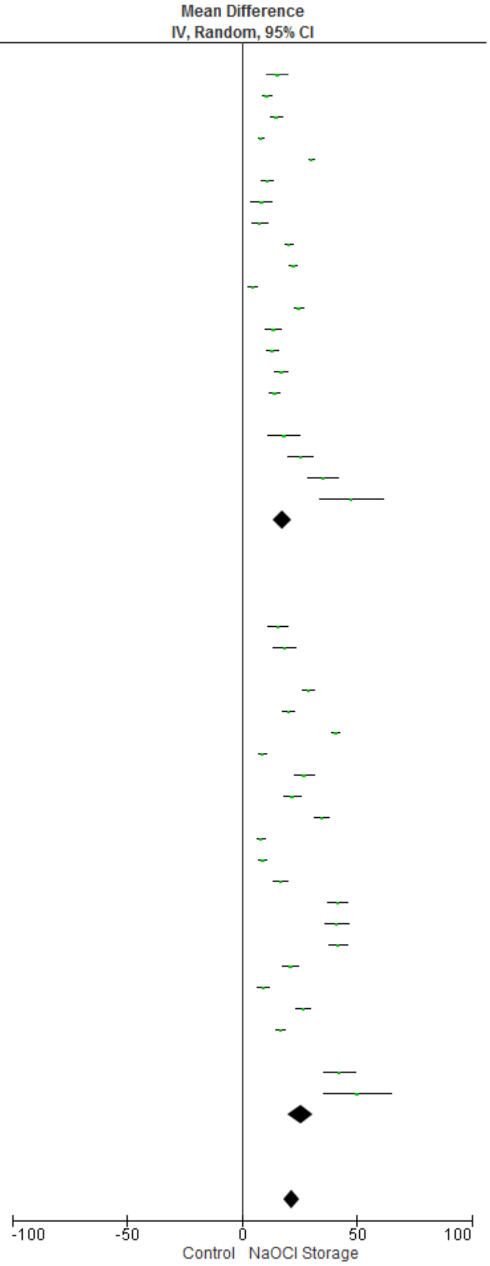
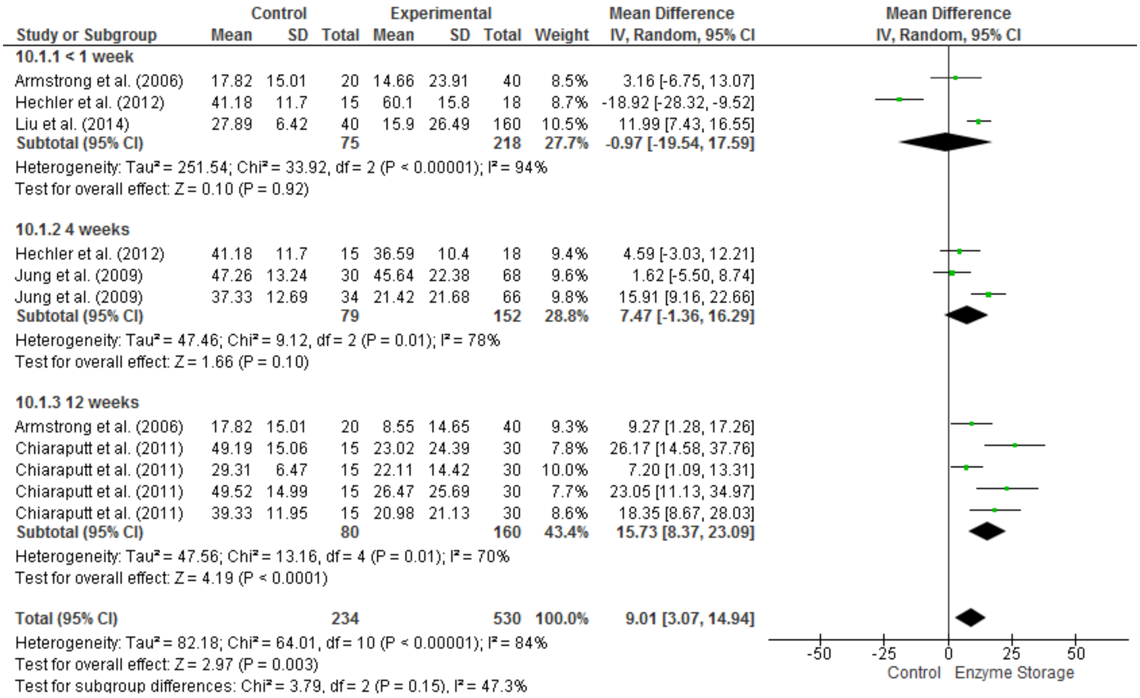
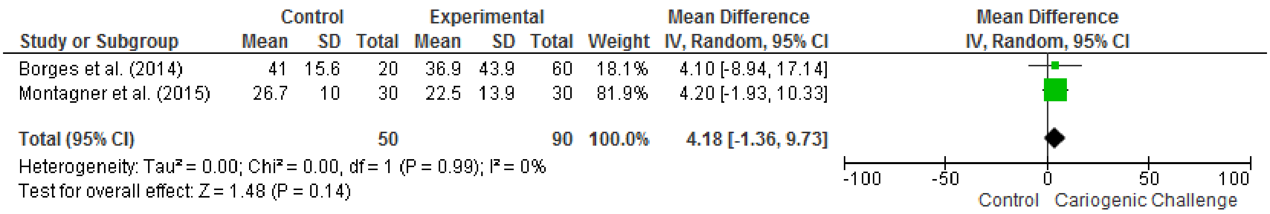


Figure 11. Meta-analysis considering NaOCl storage. The analyzes were separated into two subgroups both favoring aging and increasing with the time of storage.



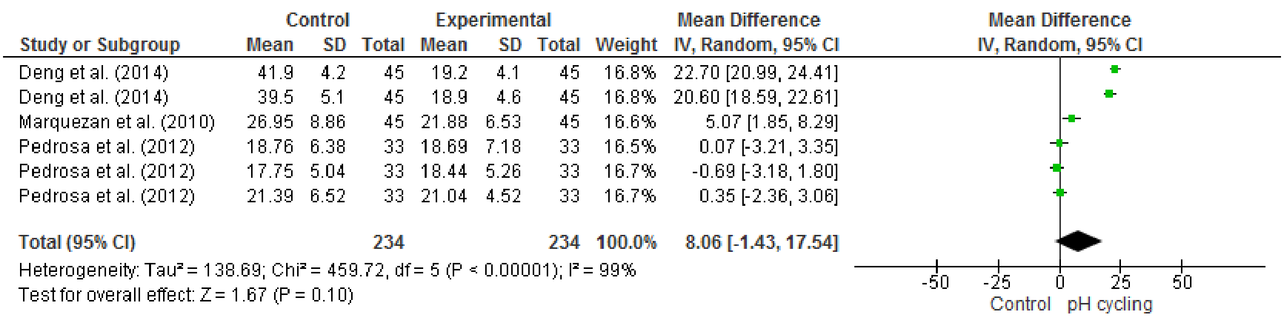
Study or Subgroup	Control Mean	Control SD	Control Total	Experimental Mean	Experimental SD	Experimental Total	Weight	Mean Difference IV, Random, 95% CI
10.1.1 < 1 week								
Armstrong et al. (2006)	17.82	15.01	20	14.66	23.91	40	8.5%	3.16 [-6.75, 13.07]
Hechler et al. (2012)	41.18	11.7	15	60.1	15.8	18	8.7%	-18.92 [-28.32, -9.52]
Liu et al. (2014)	27.89	6.42	40	15.9	26.49	160	10.5%	11.99 [7.43, 16.55]
Subtotal (95% CI)			**75**			**218**	**27.7%**	**-0.97 [-19.54, 17.59]**
Heterogeneity: Tau² = 251.54; Chi² = 33.92, df = 2 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 0.10 (P = 0.92)								
10.1.2 4 weeks								
Hechler et al. (2012)	41.18	11.7	15	36.59	10.4	18	9.4%	4.59 [-3.03, 12.21]
Jung et al. (2009)	47.26	13.24	30	45.64	22.38	68	9.6%	1.62 [-5.50, 8.74]
Jung et al. (2009)	37.33	12.69	34	21.42	21.68	66	9.8%	15.91 [9.16, 22.66]
Subtotal (95% CI)			**79**			**152**	**28.8%**	**7.47 [-1.36, 16.29]**
Heterogeneity: Tau² = 47.46; Chi² = 9.12, df = 2 (P = 0.01); I² = 78%								
Test for overall effect: Z = 1.66 (P = 0.10)								
10.1.3 12 weeks								
Armstrong et al. (2006)	17.82	15.01	20	8.55	14.65	40	9.3%	9.27 [1.28, 17.26]
Chiaraputt et al. (2011)	49.19	15.06	15	23.02	24.39	30	7.8%	26.17 [14.58, 37.76]
Chiaraputt et al. (2011)	29.31	6.47	15	22.11	14.42	30	10.0%	7.20 [1.09, 13.31]
Chiaraputt et al. (2011)	49.52	14.99	15	26.47	25.69	30	7.7%	23.05 [11.13, 34.97]
Chiaraputt et al. (2011)	39.33	11.95	15	20.98	21.13	30	8.6%	18.35 [8.67, 28.03]
Subtotal (95% CI)			**80**			**160**	**43.4%**	**15.73 [8.37, 23.09]**
Heterogeneity: Tau² = 47.56; Chi² = 13.16, df = 4 (P = 0.01); I² = 70%								
Test for overall effect: Z = 4.19 (P < 0.0001)								
Total (95% CI)			**234**			**530**	**100.0%**	**9.01 [3.07, 14.94]**
Heterogeneity: Tau² = 82.18; Chi² = 64.01, df = 10 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 2.97 (P = 0.003)								
Test for subgroup differences: Chi² = 3.79, df = 2 (P = 0.15), I² = 47.3%								

Figure 12. Meta-analysis considering Enzyme storage. The analyzes were separated into three subgroups and the only one that presented favorable results to this method of aging was the storage for 12 weeks.



Study or Subgroup	Control Mean	Control SD	Control Total	Experimental Mean	Experimental SD	Experimental Total	Weight	Mean Difference IV, Random, 95% CI
Borges et al. (2014)	41	15.6	20	36.9	43.9	60	18.1%	4.10 [-8.94, 17.14]
Montagner et al. (2015)	26.7	10	30	22.5	13.9	30	81.9%	4.20 [-1.93, 10.33]
Total (95% CI)			**50**			**90**	**100.0%**	**4.18 [-1.36, 9.73]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%								
Test for overall effect: Z = 1.48 (P = 0.14)								

Figure 13. Meta-analysis considering cariogenic challenge. This method did not show favorable results as a way of aging the interface.



