Fatigue bond strength of dental adhesive systems: Historical background of test methodology, clinical considerations and future perspectives

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Abstract
Numerous laboratory evaluations have been conducted since Dr. Rafael Bowen introduced a method for determining the bond strengths of adhesive systems to dental substrates in 1965. Most of the past studies have been conducted using static bond strength tests, such as shear and tensile bond strength testing with either macro or micro sized specimens. These static bond strength tests are conducted using a monotonically increasing load in which stress is applied continuously until failure occurs. Although the type of stress that develops in static bond strength tests is not typically encountered in clinical situations, over the years clinicians have based their choice of adhesive systems for use in daily practice on the results of such tests. However, some well-known researchers have reported that the results obtained from static bond strength testing may have limited clinical relevance and should not be used only by themselves to make recommendations for clinical use. In clinical situations, restorations undergo cyclic stress during mastication at stress levels well below the breaking stress used in static bond strength tests. Thus, dynamic bond strength tests, using cyclic loading, should be more clinically relevant than static bond strength tests. Over 15 years, a testing method designed to assess fatigue bond strengths of dental adhesive systems has been developed through inter-collegial and international collaborative efforts. This review discusses the development of fatigue bond strength testing methodology, provides both a historical perspective and current information regarding available testing data for all categories of adhesive systems to enamel and dentin and perspectives on the future development of both adhesive systems and testing methods.

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1. The importance of bond strength testing

The development of dental adhesive systems has had a significant influence on improvements in restorative dentistry. The restorative procedure known as extension for prevention proposed by G.V. Black is no longer justified and has been replaced by the concept of minimally invasive dentistry [1]. Minimally invasive dentistry focuses on the application of systematic respect for the original tooth substrates, aiming to preserve enamel and dentin while securing sufficient access for the selective caries removal [2]. The subsequent restorative procedure often relies on bonding to remaining tooth structures using an adhesive system with a resin composite, and does not typically require the removal of tooth structure to ensure additional mechanical interlocking for adequate retention [3]. Although these restorative procedures assure the bond integrity of the adhesive systems used in restorative restorations over time raised from both laboratory testing and clinical studies [4].

Clinically, the main concerns with direct resin-based composite restorations are the occurrence of secondary caries, wear of tooth substrates in total. Even in 2017, Arola [16] conducted a review of the field by saying that the application of fatigue testing to restorative dentistry had barely begun, and would hopefully foster the development of a more realistic understanding of fatigue failures in the clinical situation, allowing researchers to solve the critical issues that limit the success of restorations. Therefore, a long-term research program using dynamic bond strength testing is highly desirable.

2. From static to dynamic bond strength testing

Numerous bond strength evaluations of adhesive systems to tooth substrates have been conducted since the introduction of this type of testing in the 1960s [10]. A PubMed advanced literature search conducted in January 2022 identified around 3000 articles when the keywords ‘bond strength’ and ‘enamel’ were used, and around 6000 articles when the keywords ‘bond strength’ and ‘dentin’ were used. Most of the reported studies were conducted using static bond strength tests [11]. However, bond strength of adhesive systems in the early years were typically conducted with macro-shear or tensile tests [12]. Micro-shear and tensile bond strength test techniques have primarily served as screening tests for evaluating the bonding performance of adhesive systems over the last two decades [13]. These tests are useful for evaluating differences in the bonding performance to various substrates among adhesive systems, but the results are difficult to relate to clinical effectiveness and thus, there are recognized shortcomings to these methods [14]. Notably, these bond strength tests are static tests involving the application of a monotonically increasing stress to the adhesive interface over time, giving an indication of its strength [15]. However, this is not the likely mode of failure of an adhesive interface in the oral environment, where failure is believed to result from repeated loading from mastication, over a period of many years and at stresses well below the ultimate bond strength. It is clear that the resistance of an adhesive interface to fatigue is not directly represented by a bond strength value measured using a static load.

If a static bond strength test is like a sprint, with intense forces applied over a short period, the clinical situation is more like a marathon, with much weaker forces applied over a far longer period. The two situations are completely different. This suggests that fatigue bond strength studies, where repeated cyclic load to the adhesive interface is evaluated, may provide better insight into the potential clinical success of restorations and give more realistic information about the likely success of restorative dentistry. With this in mind, there have been calls for the development of fatigue bond strength testing that better represents clinical situations [16].

Studies of the fatigue bond strength of adhesive systems to tooth substrates are not new, with early reports on this topic appearing in the mid-1990s [17]. But, while fatigue bond strength testing seems capable of providing more clinically relevant information on the bonding performance of adhesive systems, relatively few studies have been reported in this area overall. In fact, more evaluations using micro-tensile bond strength testing are published in a typical year than have been reported on the fatigue bond strength of adhesive systems to tooth substrates in total. Even in 2017, Arola [16] concluded a review of the field by saying that the application of fatigue testing to restorative dentistry would barely begin, and there has been a call for the development of fatigue bond strength testing that better represents clinical situations [16].

3. Initial development of shear fatigue bond strength testing

Over the past decade, a method designed to assess fatigue bond strength in adhesive systems to tooth substrates has been developed through efforts between the Creighton University School of Dentistry (Omaha, NE, USA), Nihon University School of Dentistry (Tokyo, Japan), Shofu (Kyoto, Japan) and University of Iowa College of Dentistry (Iowa City, IA, USA). Early developments in the area of fatigue bond strength testing were initiated by Dr. Robert L. Erickson at the Academic Center for Dentistry Amsterdam (ACTA).
and Creighton University. The methodology for fatigue bond strength testing was further developed by researchers at Creighton University (Dr. Wayne W. Barkmeier and Dr. Mark A. Latta), Nihon University (Dr. Toshiki Takamizawa), Shofu Dental Corporation (Mr. Satoshi Fujiwara) and the University of Iowa and Creighton University (Dr. Akimasa Tsujimoto).

3.1. ACTA fatigue tester (Academic Center for Dentistry Amsterdam, Amsterdam, Netherlands)

Dr. Robert L. Erickson (Creighton University) worked with the ACTA Fatigue Tester at the Academic Center for Dentistry Amsterdam (Amsterdam, Netherlands) to develop fatigue bond strength test methods for dental adhesive systems [18,19]. These early studies utilized the ACTA Fatigue Tester to evaluate the bonding performance of adhesive systems. Dr. Erickson et al. [18,19] adopted a previously reported calculation method [20–22] to determine fatigue bond strength values.