Study or Subgroup	Control Mean	Control SD	Control Total	Experimental Mean	Experimental SD	Experimental Total	Weight	Mean Difference IV, Random, 95% CI
Deng et al. (2014)	41.9	4.2	45	19.2	4.1	45	16.8%	22.70 [20.99, 24.41]
Deng et al. (2014)	39.5	5.1	45	18.9	4.6	45	16.8%	20.60 [18.59, 22.61]
Marquezan et al. (2010)	26.95	8.86	45	21.88	6.53	45	16.6%	5.07 [1.85, 8.29]
Pedrosa et al. (2012)	18.76	6.38	33	18.69	7.18	33	16.5%	0.07 [-3.21, 3.35]
Pedrosa et al. (2012)	17.75	5.04	33	18.44	5.26	33	16.7%	-0.69 [-3.18, 1.80]
Pedrosa et al. (2012)	21.39	6.52	33	21.04	4.52	33	16.7%	0.35 [-2.36, 3.06]
Total (95% CI)			**234**			**234**	**100.0%**	**8.06 [-1.43, 17.54]**
Heterogeneity: Tau² = 138.69; Chi² = 459.72, df = 5 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 1.67 (P = 0.10)								

Figure 14. Meta-analysis considering pH cycling. This method did not show favorable results as a way of aging the interface.

Study or Subgroup	Control Mean	Control SD	Control Total	Experimental Mean	Experimental SD	Experimental Total	Weight	Mean Difference IV, Random, 95% CI
Hass et al. (2016)	39.2	3.4	75	29.1	3.7	75	80.7%	10.10 [8.96, 11.24]
Simoes et al. (2014)	28.77	11.02	36	21.38	7.27	36	19.3%	7.39 [3.08, 11.70]
Total (95% CI)			**111**			**111**	**100.0%**	**9.58 [7.48, 11.67]**

Heterogeneity: Tau² = 1.08; Chi² = 1.42, df = 1 (P = 0.23); I² = 29%
Test for overall effect: Z = 8.95 (P < 0.00001)

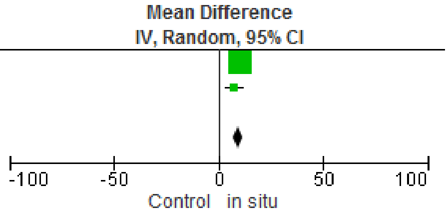


Figure 15. Meta-analysis considering in situ studies. This method showed favorable results as a way of aging the interface.

Table 1. Search strategy used in PubMed (MedLine)	
Search	**Search Terms**
#5	Search #1 AND #2 AND #3 AND #4
#4	Aging OR Longevity OR Storage OR "pH Cycling" OR Thermal OR "Thermal cycling" OR Degradation OR "in situ" OR Fatigue OR "Mechanical Loading" OR "Mechanical" OR "Load"
#3	Composite OR Composites OR "Adhes*" OR "Dental Adhesive" OR "Dental Adhesives" OR "Adhesive, Dental" OR "Adhesives, Dental" OR "Adhesive Bonding" OR Resin OR "Composite Resins"[Mesh] OR "Composite Resins" OR "Resins, Composites" OR ("Dental materials"[Mesh] OR "Dental materials" OR "Materials, Dental" OR "Dental Material" OR "Material, dental" OR Dentistry
#2	"Micro Shear" OR Shear OR "Shear Strength"[Mesh] OR "Shear Strength" OR "Strength, Shear" OR Microtensile OR Tensile OR "Tensile Strength" OR "Bond Strength" OR "Bond Test"
#1	Teeth OR Tooth OR "Dentin"[Mesh] OR Dentin OR Dentine

Table 2. Inclusion and Exclusion Criteria		
PICO	**Inclusion criteria**	**Exclusion criteria**
Population	▪ Studies with direct resin composites bonded to human dentin	▪ Papers that were not in English Studies or groups with: ▪ Bovine substrate ▪ Carious dentin
Intervention	▪ Artificial aging of the bonded dentin interface	▪ Aging methods or protocols used in only one study, making it impossible to compare Studies or groups that: ▪ Have undergone any previous treatments on dentin (eg application of fluoride) ▪ Performed only static aging through storage in water or artificial saliva
Comparison	▪ Non-aged bonded dentin interface	Studies that: ▪ Did not make clear the storage time of control ▪ Control time was bigger than 3 weeks
Outcome	Studies investigating: ▪ (micro)tensile or (micro)shear bond strength to dentin	▪ Studies with not available data or impossible to extract
Type of studies	▪ *In vitro* or *in situ*	▪ *In vivo* studies

Table 3. Division of subgroups tested according to time/number of cycles in each aging method (meta-analysis)

Aging method	**Subgroups**
Thermal cycling	Up to 500 cycles [9,18–24]
	501 - 3,000 cycles [9,18,25–35]
	3,001 - 5,000 cycles [25,26,36–52]
	5,001 - 10,000 cycles [3,9,37,51,53–74]
	15,000 - 100,000 cycles [10,11,55,78]
Mechanical cycling	Up to 100,000 cycles [25,31,68,79–88]
	100,001 - 250,000 cycles [50,89,90]
	250,001 - 750,000 cycles [31,84,90–92]
Thermomechanical cycling	Up to 100,000 mechanichal cycles [25,31,68,84,93–96]
	100,001 - 250,000 mechanichal cycles [31,84,97]
	250,001 - 500,000 mechanichal cycles [95,98,99]
Pulpal Pressure	24h [100–106]
	1 week – 3 weeks [50,103,107]
	6 months – 2 years [100,108–115]
NaOCl storage	1 – 3 hours [53,73,78,116–123]
	4 – 6 hours [4,79,82,88,116,120,124–127]
Enzyme storage	Up to 1 week [128–130]
	4 weeks [129,131]
	12 weeks [128,132]
pH cycling	10 – 15 cycles [73,87,133]
in situ	14 days [7,8]
Cariogenic challenge	3 – 14 days [134,135]
Thermocycling/storage	2,500 – 24,000 cycles / 6 – 12 months [5,18,136–141]

Table 4. Qualitative analysis of studies that performed thermal cycling

Author (year)	**n**	**Adhesive**	**Number of cycles**	**Type of aging**	**Bond Strenth test**	**Conclusion**
Akin, G. E., et al. (2012)	20 Sticks	Clearfil S3 AdheSE One Adper Easy One	10,000	Block	μTBS	Thermal cycling for 10,000 cycles had no significant bond strength reduction.
Amaral, F. L. B., et al. (2008)	100 Sticks	Adper Single Bond 2	500 2,000	Block	μTBS	Thermal cycling for 500 and 2,000 cycles had no significant bond strength reduction.
Baracco, B., et al. (2013)	28-49 Sticks	Adper Scotchbond 1 XT XP Bond Adper Scotchbond SE Filtek Silorane Adhesive System G-Bond Xeno V Bond Force	5,000	Block	μTBS	Thermal cycling for 5,000 cycles resulted in a significant bond strength reduction.
Benetti, A. R., et al. (2007)	8 cylinders	AdheSE	6,000	Block	SBS	Thermal cycling for 6,000 cycles resulted in a significant bond strength reduction.
Berry, E. A. and J. M. Powers (1994)	5 teeth	Tenure	1,000	Block	TBS	Thermal cycling for 1,000 cycles had no significant bond strength reduction.
Brueckner, C., et al. (2017)	10 cylinders	Adper Prompt-L-Pop	1,500	Block	SBS	Thermal cycling for 1,500 cycles resulted in a significant bond strength reduction.
Bumrungruan, C. and R. Sakoolnamarka (2016)	30 cylinders	OptiBond FL OptiBond all-in-one	5,000	Block	SBS	Thermal cycling for 5,000 cycles had no significant bond strength reduction.
Chang, Y. E. and D. H. Shin (2010)	15-18 Sticks	Adper Single Bond 2	10,000	Block	μTBS	Thermal cycling for 10,000 cycles resulted in a significant bond strength reduction.
Charlton, D. G. and B. K. Moore (1991)	10 cylinders	Imperva-Bond Prisma 3	2,500	Block	SBS	The shear bond strengths of both dentin bonding agents at 2 weeks (2,500 cycles) were significantly higher than at 5 minutes.
Chen, C., et al. (2015)	40 Sticks	Prime&Bond Elect Scotchbond Universal All-Bond Universal Clearfil Universal Bond Futurabond U	10,000	Block	μTBS	Thermal cycling for 10,000 cycles showed no bond strength reduction in universal adhesives applied in self-etching mode with the exception of Futurabond U.
Chiang, Y. S., et al. (2013)	12 Sticks	Scotchbond Multi-Purpose	5,000	Stick	μTBS	Thermal cycling for 5,000 cycles resulted in a significant bond strength reduction.
Daneshkazemi, A., et al. (2015)	12 Sticks	Adper Single Bond 2	1,000	Stick	μTBS	Thermal cycling for 1,000 cycles resulted in a significant bond strength reduction.
Daneshmehr, L., et al. (2013)	16 cylinders	Bond Force FL-Bond II Scotch Bond Multi Purpose	10,000	Block	SBS	Thermal cycling for 1,000 cycles resulted in a significant bond strength reduction.
De Munck, J., et al. (2005)	~12 Sticks	OptiBond FL Clearfil Protect Bond iBOND	20,000	Block/ Stick	μTBS	Thermal cycling for 20,000 had no significant bond strength reduction.
Deng, D., et al. (2013)	15 Sticks	Adper Single Bond 2 G-Bond	5,000	Stick	μTBS	Thermal cycling with water for 5,000 cycles resulted in a significant bond strength reduction.

Deng, D., et al. (2014)	45 Sticks	Adper Single Bond 2 G-Bond	10,000	Stick	µTBS	Thermal cycling for 10,000 cycles resulted in a significant bond strength reduction.
Donmez, N., et al. (2015)	15 Sticks	Single Bond Universal All-Bond Universal	1,000	Block	µTBS	Thermal cycling for 1,000 cycles resulted in a significant bond strength reduction for Single Bond Universal, while All-Bond Universal was not affected.
El-Damanhoury, H. M. and M. Gaintantzopoulou (2015)	32 Sticks	Adper Easy Bond Clearfil S3 iBOND	5,000	Block	µTBS	Thermal cycling for 5,000 cycles resulted in a significant bond strength reduction
El-Deeb, H. A., et al. (2016)	28 Sticks	Adper Scotchbond Multi-Purpose Clearfil S^3 Bond Clearfil SE Bond	10,000	Stick	µTBS	Thermal cycling for 10,000 cycles resulted in a significant bond strength reduction.
Feitosa, V. P., et al. (2012) b	22 Sticks	P90 System adhesive Clearfil SE Bond	5,000	Block	µTBS	Thermal cycling for 5,000 cycles had no effect on dentin bond strength.
Fritz, U., et al. (1997)	10 cylinders	Gluma CPS Bonding	2,000	Block	SBS	Thermal cycling for 2,000 cycles had no effect on dentin bond strength.
Fukuoka, A., et al. (2011)	12-19 Sticks	Clearfil S^3 Bond G-Bond Absolute	100,000	Stick	µTBS	Thermal cycling for 100,000 cycles resulted in a significant bond strength reduction.
Gan, J., et al. (2017)	50 Sticks	Adper Single Bond 2	10,000	Stick	µTBS	Thermal cycling for 10,000 cycles resulted in a significant bond strength reduction.
Guan, R., et al. (2016)	20 Sticks	Clearfil SE Bond Optibond XTR Scotchbond Universal	5,000 10,000	Stick	µTBS	Thermal cycling for 5,000 and 10,000 cycles had no effect on dentin bond strength.
Gunaydin, Z., et al. (2016)	15 Sticks	Adper Single Bond 2 Clearfil SE Bond Clearfil S^3 Adper Prompt-L-Pop	5,000	Block	µTBS	Thermal cycling for 5,000 cycles resulted in a significant bond strength reduction.
Guo, J., et al. (2017)	30 Sticks	Adper Single Bond 2	10,000	Stick	µTBS	Thermal cycling for 10,000 cycles resulted in a significant bond strength reduction.
Han, G. J., et al. (2014)	14-20 Sticks	Adper Scotchbond Multi-Purpose Plus	5,000	Stick	µTBS	Thermal cycling for 5,000 cycles had no effect on dentin bond strength.
Hariri, I., et al. (2012)	16 cylinders	Adper Single Bond	100 500 2,000 10,000	Block	SBS	Significant bond strength decrease was detected at 2,000 and 10,000 thermal cycles.
Hasegawa, T., et al. (1995)	15 cylinders	Scotchbond Multi-Purpose	500	Block	SBS	Thermal cycling for 500 cycles had no effect on dentin bond strength.
Inoue, S., et al. (2005)	11-17 Sticks	Clearfil SE Bond Unifil Bond Clearfil Liner Bond II	10,000 20,000 30,000 50,000 100,000	Stick	µTBS	Clearfil SE Bond remained stable regardless of the number of cycles tested. Already the others significantly decayed only with long-term thermal cycling.
Irmak, O., et al. (2017)	~42 Sticks	Single Bond Universal Clearfil Universal Bond	10,000	Block	µTBS	Thermal cycling for 10,000 cycles had no effect on dentin bond strength.
Karadas, M. and I. Caglar (2017)	15 cylinders	Clearfil S3 Bond Clearfil SE Bond	15,000	Block	SBS	Thermal cycling for 15,000 cycles resulted in a significant bond strength reduction for all deep-dentin groups. However, for superficial-dentin groups, thermal cycling had no effect on bond strength.

Khoroushi, M. and E. Rafiei (2013)	12 cylinders	Clearfil Protect Bond Beautibond	3,000	Block	SBS	Thermal cycling for 2,000 cycles had no effect on dentin bond strength.
Kim, Y. H. and D. H. Shin (2012)	5-10 Sticks	Contax Adper Single Bond 2	10,000	Block	µTBS	Thermal cycling for 10,000 cycles resulted in a significant bond strength reduction.
Korkmaz, Y., et al. (2010)	12 cylinders	Adper SE Plus Adper Single Bond 2	500	Block	SBS	Thermal cycling for 500 cycles had no effect on coronal dentin bond strength.
Lino Carracho, A. J., et al. (1991)	10 cylinders	Scotchbond Dual Cure Scotchbond 2 Mirage Bond	200	Block	SBS	Thermal cycling for 200 cycles significantly decreased the dentin bond strength of Scotchbond Dual Cure and Scotchbond 2, but not that of Mirage Bond.
Lohbauer, U., et al. (2008)	20 Sticks	G-Bond	10,000	Block	µTBS	Thermal cycling for 10,000 cycles resulted in a significant bond strength reduction.
Matsui, N., et al. (2015)	35-36 Sticks	Clearfil SE Bond Experimental adhesive	5,000 10,000	Stick	µTBS	Thermal cycling for 5,000 e 10,000 cycles resulted in a significant bond strength reduction in comercial adhesive. In Experimental adhesive thermal cycling had no effect on bond strength.
Mine, A., et al. (2012)	20 Sticks	cmf | adhesive system XP Bond	20,000	Block	µTBS	Thermal cycling for 20,000 cycles had no effect on dentin bond strength.
Nakata, T., et al. (2007)	16 Sticks	Imparva Fluoro Bond SI	1,000 2,000 3,000	Stick	µTBS	The bond strength of Imperva Fluoro Bond after 2,000 times of thermal cycling was significantly decreased, whereas SI showed no significant differences even after 3000 cycles.
Nikaido, T., et al. (2002) b	11-19 Sticks	Cleafil linerbond 2V	2,000	Block	µTBS	Thermal cycling for 2,000 cycles had no effect on dentin bond strength.
Oilo, G. and S. Olsson (1990)	10 teeth	Gluma Dentin Bond Scotchbond (Dual) Scotchbond II Tenure	5,000	Block	TBS	Thermal cycling for 5,000 cycles significantly decreased the dentin bond strength of Scotchbond (Dual), Scotchbond 2 and Tenure, but not that of Gluma Dentin Bond.
Omar, H., et al. (2007)	25 Sticks	Scotchbond Multi-Purpose Clearfil SE Bond Xeno IV	3,000	Stick	µTBS	Thermal cycling for 3,000 cycles only had effect on Scotchbond Multi-Purpose. In the others, thermal cycling had no effect on bond strength.
Ozel-Bektas, O., et al. (2011)	20 Sticks	G-Bond AdheSE Prime & Bond NT	10,000	Block	µTBS	Thermal cycling for 10,000 cycles only had effect on G-Bond. In the others, thermal cycling had no effect on bond strength.
Perdigao, J., et al. (2011)	81-122 Sticks	Adper Single Bond Plus Ambar Excite	20,000	Block	µTBS	Thermal cycling for 20,000 cycles only had effect on Excite. In the others, thermal cycling had no effect on bond strength.
Price, R. B., et al. (2003)	20 cylinders	Single Bond	5,000	Block	SBS	Thermal cycling for 5,000 cycles only had effect on high C-factor group. For low C-factor group, thermal cycling had no effect on bond strength.
Retief, D. H., et al. (1990)	15 cylinders	Original Tenure First modification of Tenure Second modification of Tenure	250	Block	SBS	Thermal cycling for 250 cycles had no effect on dentin bond strength.
Rüttermann, S., et al. (2013)	10 cylinders	Clearfil SE Bond Optibond FL	500	Block	SBS	Thermal cycling for 500 cycles had no effect on human dentin bond strength.
Sampaio, P. C., et al. (2011)	20-28 Sticks	Adper Single Bond 2	5,000	Block	µTBS	Thermal cycling for 5,000 cycles had no effect on dentin bond strength
Sangwichit, K., et al. (2016)	10-15 Sticks	Optibond FL Adper Scotchbond Multi-Purpose Optibond Solo Plus Adper Single Bond 2	10,000	Block	µTBS	Thermal cycling for 10,000 cycles only had effect on Optibond FL, Adper Scotchbond Multi-Purpose, Optibond Solo Plus. In the others, thermal cycling had no effect on bond strength.

		Clearfil SE Bond Adper SE Plus Clearfil S3 Bond Adper Easy Bond				
Shakya, V. K., et al. (2015)	15 cylinders	Adper Easy Bond Beautibond Xeno IV	500	Block	SBS	Thermal cycling for 500 cycles only had effect on Beautibond and Xeno IV. For Adper Easy Bond thermal cycling had no effect on bond strength.
Smisson, D. C., et al. (2005)	15 cylinders	Prime and Bond NT	9,000	Block	SBS	Thermal cycling for 9,000 cycles had no effect on dentin bond strength
Tezvergil, A., et al. (2003)	10 cylinders	ScotchBond Multi-Purpose	6,000	Block	SBS	Thermal cycling for 6,000 cycles had no effect on dentin bond strength
Tezvergil, A., et al. (2005)	20 cylinders	ScotchBond Multi-Purpose	6,000	Block	SBS	Thermal cycling for 6,000 cycles had no effect on dentin bond strength
Ulker, M., et al. (2010)	20 Sticks	Clearfil Tri-S Bond Hybrid Bond G-Bond Adper Prompt L-Pop AdheSE Bond Clearfil Protect Bond Clearfil SE Bond Optibond Self-etch	10,000	Block	µTBS	Thermal cycling for 10,000 cycles had no effect on dentin bond strength
Wagner, A., et al. (2014)	18-104 Sticks	Futurabond U All Bond Universal Scotchbond Universal Futurabond M Futurabond DC	5,000	Block	µTBS	Thermal cycling for 5,000 cycles had no deleteterious effect on the bonding efficacy of Universal Adhesives.
Wang, R., et al. (2017)	15 Sticks	Clearfil SE Bond Scotchbond Universal Optibond XTR Adper Easy Bond	5,000	Stick	µTBS	Thermal cycling for 5,000 cycles only had effect on Adper Easy Bond. In the others, thermal cycling had no effect on bond strength.
Xie, B., et al. (2002)	27-43 Sticks	Prime & Bond NT Prime-One Mirage	2,400	Block	µTBS	Thermal cycling for 2,400 cycles only had effect on Prime-One Mirage.
Yang, H. Y., et al. (2016)	50 Sticks	Adper Single Bond 2	10,000	Stick	µTBS	Thermal cycling for 10,000 cycles only had effect on convencional technique. The results showed that the combined use of epigallocatechin-3-gallate and ethanol–wet bonding improve immediate dentin bond strength and bond stability
Yoshihara, K., et al. (2015)	21-26 Sticks	Clearfil SE Bond (experimental primer)	100,000	Stick	µTBS	Thermal cycling for 100,000 cycles only had effect on two experimental primers. In the other, thermal cycling had no effect on bond strength.
Yu, H. H., et al. (2017)	80 Sticks	Adper Single Bond 2	5,000	Stick	µTBS	Thermal cycling for 10,000 cycles only had effect on convencional technique. Epigallocatechin-3-O-(3-O-methyl)-gallate at a concentration of 400 g/mL may be a more promising method to improve the long-term use of resinous restorations.
Zanatta, R. F., et al. (2017)	10 cylinders	Clearfil SE Bond OptiBond FL	10,000	Block	SBS	Thermal cycling for 10,000 cycles had no effect on dentin bond strength
Zhang, L., et al. (2014)	50 cylinders	Adper Single Bond 2 Clearfil S3 Bond	5,000	Block	SBS	Deep dentin showed more significant resin-dentin bond degradation than superficial dentin after thermal cycling for 5,000 cycles.