Fatigue bond strength values are not a straightforward property to measure and many testing procedures have been devised to determine the yield force for cyclic loading, including using the stress-life, strain-life, crack growth and probabilistic methods. At that time in dentistry, only a small number of studies had been conducted in the area of fatigue bond strength testing and two test methods were primarily used for measuring fatigue bond strength. 17,20–22 One was the S–N curve version of the stress-life method, in which S–N curves provided a relationship between applied stress and the logarithm of the number of cycles at which failure of the bond occurs [17]. The other method of fatigue bond strength testing, referred to as the staircase method, involves selecting a starting stress of about 50–60% of the static strength and then testing a specimen until it fails or survives [20,21]. If the specimens fails, the stress is decreased by a set amount (typically 10%) for the next specimen, but if it survives, the stress is raised by that same set amount. Continuing in this manner for a set number of specimens, the test converges on a stress that is likely to produce 50% failures [22].

Dr. Erickson focused on using the staircase method based on mean load-to-failure (stress level) data gathered under different cyclic fatigue conditions with the ACTA Fatigue Tester and developed a specimen test fixture with a pin-indexing jig for facilitating assembly (Fig. 1). As a consequence, Erickson et al. [18,19] demonstrated that fatigue testing using the ACTA machine, in conjunction with bond strength testing, provided an excellent method for assessing the performance of adhesive systems used for bonding resin composite to enamel. In addition, he and co-workers [18,19] compared the fatigue bond strength of 2-step etch-and-rinse (E&R) and strong single-step self-etch adhesive systems to enamel, including 1) Single Bond (3 M Oral Care, St. Paul, MN, USA, a 2-step E&R adhesive system), 2) a prototype etch-and-rinse adhesive with a formulation of equal parts, by weight, of Bis-GMA and TEGDMA (Prototype material, Bisco, Schaumberg, IL, USA, 2-step E&R adhesive system) and 3) Adper Prompt l-Pop Self-Etch Adhesive (3 M Oral Care, St. Paul, MN, USA, a strong 1-step self-etch adhesive system, pH < 2.0). The fatigue bond strength was 43.8–57.7% of the shear bond strength, and the enamel fatigue bond strengths (14.6–15.8 MPa) of 2-step E&R adhesive systems were significantly higher (p < 0.05) than those (8.4–9.9 MPa) of the strong 1-step self-etch adhesive system.

3.2. Four-station fatigue cycler (Proto-tech, Portland, OR, USA)

After Dr. Erickson returned to the US, he collaborated with Dr. Wayne W. Barkmeier, who was then the Dean of Creighton University School of Dentistry, and they decided to acquire a Four-station Fatigue Cycler (Proto-tech, Portland, OR, USA) to continue shear fatigue bond strength testing (Fig. 2). In addition, Dr. Erickson and Dr. Barkmeier designed a shear fatigue cycling fixture and a metal (stainless steel) ring for a mold-enclosed bonding method. Dr. Erickson had used a relatively complex fixture with the ACTA Fatigue Tester, but they designed a simpler fixture, similar to those used for macro shear bond strength tests. In addition, the metal ring was designed to minimize force concentration directly on a bonded resin composite, as the force was applied indirectly through the metal ring. Erickson et al. in 2009 [23] compared the enamel fatigue bond strengths of: 1) a 2-step E&R, 2) a 2-step self-etch, 3) a strong and 4) a mild 1-step self-etch adhesive systems. The enamel fatigue bond strengths (22.1–27.8 MPa) of 2-step E&R and self-etch adhesive systems showed significantly higher (p < 0.05) than those (11.9–15.0 MPa) of 1-step self-etch adhesives, regardless of the strength of acidity. In addition, the fatigue bond strength was 37.4–49.7% of the shear bond strength and the proportion decreased as the fatigue bond strength decreased. Barkmeier et al. [24] reported that they were able to successfully conduct fatigue bond strength testing by the staircase method with mold-enclosed samples using the Proto-tech machine, and concluded that the influence of surface moisture on enamel fatigue bond strength was different depending on the type of 2-step E&R adhesive systems. Furthermore, shear bond strengths with the mold-enclosed method were approximately 20–24% higher than the results measured using the Ultradent shear bond strength method without a mold enclosure [25].

Sultan et al. reported in 2015 [26] that macro shear bond strength tests, including the Ultradent shear bond strength method as specified by ISO 29022 [25], have been criticized as neither appropriate nor reliable tests of the adhesive interface, and may have no physical
meaning for the load/area stress calculation. Della Bona and Van Noort in 1995 [27] have shown using finite element stress analysis that the load is not evenly distributed along the adhesive interface. A study by Jin et al. [28] also confirmed that there are no bond strength tests which can measure purely shear or purely tensile bond strength. Such a non-uniform stress distribution may be a larger issue for fatigue bond strength testing than for conventional bond strength tests due to the application of a repeated subcritical load. Cheetham et al. [29,30] reported that the mold-enclosed method significantly reduced non-uniform stress on the adhesive interface, while maintaining the desired shear stress, and finite element stress analysis suggests that the mold-enclosed method is more suitable for these measurements. In addition, the mold-enclosed method had a higher incidence of adhesive failure than the non-enclosed method. Of course, aside from minimizing non-uniformity at the adhesive interface, the mold-enclosed method reduces the load bearing on the bonded specimen, as the force is applied indirectly through the mold-enclosed assembly. The reduction in non-uniform stress at the adhesive interface and of damage to the bonded restorative itself together most likely account for the 20–24% increase in bond strengths measured when compared to conventional shear bond strength tests [24].

Nevertheless, questions remain about the details of research methodologies in the area of adhesive dentistry. For example, in clinical situations, the force is applied directly to a restoration, so it seems that direct application may be more clinically relevant. In addition, the current fatigue testing protocol uses a knife-edge to apply the force, but it seems that a notched stylus, as used in the Ultradent method, might apply the force more evenly to the surface, and produce a purer shear force. Therefore, work is currently underway by Dr. Barkmeier and Dr. Tsujimoto to evaluate the difference between mold- and non-enclosed methods, and the effects of using different styluses in fatigue bond strength testing. It is anticipated that this research will provide further insight into testing methodologies.