Zhou, L., et al. (2015)	35 Sticks	Xeno V G-Bond S3 Bond	10,000	Block	µTBS	Thermal cycling for 10,000 cycles resulted in a significant bond strength reduction.
Zhuge, R. S., et al. (2017)	13 Sticks	Single Bond 2	10,000	Stick	µTBS	Thermal cycling for 10,000 cycles resulted in a significant bond strength reduction, and subpressure offered a reliable interfacial morphology, improved the shortand long-term bonding strength

Table 5. Qualitative analysis of studies that performed mechanical cycling

Author (year)	**n**	**Adhesive**	**Number of cycles**	**Strenth**	**Bond Strenth test**	**Conclusion**
Aguilera, F. S., et al. (2012)	25-30 Sticks	Adper Single Bond Clearfil Se Bond One-Up Bond F	5,000	90N	µTBS	Mechanical cycling for 5,000 cycles had no effect on bond strength.
Belli, S., et al. (2009)	15-20 Sticks	Clearfil S3 Bond G Bond Adhese One Danville Experimental Prelude Total-Etch	50,000	50N	µTBS	Mechanical cycling for 50,000 cycles resulted in a significant bond strength reduction.
Bravis, T., et al. (2012)	21-28 Sticks	G-Bond Optibond Solo Plus	250,000	80N	µTBS	Mechanical cycling for 250,000 cycles resulted in a significant bond strength reduction for Optibond Solo Plus, however, not for G-Bond.
Daneshkazemi, A., et al. (2015)	12 Sticks	Adper Single Bond 2	50,000 100,000 500,000	90N	µTBS	Mechanical cycling for 50,000, 100,000 and 500,000 cycles resulted in a significant bond strength reduction.
Daneshkazemi, A. R., et al. (2013)	12 Sticks	Clearfil Se Bond	50,000 100,000 500,000	125N	µTBS	It can be concluded that, an increase in the mechanical load cycling, leads to a decrease in the value of microTBS but the minimum mechanical load cycles to make significant changes is 100K.
Deng, S., et al. (2016)	16 cylinders	All-bond 2	40,000	70N	SBS	Mechanical cycling for 40,000 cycles resulted in a significant bond strength reduction.
Farias, D. C. S., et al. (2016)	45 Sticks	Scotchbond Universal All-Bond Universal Optibond Fl Adper Single Bond Plus Clearfil Se Bond Adper Prompt L-Pop	50,000	50N	µTBS	Mechanical cycling for 50,000 had no deleterious effect on µTBS with the exception of Adper Prompt L-Pop.

Feitosa, V. P., et al. (2012) b	22 Sticks	P90 System Adhesive Clearfil Se Bond	200,000	50N	µTBS	Mechanical cycling for 200,000 resulted in bonding degradation in a short-term period in resin–bonded dentin created using two-step/self-etch adhesives.
Kawai, T., et al. (2016)	21 Sticks	Scotchbond Universal	300,000	157N	µTBS	Mechanical cycling for 300,000 cycles resulted in a significant bond strength reduction only for the group restored with Filtek Supreme Ultra Universal Restorative
Marquezan, M., et al. (2010)	45 Sticks	Adper Single Bond 2	50,000	90N	µTBS	Mechanical cycling for 50,000 cycles had no effect on bond strength
Montagner, A. F., et al. (2016)	50-75 Sticks	Adper Scotchbond 1xt Clearfil Se Bond	250,000 500000 750,000	30N	µTBS	Rub&Roll (Mechanical load) device was able to promote mechanical cycling on samples and an increased number of load cycles resulted in decreased µTBS values.
Montagner, A. F., et al. (2017)	55-72 Sticks	Adper Scotchbond 1xt Clearfil Se Bond	750,000	30N	µTBS	Mechanical cycling for 750,000 cycles resulted in a significant bond strength reduction.
Monticelli, F., et al. (2007)	39-42 Sticks	G-Bond	5,000 50,000	90N 250N	µTBS	Mechanical cycling for 5,000 or 50,000 cycles had no effect on bond strength
Nikaido, T., et al. (2002) b	11-19 Sticks	Cleafil Linerbond 2v	50,000	50N	µTBS	Mechanical cycling for 50,000 cycles had no effect on bond strength
Osorio, R., et al. (2005) b	30 Sticks	Clearfil Se Bond	5,000	90N	µTBS	Mechanical cycling for 5,000 cycles had no effect on bond strength using convencional technique.
Toledano, M., et al. (2006) b	35-40 Sticks	Single Bond Prime&Bond Prime&Bond Xp Clearfil Se Bond Etch&Prime 3.0	5,000	90N	µTBS	After mechanical cycling for 5,000, µTBS decreased in all groups except for Prime&Bond XP. Specimens bonded with Etch&Prime 3.0 resulted in premature failures and µTBS could not be measured.
Toledano, M., et al. (2017)	18 Sticks	Adper Single Bond Plus	100,000	49N	µTBS	Mechanical cycling for 100,000 cycles had no effect on bond strength.
Ulker, M., et al. (2010)	20 Sticks	Clearfil Tri-S Bond Hybrid Bond G-Bond Adper Prompt L-Pop Adhese Bond Clearfil Protect Bond Clearfil Se Bond Optibond Self-Etch	100,000	50N	µTBS	Mechanical cycling for 100,000 cycles resulted in a significant bond strength reduction.

Table 6. Qualitative analysis of studies that performed thermomechanical cycling

Author (year)	n	Adhesive	Number of Mechanical cycles	Number of Thermal cycles	Mechanical strength	Bond Strenth test	Conclusion
Aggarwal, V., et al. (2011)	10 sticks	Adper Easy One Single Bond	150,000	5,000	60N	µTBS	Thermomechanical cycling for 150,000/5,000 cycles resulted in a significant bond strength reduction.
Daneshkazemi, A., et al. (2015)	12 Sticks	Adper Single Bond 2	50,000 100,000 500,000	1,000	90N	µTBS	Simultaneous application of thermal and mechanical load cycling decreases the value of microTBS
Daneshkazemi, A. R., et al. (2013)	12 Sticks	Clearfil Se Bond	50,000 100,000 500,000	125 625 1250	125N	µTBS	Thermomechanical cycling for 50,000/125, 100,000/625 and 500,000/1250 cycles resulted in a significant bond strength reduction.
Frankenberger, R., et al. (2005)	20 sticks	Syntac Clearfil SE Bond Xeno III iBOND	100 1,000 1,0000 100,000	3 25 250 2,500	20N	µTBS	The bond strengths of all the adhesives decreased with increasing of thermomechanical cycles
Huang, X. Q., et al. (2017)	80 sticks	G-premio bond	240,000	10,000	NI	µTBS	Thermomechanical cycling for 240,000/10,000 cycles resulted in a significant bond strength reduction.
Lodovici, E., et al. (2009)	~30 sticks	Scotchbond Multi-Purpose Clearfil SE Bond	500,000	1,000	10 KgF	µTBS	Thermomechanical cycling for 500,000/1,000 cycles had no effect on bond strength using convencional technique.
Nikaido, T., et al. (2002) a	14-20 sticks	Clearfil SE Bond Single Bond	50,000	625	50N	µTBS	Thermomechanical cycling for 50,000/625 cycles had no effect on bond strength.
Nikaido, T., et al. (2002) b	11-19 Sticks	Cleafil Linerbond 2v	50,000 (Flattened dentin surface) 10,000 (Class I) 50,000 (Class I) 100,000 (Class I)	2,000 (Flattened dentin surface) 125 (Class I) 625 (Class I) 1,250 (Class I)	50N	µTBS	On Flattened dentin Thermomechanical cycling for 50,000/2,000 cycles had no effect on bond strength. However, in class I cavity from 50,000/625 cycles there was a significant decrease in bond strength.
Rego, H. M. C., et al. (2016)	90 sticks	Adper Single Bond 2	666 120,000	33 5,000	NI*	µTBS	Thermomechanical cyclic for 666/33 cycles had no effect on bond strength. However, 120,000/5000 cycles had a significant decrease in bond strength.
Ulker, M., et al. (2010)	20 Sticks	Clearfil Tri-S Bond Hybrid Bond G-Bond Adper Prompt L-Pop Adhese Bond Clearfil Protect Bond Clearfil Se Bond Optibond Self-Etch	100,000	10,000	50N	µTBS	Thermomechanical cycling for 100,000/10,000 cycles resulted in a significant bond strength reduction.
Vidal, C. M. P., et al. (2013)	24 sticks	Adper Single Bond Plus	500,000	3,000	50N	µTBS	Thermomechanical cycling for 500,000/3,000 cycles had no effect on bond strength.