3.3. MTS 858 Mini Bionix II Servo Hydraulic System (MTS Systems Corporation, Eden Prairie, MN, USA)

Although the Four-station Fatigue Cycler was a good machine from a mechanical perspective, and had four chambers, it had limited frequency settings (up to 3.0 Hz). Thus, Dr. Barkmeier, Dr. Erickson and Dr. Latta (Creighton University) looked at using other machines to conduct fatigue bond strength tests with higher frequencies. In order to use higher frequencies in fatigue testing, Dr. Barkmeier and Dr. Mark A. Latta briefly used an MTS 858 Mini Bionix II Servo Hydraulic System for fatigue testing at Creighton University (Fig. 3). This system allowed much higher frequency settings (0.01–1000 Hz) than the Proto-tech machine (up to 3.0 Hz). Latta and Barkmeier in [31] investigated the fatigue bond strength of resin composite materials bonded to enamel using a 2-bottle 1-step self-etch adhesive system (All-Bond SE, Bisco) with and without liner resin (All-Bond SE Liner), and a 3-step E&R adhesive system (All-Bond 3). The study was successfully conducted at a frequency of 5 Hz for 40,000 cycles. The 3-step E&R adhesive system showed significantly (p < 0.05) higher fatigue bond strength to enamel than the self-etch system with and without liner resin. On the other hand, the use of the liner resin with the 2-bottled 1-step self-etch adhesive system improved fatigue bond strength. In addition, the fatigue bond strength was 38.3–56.0% of the shear bond strength and the proportion decreased as fatigue bond strength decreased. While this servo hydraulic machine offered a significant advantage regarding higher frequencies, there were some associated issues related to noise generation by the oil pump and oil leakage.

3.4. ElectroPuls E1000 (Instron, Norwood, MA, USA)

In order to continue fatigue testing studies using higher frequencies at Creighton University, Drs. Barkmeier, Erickson and Latta acquired two ElectroPuls E1000 machines (Fig. 4). The ElectroPuls E1000 is an all-electric test instrument, using an oil-free linear motor with no need for hydraulic or pneumatic air supplies, and is capable of operating at over 100 Hz. Drs. Barkmeier and Latta, during their terms as Dean, initiated and facilitated a visiting scholar program at Creighton University School of Dentistry. Over the years they invited several visiting professors from Nihon University School of Dentistry in Tokyo, Japan (Dr. Keishi Tsubota, Dr. Toshiki Takamizawa and Dr. Akimasa Tsujimoto). They also invited a visiting industrial researcher from Shofu Corporation in Kyoto, Japan (Mr. Satoshi Fujiwara). Productivity in fatigue bond strength testing at Creighton...
University was also enhanced by the hiring of a full-time laboratory technician (Mr. Jason M. Moody).

Dr. Barkmeier and Dr. Erickson were initially more focused on enamel bonding evaluations due to the development of products that utilize surface conditioning agents other than the traditional phosphoric acid treatment. In addition, they felt that enamel, as a more homogeneous substrate, was more suitable than dentin for the initial development of new fatigue bond strength testing methods. However, Dr. Takamizawa and Dr. Tsujimoto, as visiting professors, also felt that it was necessary to expand the investigation of fatigue bond strength testing to dentin. Therefore, they proposed to investigate fatigue bond strength testing methods using higher frequencies and expand the scope of research to include evaluation of bond strengths to dentin. Tsujimoto et al. using 20 Hz over 50,000 cycles in 2017 [32] compared the fatigue bond strengths to dentin of 2-step self-etch adhesives and universal adhesives and concluded that the fatigue bond strength to dentin of 2-step self-etch adhesives showed a statistically significant advantage over mild single-step self-etch and universal adhesives. This was partly confirmed by Takamizawa et al. using 10 Hz in 2015 [33]. In addition, they reported that the fatigue bond strength was 37.0 – 52.7% of the shear bond strength, and the ratio was similar to data reported for enamel at lower frequencies. Therefore, it seemed that fatigue bond strength tests at a higher frequencies (up to 20 Hz) could be conducted for adhesive systems to enamel and dentin. As a higher frequency substantially reduces the time needed for testing, this was deemed a significant advantage.

4. Standardization of test conditions

After establishing these basic principles, the research group extended fatigue bond strength evaluations to cover many factors with an influence on tooth bonding, such as the influence of acidic functional monomers [34], double coating [35], the oxygen inhibition layer [36,37], shortened application times of adhesive systems [38], the etching mode for universal adhesives [39–41], application of different etching agents [42–45], silver diamine fluoride pre-treatment [46], the prismatic structure of enamel [47], surface moisture [48] or smear layer of substrates [49], the use of different adhesive systems [50,51], phosphoric acid pre-etching [52–54], self-adhesive restorative materials [55], short fiber resin composites [56], and water storage of specimens [57]. These evaluations did provide new insights, but also raised methodological suggestions and questions from researchers. With the increasing number of researchers using the method, the apparatus configurations and choice of stress frequency and number of specimens varied from one experiment to another, making direct comparison of results somewhat difficult. As such comparisons are very important for a testing method, the researchers decided to develop more standardized conditions for fatigue strength testing.