* NI – Not informed

Table 7. Qualitative analysis of studies that performed Static storage + Thermal cycling						
Author (year)	**n**	**Adhesive**	**Cycles**	**Storage time**	**Bond Strenth test**	**Conclusion**
Amaral, F. L. B., et al. (2008)	100 Sticks	Adper SingleBond 2	12,000	6 months	µTBS	Thermal cycling for 12,000 cycles ally to 6 months water storage resulted in a significant bond strength reduction.
Duarte Jr, S., et al. (2009)	33-52 Sticks	LS System Adhesive Adper Single Bond plus	20,000	6 months	µTBS	Thermal cycling for 20,000 cycles ally to 6 months water storage had no effect on dentin bond strength. Aging of Adper Single Bond plus resulted in premature failures and µTBS could not be measured.
Ebrahimi, M., et al. (2017)	10 cylinders	Adper Single Bond Clearfil SE Bond	1,000	3 months	SBS	Thermal cycling for 1,000 cycles ally to 3 months water storage only had significant bond strength reduction for Adper Single Bond.
Galafassi, D., et al. (2013)	40 Sticks	Clearfil SE Bond Single Bond 2 XP Bond	12,000	6 months	µTBS	Thermal cycling for 12,000 cycles ally to 6 months water storage had no effect on dentin bond strength.
Galafassi, D., et al. (2014)	40 Sticks	SingleBond 2	12,000 24,000	6 months 12 months	µTBS	Thermal cycling for 12,000 cycles ally to 6 months and 24,000 cycles ally to 12 months saliva storage had no effect on dentin bond strength.
Khamverdi, Z., et al. (2015)	12 Sticks	Clearfil SE Bond Silorane Adhesive	2,500	6 months	µTBS	Thermal cycling for 2,500 cycles ally to 6 months water storage only had significant bond strength reduction for Clearfil SE Bond.
Mousavinasab, S. M., et al. (2009)	8 cylinders	Scotch Bond Multi Purpose Adper Single Bond Clearfil SE Bond Prompt L-Pop Prompt L-Pop plus Margin Bond	3,000	3 months	SBS	Thermal cycling for 3,000 cycles ally to 3 months water storage only had significant bond strength reduction for Adper Single Bond and Prompt L-Pop.
Shafiei, F., et al. (2013)	10 cylinders	Clearfil SE Bond Clearfil Protect Bond	1,000	6 months	SBS	Thermal cycling for 1,000 cycles ally to 6 months water storage resulted in a significant bond strength reduction.

Table 8. Qualitative analysis of studies that performed pulpal pressure					
Author (year)	**n**	**Adhesive**	**Time**	**Bond Strenth test**	**Conclusion**
Abdalla, A. I., et al. (2008)	20 sticks	Scotchbond 1 Clearfil SE bond Hybrid Bond Futurabond NR AdheSE Bond	24 hours 6 months	µTBS	None of the tested adhesives showed bond strength reduction when applied to dentin supplied with water pressure. After 6 months of pulpal pressure, Scotchbond 1, Clearfil SE Bond and AdheSE Bond showed significant reduction in bond strength. In contrast, Futurabond NR and Hybrid Bond were not significantly affected.

Abuna, G., et al. (2016)	~100 sticks	5 Experimental adhesives	6 months	µTBS	Pulpal pressure for 6 months only had effect on three experimental adhesives. In the others, pulpal pressure had no effect on bond strength.
Belli, R., et al. (2010)	30 sticks	Adper Single Bond 2 Clearfil SE Bond Adper Easy Bond Adper Scotchbond SE Clearfil S3 Bond Adhese One Vivapen	1 year	µTBS	Pulpal pressure for 1 year had no effect on bond strength.
El-Deeb, H. A., et al. (2013)	24 sticks	Adper Single Bond 2 Clearfil SE Bond AdheSE One AdheSE One F	6 months	µTBS	Pulpal pressure for 6 months only had effect for Adper Adper SingleBond 2and Clearfil SE Bond. In AdheSEe One and AdheSE One F, pulpal pressure had no effect on bond strength.
El-Deeb, H. A., et al. (2015)	24 sticks	Adper Single Bond 2 Clearfil SE Bond Adper Easy one	1 year	µTBS	Pulpal pressure for 1 year resulted in a significant bond strength reduction.
Feitosa, V. P., et al. (2014) b	40-50 sticks	Silorane Adhesive Adper Easy Bond G-Bond Plus	24 hours	µTBS	Pulpal pressure for 24 hours only had effect for Adper Easy Bond. In Silorane Adhesive and G-Bond Plus, pulpal pressure had no effect on bond strength.
Feitosa, V. P., et al. (2012) a	40 sticks	Clearfil S3 Bond Adper Single Bond 2 Clearfil SE Bond	6 months 1 year	µTBS	Pulpal pressure for 6 months and 1 year only had effect for Clearfil S3 Bond and Adper Single Bond 2. In Clearfil SE Bond, pulpal pressure had no effect on bond strength.
Feitosa, V. P., et al. (2012) b	22 sticks	P90 System adhesive Clearfil SE Bond	1 week	µTBS	Pulpal pressure for 1week had no effect on bond strength.
Feitosa, V. P., et al. (2013)	30 sticks	Clearfil S3 Bond Adper Easy Bond G-Bond Plus	24 hours	µTBS	Pulpal pressure for 24 hours only had effect for Clearfil S3 Bond and Adper Easy Bond. In G-Bond Plus, pulpal pressure had no effect on bond strength.
Gotti, V. B., et al. (2015)	61 sticks	Adper Single Bond 2 Clearfil SE Bond Adper Easy one	6 months	µTBS	Pulpal pressure for 6 months only had effect for Adper Single Bond 2. In Clearfil SE Bond and Adper Easy One, pulpal pressure had no effect on bond strength.
Hosaka, K., et al. (2007) a	13 sticks	One-Up Bond F Clearfil S3 Bond Clearfil Protect Bond Clearfil SE Bond	24 hours	µTBS	Pulpal pressure for 24 hours only had effect for One-Up Bond F and Clearfil S3 Bond. In Clearfil SE Bond and Clearfil Protect Bond, pulpal pressure had no effect on bond strength.
Hosaka, K., et al. (2007) b	13-17 sticks	One-Up Bond F Fluoro Bond Shake One	24 hours 1 month 3 months	µTBS	Using One-Up Bond F, pulpal Pressure for 24h, 1 and 3 months decreased bond strength values, however, using Fluoro Bond Shake One, pulpal pressure only had effect when tested for 1 and 3 months.
Mobarak, E. H. (2011)	20 cylinders	Clearfil SE Bond	2 years	SBS	Pulpal pressure for 2 years resulted in a significant bond strength reduction.
Nagi, S. M. (2015)	24 sticks	Adper Easy One Bond 1 SF	6 months	µTBS	Pulpal pressure for 6 months only had effect for Adper Easy One. In Bond 1 SF, pulpal pressure had no effect on bond strength.
Nakajima, M., et al. (2006)	10-16 sticks	Clearfil SE Bond	1 week 1 month	µTBS	Pulpal pressure for 1 week and 1 months resulted in a significant bond strength reduction.

Prati, C., et al. (1991)	6-10 cylinders	Clearfil Photo-Bond Scotchbond 2	24 hours	SBS	Pulpal pressure for 24 hours resulted in a significant bond strength reduction for Scotchbond 2 and a significant bond strength increase for Clearfil Photo-Bond.
Tao, L., et al. (1991)	10 cylinders	Gluma	24 hours	SBS	Pulpal pressure for 24 hours resulted in a significant bond strength reduction for deep dentin, however, in superficial dentin had no effect on bond strength.

Table 9. Qualitative analysis of studies that performed NaOCl storage

Author (year)	**n**	**Adhesive**	**Time**	**%**	**Bond Strenth test**	**Conclusion**
Apolonio, F. M., et al. (2015)	42-49 sticks	Adper Scothbond Multi -Purpose Adper Scotchbond 2 Clearfil SE bond Adper Scothbond SE Plus	1 hour	10	µTBS	NaOCl storage for 1 hour resulted in a significant bond strength reduction.
Barros, L. O., et al. (2013)	27-42 sticks	Adper Single Bond 2 XP Bond	1 hour	10	µTBS	NaOCl storage for 1 hour resulted in a significant bond strength reduction.
De Munck, J., et al. (2007)	9-11 sticks	G-Bond	1 hour	10	µTBS	NaOCl storage for 1 hour resulted in a significant bond strength reduction.
Deng, D., et al. (2014)	45 Sticks	Adper Single Bond 2 G-Bond	1 hour	10	µTBS	NaOCl storage for 1 hour resulted in a significant bond strength reduction.
Erhardt, M. C., et al. (2011)	28-32 Sticks	Single Bond Clearfil SE Bond	5 hours	10	µTBS	NaOCl storage for 5 hours resulted in a significant bond strength reduction.
Gan, J., et al. (2017)	50 sticks	Adper Single Bond 2	1 hour	10	µTBS	NaOCl storage for 1 hour resulted in a significant bond strength reduction.
Garbui, B. U., et al. (2012)	83-100 sticks	Adper Single Bond 2	1 hour 3 hours 5 hours	10	µTBS	NaOCl storage for 1, 3 and 5 hours resulted in a significant bond strength reduction.
Kim, D. S., et al. (2011)	20 sticks	Adper Single Bond 2	1 hour	10	µTBS	NaOCl storage for 1 hour resulted in a significant bond strength reduction.
Li, F., et al. (2012)	40 sticks	Adper SingleBond 2 Prime & Bond NT Gluma Comfort Bond	2 hours	10	µTBS	NaOCl storage for 2 hours resulted in a significant bond strength reduction.
Monticelli, F., et al. (2007)	39-42 sticks	G-Bond	5 hours	10	µTBS	NaOCl storage for 5 hours resulted in a significant bond strength reduction.
Osorio, R., et al. (2005)	30 sticks	Adper Single Bond Clearfil SE Bond	5 hours	10	µTBS	NaOCl storage for 5 hours resulted in a significant bond strength reduction.

Osorio, R., et al. (2005) b	30 sticks	Clearfil SE Bond	5 hours	10	µTBS	NaOCl storage for 5 hours resulted in a significant bond strength reduction.
Sauro, S., et al. (2009)	30 sticks	Scotchbond 1 XT Optibond Solo Plus	1.5 hours	12	µTBS	NaOCl storage for 1.5 hours resulted in a significant bond strength reduction.
Toledano, M., et al. (2006) a	39-42 sticks	Clearfil SE Bond Single Bond Prime&Bond XP Prime&Bond NT Etch&Prime 3.0	5 hours	10	µTBS	NaOCl storage for 5 hours resulted in a significant bond strength reduction. * For Etch&Prime 3.0, no µTBS data could be obtained due to premature failure of all the specimens during sticks preparation.