4.1. Number of specimens

As indicated earlier, the research group at Creighton University has long used the staircase method to calculate the fatigue bond strength value. In the staircase method of fatigue testing described by Draughn [22], the minimum number of recommended specimens per group is sixteen. Before Dr. Erickson began his investigations at ACTA, the staircase method had been used in fatigue bond strength testing by Dewji et al. [21], who used 10 specimens, and by Zaradiackas et al. [20], who used 20 specimens. Collins [58] has specified in a textbook that the minimum number of specimens necessary to obtain a precise estimation using the staircase method is 15 per group. Thus, Dr. Erickson at ACTA, and he and Dr. Barkmeier at Creighton University, chose a specimen number within this range based on a comprehensive assessment of the experimental conditions, and used 12–20 specimens [18,19,23,24]. However, Dr. Takamizawa used 30 specimens [33,39,42,43,52,57]. His rationale for using 30 specimens was that the ISO technical specification [25] for the shear bond strength testing recommended at least 15 specimens for each group, and so Dr. Takamizawa believed that the results should be based on at least 30 specimens for the staircase method. In this approach, some specimens fail, while others survive, and the fatigue bond strength is calculated based on the number of specimens that fail at a particular load (Note: calculations using the staircase method can also be based on the number of survivors). Dr. Takamizawa ascertained that it was important for there to be about 15 failed specimens used in this calculation. During fatigue testing about half of the samples fail, so in order for the result to be calculated based on at least 15 results, it is necessary to start with about twice that many, or 30 specimens. On the other hand, Dr. Barkmeier, Dr. Erickson, and Dr. Latta had previously used 12–20 specimens [18,19,23,24,31], making it desirable to compare the results gained with greater or smaller numbers of samples. Furthermore, if the number of samples needed to perform the test could be reduced, the test would be more time efficient as a screening technique. Against this backdrop, Mr. Fujisawa from Shofu evaluated the effect of the number of specimens on shear fatigue bond strength testing, while he was a visiting scholar at Creighton University, using 8, 12, 16, 24 and 32 specimens with both a 2-step self-etch adhesive and universal adhesives [59]. The number of specimens within the range of 8–32, did not have a significant effect (p > 0.05) on the results of shear fatigue bond strength testing. Based on these results, it appeared that it should be possible to determine fatigue bond strength from a limited number of samples (i.e. 8), reducing the testing time and making the procedure more efficient. Nevertheless, in later experiments, Dr. Barkmeier and Dr. Tsujimoto used a larger number of samples to make it possible to also determine the shear bond strength of the surviving fatigue test specimens through static shear bond strength tests [32,36–38,40,44–46,49,50]. For these tests, they used a sample size that would produce at least 10 surviving specimens. (Note: If there are only 4 surviving fatigue test specimens, the standard deviation of the measured bond strength becomes extremely high.) Thus, Dr. Barkmeier and Dr. Tsujimoto typically used 20 specimens in their laboratory investigations [32,36–38,40,44–46,49,50].

A fatigue study conducted by Kelly et al., using fewer than 20 specimens per group in the staircase method, reported a mean coefficient of variation of 8.6% for the overall results of fatigue testing for bonded ceramic crowns at frequencies of 2 Hz (11.8%), 10 Hz (6.8%), and 20 Hz (7.2%) over 1,000,000 cycles [60]. Therefore, while it can be said that choosing 20 specimens as the default value is reasonable, the number of specimens should be chosen based on the design of a particular research protocol. In general, a statistics specialist should be consulted to determine the appropriate number of specimens for each group in a particular study.

4.2. Frequency

The frequency setting for fatigue testing is often limited by the specific equipment used for the fatigue test. In early studies utilizing the staircase method for fatigue bond testing, before Dr. Erickson began his studies at ACTA, Dewji et al. [21] did not record the frequency, while Zaradiackas et al. [20] used 5 Hz. Po et al. [61] have shown that physiological mastication cycling generally occurs in the range of 0.94 – 2.17 Hz, and Poitevin et al. [15] reported that cyclic fatigue testing at 2 Hz showed good correlation with clinical studies of Class V restorations. Thus, it can be said that it is worth using a frequency close to physiological mastication, to mimic clinically relevant conditions. However, Wiskott et al. [62] acknowledged that, in spite of some shortcomings, such as higher frequencies potentially leading to heating within the samples being tested, it is important to
be able to conduct fatigue testing more quickly, because a challenge for researchers conducting fatigue evaluations is the fact that lower frequency testing methods prolong the assessment. In addition, there is a wide variation in the frequency rates reported in the literature for fatigue testing of dental materials.

Scheidel et al. [63] and Takamizawa et al. [64] conducted research on the effect of frequency (5, 10 or 20 Hz) on the measured fatigue bond strength to tooth substrates. The results showed no significant differences (p > 0.05) in measured bond strength among the three frequency rates for 2- and 1-step self-etch adhesive systems and a universal adhesive. These results showed that the use of a higher frequency does not necessarily cause issues, but high frequencies have been criticized by other researchers for being very different from the normal physiological mastication cycle. Nevertheless, Tsujimoto et al. [65,66] obtained similar results when comparing 2 Hz and 20 Hz. Thus, at present, 20 Hz is used with the staircase method at Creighton University as the basic frequency for ongoing fatigue studies. However, the ElectroPuls E1000 is capable of frequencies up to 100 Hz, and thus it is worth investigating whether the S-N curve and staircase methods can be used with even higher frequencies to obtain fatigue bond strengths in a shorter time frame.

4.3. Number of cycles

In the research reported before the start of Dr. Erickson’s studies at ACTA, Dewji et al. [21] used 1000 cycles, while Zardjiaakas et al. [20] used 100,000 cycles, judging that 1000 cycles produced limited information, the initial tests with the ACTA Fatigue Tester were performed using 100,000 cycles. When using the ElectroPuls E1000 at Creighton University, a higher frequency rate could also be used, and for ease of comparison with earlier experiments, 100,000 cycles was again chosen.

On the other hand, Wiskott et al. [62] and other researchers have recommended that fatigue testing should be conducted with over 10,000,000 cycles to provide clinical relevance. For example, Gratton et al. [67] estimated that a person chews approximately 2700 chewing cycles per day, or approximately 1,000,000 cycles per year. Another study [68] reported that a combination of 12,000,000 cycles and 6000 thermal cycles are often used to simulate a service time of 5 years in wear testing. In addition, Tsujimoto et al. related that the maximum chewing frequency for humans is reported around 2 Hz [66]. Thus, shear fatigue strength testing at 2 Hz, over 1,000,000 cycles, appears to be a clinically relevant condition, simulating 1–5 years of clinical usage of a restoration. Thus, it can be argued that a low number of cycles provides limited information concerning the long-term performance of materials. However, it can also be argued that an excessive number of cycles is time consuming and may not provide additional information compared to shorter cycling periods. If a single specimen is run at 2 Hz for 1,000,000 cycles, it takes approximately 139 h, or almost six days, to complete the cycling period.

Tsujimoto et al. [65,66] decided that it was important to compare fatigue testing using the recommended number of cycles (1,000,000 cycles) at a physiological frequency (2 Hz) with tests performed using parameters more realistic for screening (50,000 cycles at 20 Hz), and at intermediate values (combining frequencies of 2 Hz and 20 Hz with 50,000, 100,000, and 1,000,000 cycles). While these experiments were time intensive, the investigators believed that it was important to obtain data allowing a direct comparison of these conditions. Somewhat surprisingly, the results showed that the measured fatigue bond strength of the adhesive used in self-etch mode was not influenced by the frequency rate (2 or 20 Hz) or the number of cycles (50,000, 100,000 or 1,000,000 cycles) with both enamel and dentin substrates. Thus, regardless of bonding to enamel or dentin and the frequency, the measured shear fatigue bond strength was not influenced by the number of cycles used for testing [65,66]. Based on the results of these important studies, it is clear that the information gained from using 50,000 cycles at 20 Hz, which takes about 40 min, are not significantly different (p > 0.05) from those gained from using 1,000,000 cycles at 2 Hz, which takes about a week. Currently, at Creighton University, the fatigue load is applied using a sine wave at a frequency of 20 Hz for 50,000 cycles or until failure occurs to minimize the resources needed for studies serving as screening tests for adhesive systems.