Table 10. Qualitative analysis of studies that performed enzyme storage

Author (year)	**n**	**Adhesive**	**Enzyme type**	**Storage time**	**Bond Strenth test**	**Conclusion**
Armstrong, S. R., et al. (2006)	20 sticks	Scotchbond Multi-Purpose	Collagenase Esterase	24 hours 12 weeks	µTBS	Enzymatic challenge only had significant bond strength reduction for 12 weeks group.
Chiaraputt, S., et al. (2011)	15 sticks	Adper Single Bond 2 Clearfil SE Bond Clearfil tri-S Bond G-Bond	Collagenase Acetylcholinesterase	12 weeks	µTBS	Enzymatic challenge for 12 weeks had significant bond strength reduction for all adhesives with the exception of G-Bond.
Hechler, B., et al. (2012)	15 – 18 sticks	Experimental adhesive	Collagenase	1 week 4 weeks	µTBS	Enzymatic challenge for 4 weeks had significant bond strength reduction, but for 1 week the bond strength values were higher than control.
Jung, Y. J., et al. (2009)	30 – 36 sticks	Single Bond 2 Clearfil SE bond	Collagenase Esterase	4 weeks	µTBS	Enzymatic challenge for 4 weeks had significant bond strength reduction for Single Bond 2, but not for Clearfil SE Bond.
Liu, R. R., et al. (2014)	40 sticks	Adper Single Bond 2	Collagenase type I Collagenase type II	24 hours 5 days	µTBS	Enzymatic challenge for 24 hours and 5 days resulted in a significant bond strength reduction for both collagenases types.

Table 11. Qualitative analysis of studies that performed cariogenic challenge

Author (year)	**n**	**Adhesive**	**Time**	**Bond Strenth test**	**Conclusion**
Borges, F. B., et al. (2014)	20 sticks	Single Bond 2	3 days 5 days 10 days	µTBS	Cariogenic challenge under protocols of 3, 5 and 10 days had no effect on bond strength
Montagner, A. F., et al. (2015)	30 sticks	Single Bond 2	14 days	µTBS	Cariogenic challenge under the protocol of 14 days had no effect on bond strength

Table 12. Qualitative analysis of studies that performed pH cycling

Author (year)	**n**	**Adhesive**	**Time**	**Bond Strenth test**	**Conclusion**
Deng, D., et al. (2014)	45 sticks	Adper SingleBond 2 G-Bond	15 days	µTBS	pH cycling under protocol of 15 days resulted in a significant bond strength reduction.
Marquezan, M., et al. (2011)	45 sticks	Adper SingleBond 2	14 days	µTBS	pH cycling under protocol of 10 days had no effect on bond strength
Pedrosa, V. O., et al. (2012)	30-35 Sticks	Clearfil Protect Bond Clearfil SE Bond One-up Bond-F	15 days	µTBS	pH cycling under protocol of 15 days had no effect on bond strength

Table 13. Qualitative analysis of studies that performed *in situ* model

Author (year)	**n**	**Adhesive**	**Time**	**Bond Strenth test**	**Conclusion**
Hass, V., et al. (2016)	10 volunteers 75 sticks	Single Bond Plus	14 days	µTBS	*In situ* model under the protocol of 14 days of cariogenic oral environment resulted in a significant bond strength reduction.
Simoes, D. M., et al. (2014)	9 volunteers 36 sticks	All Bond 3	14 days	µTBS	*In situ* model under the protocol of 14 days of cariogenic oral environment had no effect on bond strength.

3 Capítulo 2

Title. Effect of different accelerated aging methods on microtensile bond strength to dentin[2]

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Abstract

This study evaluated the microtensile bond strength (µTBS) of an etch-and-rinse adhesive and a self-etch adhesive after aging with different methods. Thirty-six third molars were divided according to the adhesive systems: self-etch or etch-and-rinse; and aging method: water storage for 5 weeks, 10,000 thermal cycles, 250,000 axial mechanical cycles, 250,000 Rub&Roll mechanical cycles or cariogenic challenge under 14 days; the control group remained in water at 37°C for 24 h. After aging, the teeth were sectioned on sticks to microtensile test. The µTBS values were submitted to two-way ANOVA and Tukey's post hoc test ($p < 0.05$). The µTBS of the etch-and-rinse adhesive was significantly decreased after 14 days only by cariogenic challenge ($p=0.02$). However, the µTBS of the self-etching adhesive was solely reduced by mechanical cycling ($p=0.04$). Thermal cycling, Rub & Roll and 5 weeks water storage were unable to affect µTBS of both tested adhesives ($p>0.05$). Failures in all groups were predominantly adhesive. In conclusion, the µTBS of adhesives to dentine was not affected by the mostly used ageing methods, thermal cycling and short-term water storage.

Keywords: Dentin; Adhesives; Microtensile bond strength; Aging; Adhesives.

1. Introduction

Dentin is the most common and challenging substrate when it comes to adhesion [1,2]. Although the longevity and success of restorations depends on a number of factors, the search for the best adhesive techniques seems to be endless [3–5], since tooth-restoration stability is one of the most important aspects in dentistry and an unstable adhesive interface can result in many negative effects that can lead to failure of the restoration over time [5–7].

The aging of restorations can lead to defects such as superficial and marginal staining, increased surface porosity, degradation of the adhesive interface and fractures, resulting in the need of replacement of the restorations [3,5]. Many laboratory studies test the performance of dentin adhesives systems focused on its relationship with clinical performance [8,9]. Therefore, aging processes resembling those taking place in the oral environment were introduced in laboratory testing procedures [10,11].

Water storage is the most used procedure for specimen aging in durability tests of dentin-resin interfaces [12–16]. However, reduction in bond strength values normally requires a period of 6 months or more [12,17,18]. Thus, comparative studies of methods able to shorten this period are used. Thermal and mechanical cycling are already widely used for bond strength tests, mainly because they simulate common conditions in the oral cavity [11,13,14]. Changes of temperatures in thermal cycling may accelerate hydrolysis of non-protected collagen and generate repetitive contraction/expansion stresses at the tooth–material interface [1,11] and the use of mechanical cycling attempts to simulate fatigue and wear events that challenge the bond strength over time [15]. On the other hand, the cariogenic challenge is a condition that the oral environment is exposed daily and a small number of studies have evaluated its effects on the longevity of restorations [16,19].

To understand how the adhesion will behave in the long-term is a very important issue in restorative dentistry. However, there is a huge amount of aging methods and protocols described in the literature, and very few studies designed to compare these methods under standardized conditions. Based on this, the objective of this study was to evaluate the microtensile bond strength (µTBS) of an etch-and-rinse adhesive and a self-etch adhesive using different aging methods: control (24h), water for 5 weeks (5w), thermocycling (TC), axial mechanical cycling (MC), Rub&Roll mechanical cycling (RRMC) and cariogenic challenge (CC). The hypothesis tested was that all aging methods would result in decrease of µTBS, on both adhesives tested.

2. Materials and Methods

2.1. Study design

This in vitro study involved a 2 × 6 factorial design. The research factors were: type of adhesive (self-etch and etch-and-rinse) and type of accelerated aging (5-weeks water storage, thermal cycling, mechanical cycling, Rub&Roll mechanical cycling and cariogenic challenge). The response variable was microtensile bond strength to dentin.

2.2. Tooth preparation

Thirty-six third molars were obtained from the Tooth bank/UNOESC (Faculdade do Oeste de Santa Catarina – Joacaba/SC), and approved by the Local Ethics Committee, 1.634.704). The teeth were stored in 0.5% aqueous chloramine solution at 4°C until their use. The occlusal surface of the teeth was sectioned transversally to remove occlusal enamel and to expose the dentin. The cuts were obtained using precision rotating machine at 200 rpm (Isomet 1000; Buehler, Lake Bluff, IL, USA) with watercooled diamond saw. Dentin surfaces were polished with #600 silicon carbide sandpaper in a circular polishing machine (Arotec PL 4, São Paulo, SP, Brazil).

The samples were randomly allocated into 2 groups according to the adhesive system used: Scotchbond Multi-Purpose and Single Bond Universal (3M ESPE Dental Products, St Paul, MN, USA). The bonding procedures followed manufacturer's instructions (Table 1). Immediately after adhesive system application the bonding procedure was performed by one previously trained operator. Each composite resin horizontal increment (3 increments) was light cured for 20 s using a LED light unit (Radii-Call; SDI, Bayswater, VI, Australia) with irradiance of 650 mW/cm2. The samples were stored in distilled water at 37°C for 24 h.

2.3. Aging Conditions

The samples were again randomly divided in new 6 groups about aging methods (Table 2). For each aging method the samples were prepared according to the need of each protocol, respecting the bonding and restoration procedures mentioned previously. With the exception of the control group the other five groups remained in water during the same time independent of the protocol (5 weeks).

2.3.1. Thermal Cycling

This group was subjected to 10,000 intermittent thermal cycles between water baths at 5 and 55°C (dwell time 30 s) [20]. The time of cycling was 7 days, after that, the specimens stayed in water at 37°C until completing 5 weeks.

2.3.2. Mechanical Cycling

In this group teeth were prepared by embedding each root into plastic cylinders with self-cured acrylic resin (Jet Classico, Sao Paulo, SP, Brazil) and by using a polyether impression material (Impregum Soft, 3M ESPE Dental Products, St Paul, MN, USA) to simulate the periodontal ligament [21]. Each sample (plastic cylinder plus tooth) was submitted to mechanical load testing, which was performed using a piston (6 mm in diameter) in a fatigue simulator (Biocycle V2; Biopdi, Sao Carlos, SP, Brazil) with the regimen of: 250,000 cycles [22], 1 Hz, 100 N at 37°C . The time of cycling was 10 days; after that, the specimens stayed in water at 37°C until completing 5 weeks.

2.3.3. Rub&Roll Mechanical Cycling

In this group teeth were embedded in acrylic resin resulting in samples of 16 mm in height × 14 mm width × 10 mm length. Samples were mounted into the Rub&Roll device and mechanical loading was applied by the rotation movement of the inner cylinder [23]. In this study, samples were loaded at 20 rpm, and ±30 N. Mechanical loading took place in distilled water, which was weekly changed. The time of cycling was 20 days; after that, the specimens stayed in water at 37°C until completing 5 weeks.

2.3.4. Biofilm Aging

In this group teeth were protected with nail varnish except for the adhesive interface and sterilized with UV radiation. In the microcosm model, biofilm was formed on samples in cell tissue culture plates with the saliva inoculum obtained from a healthy adult volunteer that refrained oral hygiene for 24 h prior to saliva collection. Defined medium enriched with mucin (DMM) was carried out according to a previously described protocol of [24]. Saliva was inoculated onto the teeth in each well (0.1 mL). After 1 h, 1.8 mL of previously prepared DMM was added in each well. Teeth received DMM with and without 1% sucrose during 6 and 18 h respectively and were daily replaced. Biofilms were formed independently on the samples. The micro-wells were incubated in anaerobic condition under controlled temperature (37ºC) for 14 days. Next, the specimens stayed in water at 37°C until completing 5 weeks.