5. Bonding effectiveness of dental adhesive systems to enamel and dentin from a fatigue bond strength perspective

The authors have reviewed the results for the fatigue bond strengths of representative adhesive systems of each category to both enamel and dentin: stainless-steel mold-enclosed samples using the staircase method with an ElectroPuls E1000 over 50,000 cycles at 20 Hz.

5.1. Considerations for the E&R approach: 3- and 2-step E&R adhesive systems, and universal adhesives in E&R mode

E&R adhesive systems are characterized by phosphoric acid etching followed by a required water rinse, which is responsible for the complete removal of the smear layer [69]. Simultaneously, the etching promotes demineralization of enamel and dentin, thereby exposing enamel prisms or a scaffold of dentin collagen fibrils that is nearly completely demineralized of hydroxyapatite [70]. The following step consists of the application of a primer containing hydrophilic resin monomers, such as 2-hydroxyethyl methacrylate (HEMA) dissolved in solvents such as acetone, ethanol or water [71]. While HEMA is responsible for improving the wettability of the demineralized tooth substrates and promoting the re-expansion of the exposed collagen fibrils, the solvents are able to displace bonded water from the demineralized surface, thus preparing the adherent surface for subsequent adhesive penetration. In the bonding step, a solvent-free bonding agent is applied on the prepared surface, leading to the penetration of hydrophilic resin monomers not only into the etched enamel honeycomb structure but also into the interfibrillar spaces of the demineralized collagen and dentine tubules [72]. After infiltration, these monomers are light cured, resulting in the formation of mechanical interlocking with the enamel prism structure and a hybrid layer with dentin, which in combination with the presence of resin tags inside dentine tubules provides mechanical retention.

From 3-step E&R adhesive systems, such as Adper Multi Purpose and OptiBond FL, 2-step E&R adhesive systems, such as Prime & Bond NT and Single Bond have been developed that combine the primer and the adhesive resin into one single solution. It has been reported that despite being more user-friendly, 2-step E&R adhesive systems tend to show inferior dentin bonding when compared to their conventional 3-step counterparts [51]. The results for fatigue bond strength to enamel and dentin of representative E&R adhesive systems on the market are shown in Fig. 5. If the mean fatigue bond strengths of the systems are compared, representative 3-step E&R adhesive systems had values of 16.1 MPa to enamel and 16.8 MPa to dentin, while 2-step E&R adhesive systems showed 23.1 MPa to enamel and 11.1 MPa to dentin. Thus, the fatigue bond strengths of representative 2-step E&R adhesive systems were significantly higher (p < 0.05) to enamel and lower to dentin than those of 3-step E&R systems.

Recently, universal adhesives, which can be used in E&R or self-etch mode, have increased in popularity due to the reduced number of application steps and their versatility [73]. Thus, three groups of E&R adhesive systems are available: 3- and 2-step E&R adhesive systems, and universal adhesive systems in E&R mode (Fig. 6). Of
course, when universal adhesives are used in E&R mode, the clinical application steps are exactly the same as those for 2-step E&R adhesives. However, surprisingly, the mean fatigue bond strength of universal adhesives which are newest category of adhesive systems (Scotchbond Universal Adhesive and Scotchbond Universal Adhesive Plus) showed better results than its 3- or 2-step counterparts, 21.5 MPa to enamel and 17.4 MPa to dentin. This might be because adhesive dentistry has advanced in many different respects through the application of advanced materials science. In addition, comparing the fatigue bond strength of universal adhesives from different manufacturers between E&R and self-etch modes showed that universal adhesives have superior fatigue bond strength in E&R mode when compared to self-etch mode, in agreement with a systematic review of earlier laboratory bond strength evaluations.73 Thus, current research studies suggest that universal adhesives are a great choice for clinicians who prefer to use E&R mode.

5.2. Considerations for the self-etch approach: 2- and 1-step self-etch adhesive systems and universal adhesives in self-etch mode

Unlike E&R adhesive systems, self-etch adhesive systems do not require a separate phosphoric acid etching step, as they contain acidic functional monomers that simultaneously etch and prime the tooth substrates [74]. Due to such acidic characteristics, self-etch adhesive systems are able to dissolve the smear layer and demineralize the underlying tooth substrates [75]. Consequently, self-etch adhesive systems have been claimed to be more user-friendly and less technique-sensitive than E&R adhesive systems, and researchers have shown them to perform satisfactorily, both clinically, and in the laboratory [76].

Self-etch adhesive systems demineralize only superficial dentin, leaving a substantial presence of hydroxyapatite crystals around the collagen fibrils [77]. This remains available for possible additional chemical interaction. This mechanical and chemical bonding to tooth substrates is believed to be advantageous in terms of bond strength [78]. The hybrid layer formed by self-etch adhesive systems is no deeper than 1 µm, and resin tags are hardly observed [79]. Currently, three categories of self-etch adhesive systems are available: 2-step self-etch adhesive systems, 1-step self-etch adhesive systems, and universal adhesive systems in self-etch mode (Fig. 7).

The results for fatigue bond strength to enamel and dentin of representative self-etch adhesive systems on the market are shown in Fig. 8. When the mean fatigue bond strengths of the systems were compared, representative 2-step self-etch adhesive systems had mean values of 18.0 MPa to enamel and 23.4 MPa to dentin, while 1-step self-etch adhesive systems and universal adhesives in self-etch mode showed 13.8 MPa to enamel and 17.5 MPa to dentin. Thus, the fatigue bond strengths of representative 2-step self-etch adhesive systems were significantly higher (\(p < 0.05\)) to enamel and dentin than those of 1-step self-etch adhesive systems and universal adhesives in self-etch mode. This was also confirmed by a previous study comparing the fatigue bond strength of 2-step self-etch adhesive systems and universal adhesives in self-etch mode [32,50]. However, there are other studies which report either a higher bond strength for current simplified adhesive systems than for 2-step self-etch adhesives [80] or no significant difference [81,82], and thus this issue remains controversial. However, the overall evidence suggests that 2-step self-etch adhesives are currently the gold standard for self-etch adhesives [74], and the results from fatigue bond strength

Fig. 5. The results for fatigue bond strength of 3- and 2-step etch-and-rinse (E&R) adhesive systems and universal adhesives in E&R mode to enamel and dentin.