2.4. Microtensile bond strength test

After each aging procedure, teeth from each group were longitudinally sectioned in both "x" and "y" directions across the bonded interface with a low-speed diamond saw (ISOMET 1000; Buheler, Lake Bluff, IL, USA). Resin–dentin sticks (n = 15-20) with a cross-sectional area of approximately 1.0 mm2 were fixed with cyanoacrylate resin (Super Bonder Gel, Loctite, São Paulo, Brazil) to the grips of a microtensile device and tested on a mechanical testing machine (DL500; EMIC, São José dos Pinhais, PR, Brazil) at a crosshead speed of 0.5 mm/min until failure.

2.5. Mode of failure analysis

Fractured specimens were observed under 40× magnification using a stereomicroscope to determine the failure mode as: apparently interfacial (AI fracture occurred within the adhesive interface, between the dentin and composite); cohesive in composite (CC - fracture occurred at the resin-based composite portion) or mixed failures (M - designates a mixture of adhesive and cohesive failure within the same fractured surface). Some sticks were selected and both parts of debonded specimens were dehydrated in silica gel, mounted on stubs, gold-sputter coated and observed in Scanning Electron Microscopy (SEM) (Inspect S50, FEI Company, Amsterdam, Netherlands) operated at 20 kV.

2.6. Statistical analysis

The µTBS values were obtained in MPa and data were submitted to two-way ANOVA using SigmaPlot version 12 (Systat Software Inc., San Jose, CA, USA). Pre-testing failures were included in the calculation of mean µTBS as 0 MPa. All pairwise multiple comparison procedures were performed using the Tukey method ($p < 0.05$).

3. Results

There was no statistically significant difference between the adhesives (p=0.99). The µTBS of the etch-and-rinse adhesive was significantly decreased after 14 days of cariogenic challenge (p=0.02) (Table 3). On the other hand, when we aged the adhesive interface bonded with self-etching, the only method capable of significantly reducing µTBS was mechanical cycling (p=0.04). Thermal cycling, five weeks water storage and Rub&Roll mechanical cycles were not able to reduce µTBS in this study for any tested adhesive (p>0.05).

Three types of failure were observed: mixed failure, interfacial failure, and cohesive failure occurring in resin composite (Table 4). Most of the post-test specimens consisted of interfacial failure. Groups tested with mechanical load presented similar or equal numbers of mixed and adhesive failures. For all groups, few failures occurred in resin and the representative scanning electron micrographs of the most occurred fractures can be observer in Figure 1.

4. Discussion

The present study was the first to investigate the influence of aging as applied by five different methods on adhesive bond strength of restored teeth and the results demonstrate that some methods result in a decreased µTBS, but most of the protocols mostly used in literature did not affect the microtensile bond strength. Therefore, the null-hypothesis was partially rejected.

The methodologies tested were chosen by simulating different events that occur in the oral cavity such as chewing and occlusal wear, expansion and contraction associated with temperature changes [1,25], as well as challenges in dental structures and restorative materials through bacteria acting on the surface by degrading unprotected collagen fibrils and adhesive components at the tooth-restoration interface [26,27].

Thermal cycling is commonly used for many years in dental laboratory testing and addresses a method of aging through repetitive contractions and expansions between the dental substrate and the restoration [28]. The relationship of 10,000 cycles with one year of clinical service has already been reported in the literature [1,29], that protocol is one of the most used in the literature as well as the immersion time for 30s in temperatures of 5 to 55ºC [11]. In this study 10,000 cycles were tested and the decrease in bond strength was not significant when compared to the control group for none of the adhesives tested, but this finding corroborates with other studies [25,30,31].

When we considering mechanical cycling the goal is to challenge the restorations to loads that simulate chewing and one year of clinical service was reported to be simulated by 240,000 mechanical cycles [15]. In this study two methodologies were performed using mechanical load, with the traditional mechanical cycling a perpendicular force was applied through a metal piston directly in the restoration. For the group restored with self-etch adhesive the bond strength was significantly lower whereas for the etch-and-rinse there was no difference. The decrease in µTBS of self-etching adhesives after no more than 250,000 cycles has been reported in other studies [31,32]. The cycling performed on Rub&Roll is through the application of different forces similar to wear, few studies have been performed using this equipment and none with these classifications of adhesive. In another study [33], 250,000 cycles were able to decrease the bond strength of Adper Scotchbond 1XT and Clearfil SE Bond but in ours the values were similar to that of the control for both adhesives, however in this other study the cycling was uninterrupted, and in ours, only 8 hours of cycling per day were performed, which leads us to think that the parameters used in each experiment can directly influence the results.

Biofilm accumulation and cariogenic challenge are crucial factors and very related to the longevity of restorations, mainly because one of the major causes of failure is secondary caries. An unexplored method to simulate these events is the biofilm storage and the cariogenic challenge through biofilm with and without sucrose, however it is a more laborious methodology because it involves microbiology and few studies have done it [16,19,34]. No studies evaluated self-etching adhesives after 14 days of cariogenic challenge, but the only one that evaluated this period with etch-and-rinse adhesives found a difference between the aged interface and the control like in our study, where Scotchbond Multi-purpose presented significantly lower values after CC.

All the methods tested were standardized so that at the end of the aging process the specimens had stayed the same time in water. After each aging protocol the teeth were kept in water until completing the remaining time for 5 weeks. The purpose of this was to equate the hydrolysis that the interface undergoes after the aging methods and other studies can be done by testing longer or challenging protocols.

All protocols involve water or culture medium, which may lead to a bigger or lesser degradation not only by the number of cycles but also by the time that the chemical bonds that occur in the adhesion process are exposed to hydrolytic degradation. Generally, when the studies involve cycling, the total duration of the aging process is not usually reported in the paper, although it is a determining factor in the results because we can do 15,000 cycles in a week or a month, depending on how many cycles we will do per day.

5. Conclusion

Thermal cycling, Rub & Roll and 5 weeks water storage were not able to affect µTBS in this study. Cariogenic challenge for 14 days was able to reduce the bond strength of the Scotchbond Multi-purpose and Mechanical cycling of Single Bond Universal.

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Tables

Table 1. Manufacturer, Composition, and Application Procedure of the Adhesive Systems		
Adhesive	**Composition**	**Application Procedure**
Adper Scothbond Multi-purpose (3M – ESPE, St. Paul, MN, USA)	Etching agent: 35% phosphoric acid	Apply. Wait 15 s. Rinse for 15 s. Dry with absorbent paper.
	Primer: Polyalkenoic acid copolymer HEMA, water	Apply, then gently air-dry for 5 s
	Bond: Bis-GMA, HEMA, tertiary amines, photo-initiator	Apply, then light-cure for 10 s
Single Bond Universal (3M – ESPE, St. Paul, MN, USA)	10-MDP, HEMA, silane, dimethacrylate resins, Vitrebond™ copolymer, filler, ethanol, water, initiators	Apply and rub for 20 s. Gently air-dry for 5s. Light-cure for 10 s.
10-MDP: 10-methacryloyloxydecyl dihydrogen phosphate; HEMA: 2-hydroxyethyl methacrylate; Bis-GMA: bisphenol A glycidyl methacrylate;		

Table 2. Accelerated aging methods and protocols	
Aging Method	**Protocol**
Control (water)	24 hours, 37ºC
Water Storage	5 weeks, 37ºC
Thermal Cycling	10,000 cycles, 5-55ºC (dwell time 30 s)
Mechanical Cycling	250,000 cycles, 1 Hz, 100 N at 37°C
Rub&Roll Mechanical Cycling	250,000 cycles, 20 rpm, 30N at room temperature
Cariogenic Challenge	14 days under biofilm with and without sucrose at 37ºC

Table 3. Microtensile bond strength in MPa, standard deviations. (±SD)						
	Aging methods					
Materials	**24-h**	**5 weeks water storage**	**Thermal cycling**	**Rub&Roll**	**Mechanical cycling**	**Cariogenic challenge**
Scotchbond Multi-purpose	29.7 ±12.1[a]	33.0 ±10.8[a]	25.2 ±7.7[a]	22.3 ±12.4[a]	24.5 ±14.4[a]	20.5 ±11.9[b]
Single Bond Universal	32.4 ±10.7[a]	30.8 ±14.9[a]	24.6 ±10.8[a]	23.6 ±11.2[a]	19.8 ±11.5[b]	24.2 ±11.9[a]

Different letters mean statistically significant difference among the aging methods for each adhesive (row). There was no statistically significant difference between the adhesives.

Table 4. Percentage of mode of failure (%) and pre-testing failures [PTF] using different adhesive system and aging conditions.