Fig. 6. Categorization of available etch-and-rinse (E&R) adhesive systems.
testing support the continued use of two-step self-etch adhesive over single-step self-etch adhesive systems and universal self-etch adhesives in self-etch mode.

5.3. Discussion of enamel fatigue bond strength

In an overall review of fatigue bond strength results to both enamel and dentin, fatigue bond strength results for different adhesive systems show different tendencies in E&R and self-etch adhesive systems, as discussed earlier. In E&R adhesive systems, universal adhesives in E&R mode showed better results than 3- and 2-step E&R adhesive systems. In contrast, self-etch adhesive systems and 2-step self-etch adhesive systems showed better results than 1-step self-etch adhesive systems and universal adhesives in self-etch mode.

On the other hand, a detailed analysis of the differences in fatigue bond strength to enamel and to dentin provides further insight into bonding effectiveness. In the results for E&R adhesive systems, the average enamel fatigue bond strengths of 2-step E&R adhesive systems (23.1 MPa) and universal adhesive systems in E&R mode (21.7 MPa) were higher than that of 3-step E&R adhesive systems.
On the other hand, in the results for self-etch adhesive systems, the enamel fatigue bond strength of a 2-step self-etch adhesive system (Clearfil SE Bond 2, 20.2 MPa) was significantly higher than the other systems (13.4–15.7 MPa). An explanation of these results is possible in terms of the thickness of the adhesive layer as seen in observations using field-emission SEM, shown in Fig. 10. Generally, the thickness of the adhesive layer in 3-step E&R adhesive systems is approximately 50 µm, while it is less than 10–20 µm for 2-step E&R adhesive systems and less than 10 µm for universal adhesive systems in E&R mode [51], as can be seen in the SEM images shown in Fig. 9. The stiffness of the adhesive layer of 3-step E&R adhesive systems is much higher than that of 2-step E&R and universal adhesive systems, due to their hydrophobicity [83]. On the other hand, 2-step E&R and universal adhesive systems appear to be more compatible with the hydrophilic etched surface than the adhesive agents of 3-step E&R adhesive systems [84]. When phosphoric acid etched enamel is the adherend, compatibility between etched enamel and adhesive agents appears to be more important than the stiffness of the adhesive layer. Generally, a phosphoric acid etched surface is rougher, as shown in Fig. 10, and more hydrophilic than ground enamel, due to demineralization and the exposure of hydroxyl groups, giving a polarized surface with a high surface free energy that enhances chemical bonding [85,86]. Thus, it is possible that 2-step E&R adhesive systems and universal adhesives in E&R mode that penetrate the compatible surface before curing, securing both mechanical interlocking and chemical bonding with the enamel prisms, have a greater resistance to fatigue than 3-step E&R adhesive systems with a rigid, thicker adhesive layer. Needless to say, no matter how hydrophobic the adhesive is, it is not as strong as the resin composite placed above it, and thus stress becomes concentrated in the adhesive layer, which is a possible point of failure. This may be why adhesive systems with a thinner adhesive layer show higher fatigue bond strengths.

With self-etch adhesives, the thickness of the adhesive layer using Clearfil SE Bond 2 is approximately 30 µm, and with Optibond eXTRa, a 1-step self-etch adhesive system and a universal adhesive systems in self-etch mode, it is less than 10 µm, as shown in SEM observations (Fig. 11). A previously reported study [87] found that bonding agents in 2-step self-etch adhesive systems showed a higher degree of conversion than in simplified adhesives, such as 1-

Fig. 10. Atomic force microscopy (AFM) and scanning electron microscopy (SEM) observations of ground and phosphoric acid etched enamel.

Fig. 11. Scanning electron microscopy (SEM) observations of enamel-adhesive interfaces for 2- and 1-step self-etch adhesive systems and universal adhesives in self-etch mode. A: adhesive; E: enamel; R: resin composite.
step self-etch adhesive systems, and thus, it would naturally be predicted that the 2-step self-etch adhesive system would have higher fatigue resistance. However, in the case of enamel bonding using self-etch adhesive systems, strong mechanical interlocking between enamel and adhesive is not established due to the lack of phosphoric acid etching [88]. As a result, adhesion at the interface between enamel and adhesive is weak compared to that seen with E &R adhesive systems, which may explain the superior performance of adhesives with a thicker and more rigid adhesive layer in terms of fatigue bond strength to ground enamel. Thus, it can be postulated that, in terms of the fatigue bond strength of the adhesive/enamel interface, a compatible system with a thin adhesive layer is best for phosphoric acid etched enamel, while a thicker and more hydrophobic adhesive layer is better for ground enamel.

5.4. Discussion of dentin fatigue bond strength

In the results for E&R adhesive systems, in contrast to the results for enamel, the average dentin fatigue bond strength of 2-step E&R adhesive systems (11.1 MPa) was significantly lower than that of 3-step E&R adhesive systems (16.8 MPa) or universal adhesive systems (17.6 MPa) in E&R mode, as seen in Fig. 6. A previous study found that the fatigue behavior of adhesive systems using the Twin Bonded Interface (TBI) approach with a 3-step E&R adhesive system (Scotchbond Multi-Purpose, 3M Oral Care) attained significantly higher fatigue resistance than a 2-step E&R adhesive system (Single Bond Plus, 3M Oral Care) [89]. Therefore, the dentin fatigue strength results for the E&R approach reported in this review were consistent with the results of the previously reported study.

These results can perhaps be explained based on the thickness of the adhesive layer, as mentioned earlier, and of SEM images (Fig. 12) of the dentin-adhesive interface. In the SEM observations with acid-base treatments (Fig. 13), the quantity and length of resin tags in 2-step E&R adhesive systems were much lower than in 3-step E&R adhesive systems or universal adhesives in E&R mode. Of course, the relationship between the length of resin tags and the bond strength of adhesives is still under active discussion [90,91]. However, it seems very likely that a large number of long tags would be able to resist repeated sub-critical loading, and that tags formed by a more hydrophobic adhesive might have stronger resistance. As is visible in the SEM images (Fig. 14), the hybrid layer is of roughly the same thickness, approximately 2 μm, in all systems, but, as with enamel, the adhesive layer is thicker in 3-step E&R adhesive systems. This suggests that, although the quantity and length of resin tags were similar to universal adhesives, the 3-step E&R adhesive systems were probably more hydrophobic, with fatigue stresses building up in the adhesive layer backed by the hybrid layer, and that the 3-step E&R adhesive systems were unable to achieve a superior fatigue bond strength when compared to a universal adhesive in E&R mode. As noted in the section on E&R adhesive systems, universal adhesives are a great option in this mode, but it appears that there is room for improvement, by enhancing the physical properties of the adhesive, such as improved hydrophobicity, curing rate and so on, while preserving its compatibility and penetration ability with enamel and dentin.

In the results for self-etch adhesive systems, the average dentin fatigue bond strengths of 2-step self-etch adhesive systems (23.4 MPa) were significantly higher than those of single-step self-etch adhesive systems (15.9 MPa) and universal adhesive systems (20.4 MPa) in self-etch mode. There were no significant differences (p > 0.05) in 2-step self-etch adhesive systems between Clearfil SE Bond 2 and Optibond eXTRA in E&R mode, even though they have different adhesive thicknesses. With the exception of Kuraray Noritake Dental’s patent on 10-methacryloyloxydecyl dihydrogen phosphate (MDP), manufacturers began exploring the usage of MDP and phosphoric acid esters which have similar chemical structure formulae in novel adhesive formulations [92]. Scotchbond Universal Adhesive (3 M Oral Care, St. Paul, MN, USA) was introduced in 2012 as the first universal adhesive, and other universal adhesives were later marketed by different manufacturers with distinctive characteristics [93]. With the introduction of these universal adhesives, the role played by MDP and other phosphoric acidic monomers, which are key for chemical bonding to dentin in the self-etch approach, became much clearer [94]. It is true that the results for dentin fatigue bond strength in universal adhesives in self-etch mode were higher than for single-step self-etch adhesives. Thus, it appears that with 2-step self-etch adhesives the MDP and other phosphoric acid monomers included in both the self-etching primer and the bonding agent react more with the dentin than do those in single-step self-etch adhesive systems and universal adhesives in self-etch mode, creating firmer chemical bonding to dentin and securing a high fatigue bond strength which was also seen as the different morphological characteristics for SEM images in Fig. 15. Therefore, it appears that, in the use of adhesive systems in self-etch mode, 2-step self-etch adhesive systems will remain the gold standard, as was noted before.

However, with adhesion to both enamel and dentin in self-etch mode, a thick adhesive layer improves adhesion to enamel, but no such benefit was found with dentin. Accordingly, to improve the fatigue bond strength of adhesive systems in self-etch mode, it seems that it would be valuable to develop a 2-step self-etch adhesive system with an adhesive layer thickness of several tens of
micrometers to achieve more effective chemical bonding and higher physical properties.

5.5. Correlation to clinical results

The real interest in laboratory studies of dental bonding is in how well they predict clinical performance. Early in this review, we argued that dynamic bond strength tests are testing features of the adhesive more closely related to clinical stresses, and thus likely to be more predictive of clinical results. It is certainly true that static tests have known limits: a review by Van Meerbeek et al. [8] found some potential connections between laboratory bond strength results and clinical performance, but they were not as strong as might be hoped. In addition, Heintze et al. [95] reported that the weak correlation on the results between static bond strength test and clinical studies.

Recently, Van Meerbeek et al. [96] has conducted a systematic review of the clinical performance of dental adhesives, and concluded that Optibond FL was the gold standard for etch-and-rinse adhesives, while Clearfil SE Bond with selective etching technique was the gold standard for self-etch adhesives. Optibond FL has been on the market for over 25 years, and extensive clinical data has been collected. Universal adhesives have much less history, and thus the clinical data is more limited, but some clinical studies have been reported.

As of January 2022, the longest period of clinical reported for universal adhesives is five years, for a study of non-caries cervical lesions (NCCL) [97]. This reported a retention rate in E&R mode of 93% for Scotchbond Universal. A clinical study of Optibond FL over six years in 2021 [98] reported by Peumans et al. [98] a retention rate in NCCL of 88.9%, while a 5-year study in 2014 reported a retention rate of 93.5%. A 13-year study of Optibond FL by the same group [99] found a retention rate of 93%. These clinical results are clearly very similar to those found for Scotchbond Universal, and while a direct statistical comparison is not possible, they do not suggest an important difference in clinical performance.

However, the conventional static bond strength tests give significantly different results for these two adhesives. A 2021 study [51] found that the static shear bond strength of Scotchbond Universal in etch-and-rinse mode was 33.3 MPa, while that of Optibond FL was 41.2 MPa, a difference that was statistically significant. On the other hand, the same study reported fatigue bond strengths of 19.1 MPa for Optibond FL and 19.0 MPa for Scotchbond Universal, values that did not show a significant difference. This is consistent with the clinical data, while the difference in the static results is in tension with it. Thus, while the evidence is still limited, there are suggestions that dynamic fatigue bond strength tests may be a better predictor of clinical performance than static bond strength tests. These results are certainly a reason to take fatigue bond strength results into account when assessing a new adhesive system, and further studies of

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**Fig. 13.** Scanning electron microscopy (SEM) observations of dentin-adhesive interfaces for 3- and 2-step etch-and-rinse (E&R) adhesive systems and universal adhesive in E&R mode after acid-base treatment. A: adhesive; D: dentin; RT: resin tag.

**Fig. 14.** Scanning electron microscopy (SEM) observations of hybrid layer for 3- and 2-step etch-and-rinse (E&R) adhesive systems and universal adhesive in E&R mode. D: dentin; HL: hybrid layer.
In various international journals. On the other hand, while the researchers have published important research results worldwide conducting adhesion research from the perspective of Erickson began developing at ACTA, and which was further refined at Creighton University. In addition, as there are few research groups worldwide conducting adhesion research from the perspective of fatigue, these researchers have published important research results in various international journals. On the other hand, while the results of a style of investigation that is only pursued in a limited number of groups have rarity value, they suffer from a limited range of perspectives. When multiple groups use the method confidently, the correlation between fatigue bond strength and clinical performance would be valuable.