Aging methods	**Scotchbond Multi-purpose**				**Single Bond Universal**			
	AI	**M**	**CC**	**PTF**	**AI**	**M**	**CC**	**PTF**
24-h	61	33	6	3	60	35	5	0
5 weeks water storage	63	26	11	1	65	30	5	0
Thermal cycling	52	29	19	1	59	29	12	1
Rub&Roll	47	41	12	3	41	53	6	1
Mechanical cycling	47	40	13	3	47	47	6	3
Cariogenic challenge	63	31	6	4	59	35	6	3

AI - Apparently interfacial; M – Mixed; CC: Cohesive in composite

Figure

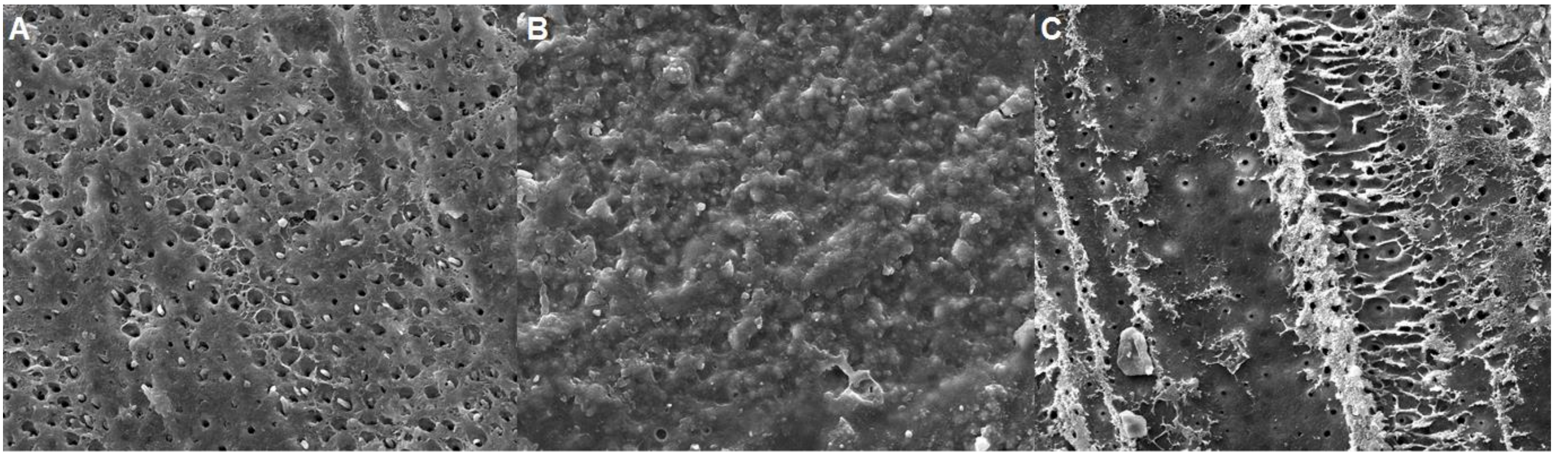

Figure 1. Representative scanning electron micrographs of the most occurred fractures (×2,000). (A) With the presence of dentin tubules with resin tags inside them, it can be assumed that fracture occurred at the base of the hybrid layer; (B) Failure occurred exclusively in resin; (C) Mixed failure involving adhesive and dentin.

6 Considerações finais

Esta tese se propôs a testar e comparar diferentes métodos de envelhecimento acelerado usados para testes de adesão à dentina. Como citado anteriormente, muitos métodos são amplamente usados em diferentes estudos em odontologia, porém, poucos critérios são avaliados na hora da escolha do método e protocolo. Poucos estudos se propõem a comparar diferentes métodos de envelhecimento, e mesmo quando comparam mais de um tipo, acabam deixando esse fator em segundo plano e se atentando primeiramente a diferentes tratamentos, materiais e métodos de aplicação. Quando comparamos os estudos disponíveis na literatura pudemos perceber que muitos testes e protocolos parecem, em geral, funcionar para envelhecer a interface adesiva. Alguns métodos são comumente aplicados como termociclagem, ciclagem mecânica e armazenamento em NaOCl, já outros como desafio cariogênico, ciclagem de pH e protocolos *in situ*, nem tanto.

Desafio cariogênico foi uma das únicas metodologias que não foi efetiva nas comparações da nossa revisão sistemática, porém, em nosso estudo *in vitro* ela mostrou reduzir a resistência de união significativamente quando comparada ao controle. Dois estudos foram incluídos na revisão sistemática, um testando 3, 5 e 10 dias de desafio cariogênico o qual não apresentou resultados significativos para nenhum dos tempos, e outro testando 14 dias o qual reduziu significativamente os valores de resistência de união e corroborou com nossos achados *in vitro* por termos usado o mesmo tempo de protocolo. Comparando esses resultados podemos inferir que o desafio cariogênico pode ser efetivo, desde que testado por no mínimo duas semanas.

Muitos resultados são controversos na literatura, o que se deve por os resultados não dependerem só do método e protocolo de envelhecimento, mas também do material utilizado e parâmetros adotados na metodologia. Quando se trata de microtração, em alguns métodos os dentes restaurados podem ser envelhecidos para porterior corte dos palitos ou o envelhecimento pode ocorrer diretamente nos palitos, o que pode potencializar o efeito do envelhecimento. A falta de normativas específicas para este tipo de teste dificulta a comparação dos estudos, porém nesta tese buscamos respostas e panoramas globais que possam nortear os pesquisadores neste tema que é amplamente utilizado e pouco discutido em odontologia.

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Apêndices

Apêndice A – Nota da tese

Nota da tese

Métodos de envelhecimento da interface adesiva para testes de adesão à dentina

Aging methods for dentin bond strength tests

Dentes restaurados são desafiados diariamente através da mastigação, dieta, doenças e até mesmo pela própria saliva. Na tentativa de mimetizar esses processos de forma acelerada em laboratório, muitas metodologias são empregadas, porém, pouco padronizadas. A presente tese avaliou diferentes métodos existentes para simular esses eventos que ocorrem clinicamente. Foram discutidos diversos fatores como tempo de protocolo, número de ciclos de simulação, parâmetros utilizados nos testes. Através dos estudos desenvolvidos, métodos e protocolos foram sumarizados na tentativa de avaliar os protocolos que podem ser efetivos para acelerarem o processo de envelhecimento da ligação dente-material em laboratório. Com esta tese podemos concluir que muitos métodos de envelhecimento acelerado podem ser efetivos na degradação da interface, porém muitos parâmetros devem ser considerados como tempo de envelhecimento, condições de armazenagem e material utilizado.

Campo da pesquisa: Biomateriais e Biologia oral/Materias Odontológicos.
Candidata: Katielle Valente Brauner, Biotecnologista (2014) pela Universidade Federal de Pelotas.
Data da defesa e horário: 13/02/2019 às 8:30 horas.
Local: Auditório do Programa de Pós-graduação em Odontologia da Universidade Federal de Pelotas. 5º andar da Faculdade de Odontologia de Pelotas. Rua Gonçalves Chaves, 457.
Membros da banca: Prof. Dr. Fabricio Mezzomo Collares, Profª. Drª. Tamires Timm Maske, Prof. Dr. Wellington Luiz Oliveira da Rosa, Profª. Drª. Giana da Silveira Lima (Suplente) e Profª. Drª Lisia Lorea Valente.
Orientadora: Prof. Dr. Maximiliano Sérgio Cenci
Co-orientador: Prof. Dr. Rafael Ratto de Moraes e Profª. Drª. Tatiana Pereira Cenci

Informação de contato: Katielle Valente Brauner, katiellevb@gmail.com,
Rua Gonçalves Chaves, 457- Programa de Pós-Graduação em Odontologia.

Apêndice B – Súmula do currículo da candidata

Katielle Valente Brauner, nasceu em 18 de maio de 1994, em Pelotas, Rio Grande do Sul (RS). Completou o ensino fundamental e médio na Escola Santa Mônica sua na cidade natal. Possui graduação em Biotecnologia pela Universidade Federal de Pelotas (2014). Desde a iniciação científica realiza e auxilia trabalhos relacionados à biologia oral e por isso ingressou no doutorado direto em 2015 no Programa de Pós-graduação em Odontologia da Universidade Federal de Pelotas na área de concentração em Materiais Odontológicos. Tem orientação desde a graduação pelo Prof. Dr. Maximiliano Sergio Cenci com o qual desenvolveu pesquisas relacionadas à cariologia e envelhecimento acelerado de materiais odontológicos. Está tendo seu doutorado co-orientado pela Profa. Dra. Tatiana Pereira Cenci e pelo Prof. Dr. Rafael Ratto de Moraes.

Publicações na área:

MASKE, T. T. ; BRAUNER, K. V. ; NAKANISHI, L. ; ARTHUR, R. A. ; VAN DE SANDE, F. H. ; CENCI, M. S. . An in vitro dynamic microcosm biofilm model for caries lesion development and antimicrobial dose-response studies. Biofouling (New York. Print), v. 32, p. 339-348, 2016.

CARVALHO, T. P. ; TIMM MASKE, TAMIRES ; SIGNORI, C. ; BRAUNER, K. V. ; Oliveira, EF ; CENCI, M. S. . Desenvolvimento de lesões de cárie em dentina em um modelo de biofilme simplificado in vitro: um estudo piloto. REVISTA DE ODONTOLOGIA DA UNESP (ONLINE), v. 47, p. 40-44, 2018.

Anexos

Anexo A – Parecer do Comitê de Ética em Pesquisa

FACULDADE DE ODONTOLOGIA DA UNIVERSIDADE FEDERAL DE

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Protocolos de envelhecimento da interface adesiva para testes de adesão à dentina

Pesquisador: Maximiliano Sérgio Cenci
Área Temática:
Versão: 2
CAAE: 53465716.6.0000.5318
Instituição Proponente: Faculdade de Odontologia da Universidade Federal de Pelotas/ FO-UFPel
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.634.704

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_664597.pdf	02/06/2016 11:38:29		Aceito
Outros	CartaResposta.pdf	02/06/2016 11:37:32	Katielle Valente Brauner	Aceito
Outros	ParecerUNOESC.pdf	02/06/2016 11:35:44	Katielle Valente Brauner	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO2.pdf	02/06/2016 11:33:06	Katielle Valente Brauner	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE22.pdf	02/06/2016 11:32:24	Katielle Valente Brauner	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE11.pdf	02/06/2016 11:31:29	Katielle Valente Brauner	Aceito
Folha de Rosto	FOLHADEROSTO.pdf	18/02/2016 16:13:35	Katielle Valente Brauner	Aceito
Orçamento	ORCAMENTO.pdf	18/02/2016 15:58:11	Katielle Valente Brauner	Aceito
Cronograma	CRONOGRAMA.pdf	18/02/2016 15:55:44	Katielle Valente Brauner	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PELOTAS, 13 de Julho de 2016

Assinado por:
ANDREIA MORALES CASCAES
(Coordenador)

Anexo B - Declaração de doação de dentes humanos – Banco de Dentes Humanos/Universidade do Oeste de Santa catarina

UNOESC

Universidade do Oeste de Santa Catarina

DECLARAÇÃO

Declaro para os devidos fins e efeitos legais que o Banco de Dentes Humanos da UNOESC aprovado pelo CEP número 157/09 em 18 de outubro de 2009, objetivando atender as exigências para a obtenção de parecer do Comitê de Ética em Pesquisa com Seres Humanos, e como representante legal da Instituição, Universidade do Oeste de Santa Catarina - UNOESC, tenho conhecimento do projeto de pesquisa: envelhecimento *in vitro* da interface adesiva, e nos comprometemos a fornecer os dentes humanos necessários para o desenvolvimento da pesquisa.

Joaçaba, 30/05/2016.

Professora Ms. Léa Maria Franceschi Dallanora.

Responsável técnica