6. Future perspectives

Macro shear fatigue bond strength testing methodology has been developed over a long period of time, and a set of standard conditions (50,000 cycles at 20 Hz) has been established. Fatigue testing methods have evolved over the years to investigate the fatigue bond strength of representative adhesive systems to tooth substrates and have provided valuable insights beyond those offered by static bond strength testing. There is, however, still much more research to be done.

6.1. Limited usage of fatigue strength testing

It is undeniable that a number of new insights have been produced through the fatigue bond strength testing method that Dr. Steve L. Armstrong at University of Iowa College of Dentistry suggested that he work with Dr. Tsujimoto to develop a micro version of the fatigue test. The initial plan is to fabricate metal molds matching the dimensions that have been used for micro shear bond strength tests [105], an internal diameter of 1/32 in. (0.79 mm) and external diameter of 3/32 in. (2.38 mm Ultradent nominal size), which is based on the size of Tygon tubes, and conduct comparative experiments using the mold-enclosed method. It is expected that this micro shear fatigue strength test will be a useful screening tool for newly developed adhesive systems, and that the unified consideration of results obtained from both macro and micro fatigue bond strength tests will offer further valuable insights. Naturally, as there are some concerns regarding the importance of shear bond strength measurements, some investigators may wonder why a tensile version of this test is not being developed. However, it is important to first build on the results that have been accumulated over the course of the last decade and more and then look forward to the development of macro and micro tensile fatigue bond strength tests as an important component of future testing.

6.2. Development of a micro fatigue bond strength test

Existing macro bond strength tests have become even more valuable when extended to cover micro scale adherent areas [100]. For example, micro shear or tensile bond strength tests offered a flexibility that could not be achieved using macro specimens [101]. This approach allowed bond strength evaluations to be made of much smaller areas, so that it was no longer a case of testing adhesion to enamel or dentin, but to particular areas of the tooth, or to substrates under particular conditions, such as caries-affected dentin [113]. In addition, micro tests are able to make distinctions that are not possible with macro tests [102]. Generally, micro tensile bond strengths tend to be much higher (often 2× to 4×) than macro bond strengths because the defect concentration in the small cross-sectional interfacial areas is lower [103,104]. This allows the experiments to detect differences between systems that are lost in the noise, or masked by bond failure in macro tests.

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6.3. Application of macro fatigue bond strength test of resin cement to various substrates

Research using this method has so far focused on the question of how to best ensure the success of direct resin-based composite restorations and has thus focused on fatigue bond strength to enamel and dentin. Through the determination of adhesive systems with high fatigue strength to tooth substrates, and the indication of ways in which the quality of these systems can be improved, this research will contribute to the improvement of minimal invasive dentistry, which is focused restoring the tooth while removing as little of the tooth structure as possible to preserve sound tooth structures.

Naturally, the current trend towards selective caries removal will continue and remain a fundamental concept in restorative dentistry. On the other hand, restorative dentistry is currently in the throes of a revolution brought about by digital techniques such as intraoral...
scanning [106], computer-aided design computer-aided manufacturing (CAD-CAM) [107] and 3D printing technology [108]. The question of how best to incorporate these techniques is an important challenge for the field. In this context, in addition to existing materials such as CAD/CAM resin [107], ceramics [109], and zirconia [110], restorative materials for 3D printing are also being developed [111]. Further, through the reduction in the preparation time necessary for restorative dentistry achieved through the introduction of intraoral scanning and CAD/CAM technology, it is becoming feasible to complete treatment in a single day within the clinic, without asking a dental technician to fabricate restorations [112]. In this way, the problems that have been caused by contamination from the impression process and provisional or temporary restorations [113] can be avoided, and more reliable indirect restorations are likely to become a reality in the future.

In this way, through the restoration of dentin with direct resin composites and the replacement of enamel with materials created through digital technology, it may be possible to extend the principles of minimally invasive dentistry to cases with extensive enamel decalcification. The newer technologies may permit the replacement of full coverage crowns, which rely on extension for prevention for retention, with overlays and ultrathin veneers [114,115]. As restorative dentistry stands at this turning point, it is of great importance to assess the bond strength of resin cements to various restorative materials which will be introduced in the future. In addition, through the achievement of stronger adhesion, it should be possible to move away from removing tooth material to ensure retention and towards a more minimally invasive style of restorative treatment.

In order to measure the bond strength of resin cement to various substrates, bonding specimens are normally created by bonding a metal (stainless steel) rod to a ground substrate using a resin cement, and applying a force [116]. However, as the bond strength may be influenced by the diameter of the metal rod, the thickness of the cement, and the strength of the force, there is a call for a more standardized testing method. To answer this demand, an apparatus that can apply a fixed 250 g force to a 4.0 mm diameter stainless steel rod, as is widely used in these experiments, has been developed to simplify the procedures. This has enabled experiments comparing the bond strengths of resin cements with primer and self-adhesive resin cements to tooth substrates, and has shown that conventional resin cements have high bond strength. It is thought that this type of specimen preparation can be adapted for fatigue bond strength testing. That is, in previous experiments, the mold-enclosed method has been used to transfer force to materials that are vulnerable to load, but in the case of cement adhesion, the force can be applied directly to the stainless-steel sample. The knife edge contact has also been flattened to apply force through a surface. As this new chapter opens, valuable information will be gained by using fatigue bond strength testing to investigate the bonding of resin cements to a wide range of substrates for the further development of indirect restorations.

7. Conclusion
The cyclic nature of the mastication process and the failure of restorations after prolonged periods in the oral environment are indications of the relevance of fatigue to the practice of dentistry. Adhesive dentistry has not yet adopted fatigue testing as a principal method for evaluating the potential clinical success of new restorative materials and the approaches used for their placement. In this review paper, the development of fatigue bond strength testing was described, along with its historical background and research importance related to the understanding the fatigue properties of enamel and dentin bonding with different types of adhesive systems. The review offers clinical recommendations for the selection of adhesives systems in both the E&R and self-etch approaches and suggests future directions for the development of adhesive testing methods. In addition, the further expansion of this approach to micro sized specimens and to resin cement bonded to many kinds of dental restorative materials promises further advances.

The application of these approaches is just beginning and will hopefully foster a better understanding of fatigue failures of the many kinds of restorations in the oral environment. Further refinements and developments of the methods and a growing emphasis on their application is essential to solving the issues that limit the success of restorative dentistry.

Conflict of interest
The authors of this manuscript certify that they have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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