The clinical potential and limits of the all-ceramic fixed partial denture restorations

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ABSTRACT

High-strength all-ceramic systems for fixed partial dentures (FPDs) is gaining popularity as an alternative to the well established metal-ceramic FPDs. Several new framework materials and technique such as lithium disilicate, aluminum oxide and yttrium tetragonal zirconia polycrystal have been developed with improved strength, marginal discrepancy and esthetics. Since not every all-ceramic system can be used for a variety application, proper selection of the materials is an important for the success of all-ceramic FPDs. The longevity of dental restorations is an important health concern and the clinician placed great emphasis on mechanical properties to define the clinical indication of the ceramic materials because of their brittleness and low fracture toughness. The stronger and tougher framework material would improve the reliability and the longevity of dental restoration. To fabricated of an all-ceramic FPDs, material would be required with a flexural strength in excess of 300 MPa and fracture toughness 3 MPa/m^{1/2}. Zirconium has a better mechanical properties than alumina and lithium disilicate glass-ceramic, result from the transformation toughening, free of glass phase and minimal flaws. Whereas lithium disilicate glass-ceramic has a better translucency than alumina and zirconium based ceramic, result from the higher content of glass phase than that two materials. The purpose of this article is to present the information that can guide the practioner in the decision making process about all-ceramic FPDs systems. It can be concluded that the all-ceramic FPDs are seems to be an acceptable clinically prosthodontic treatment according to the short-term studies and the lithium disilicate and alumina-based ceramic materials are acceptable for 3 units anterior FPDs, whereas zirconia-based ceramic are acceptable for 3-5 units anterior and posterior FPDs with 2 pontics. However, further investigation and more clinical long-term follow-up studies are needed.

Key words: all-ceramic, fixed partial dentures, framework

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INTRODUCTION

Increased patients and clinicians for more esthetics with biocompatible properties for fabricating fixed partial dentures (FPDs) and public scare about allegedly adverse side effects of dental metals and alloys has accelerated the development of alternatives to metallic dental restoration.¹ It have led to widespread use of all-ceramic systems for full-coverage restoration use ceramic framework materials for fabrication and processing of infrastructure that are then veneered with porcelain,^{2,3} and the acceptance of this restorations because of their inherent esthetics, excellent biocompatibility, durability and the ability to withstand oral conditions for a long time without significant deteriorations.⁴ However, the strength of the ceramic remains a problem for a restoration longetivity,⁵ because they are brittle and weak when placed under tensile and torsional stress^{2,6} and the potential of catastrophic fracture is one of the disadvantage.⁷

Recent progress in technology and research of new dental materials has resulted in an increased number of materials available for all-ceramic restorations. Due to the successful of all-ceramic crowns both in anterior and posterior regions and with the introduction of high-strength ceramic framework materials, all ceramic systems for FPDs may became a viable treatment option to the established metal-ceramic FPDs.^{2,8} As an alternatives, this restoration must fulfill biomechanical requirement and provide longevity similar to metal-ceramic restorations while providing enhanced esthetic.^{9–11}

Several high-strength ceramic framework materials have been developed for fabricating FPDs with several types of technologies applied for the fabrication.⁸ Not all of these materials are alike, and as such they present with different properties that may affect their indication and limitation, the laboratory procedure used for their processing and their clinical handling.³ The benefits of the materials include a substantial improvement mechanical properties and longevity¹² and long-term survival of prosthetic cases are the important factor in rehabilitation.⁸ The longevity of restoration is dependent upon many different factors including materials. Proper selection of the materials and its properties if of utmost importance, since not every allceramic can be used for a variety of applications without restrictions and its influence the load-bearing capabilities of restoration.¹¹ Mechanical properties such as strength and

fracture toughness are the parameter assessed to understand the clinical potential and limits of the materials because allceramic FPDs are submitted to intermittent forces during fabrication and mastication.¹³ Although this seems to be very promising, but long-term clinical data on the success of all-ceramic FPDs are limited.¹⁴

The purpose of this article is present the information that can guide the practioner in the decision making process about all-ceramic FPDs system.

Lithium disilicate glass ceramic

The Empress 2[®] system (Ivoclar Vivadent) uses a lithium disilicate glass framework material. The framework is fabricated with the lost wax and heat-pressure technique or CAD/CAM technique with milled out of prefabricated blanks.^{8,15} Lost wax and heat-pressure technique employs wax models that are invested and after preheating the investment ring, the ceramic material is pressed into the investment ring in the press furnace.^{16,17} CAD/CAM technique generally consist of computer integrated imaging and milling system that allow the user to design various types of restorations using computer technology (CAD software) and the data is transferred to a milling unit (CAM) for fabricating the framework.⁸ The fracture toughness of the framework material between 2.8-3.5 MPa/m^{1/2} and flexural strength a range of 300–400 MPa.^{8,15} The system is confined to fabricating 3-unit FPDs that replace a missing tooth anterior to the second premolar. The minimal critical dimensions for the connector are 4-5 mm occlusogingivally and 3-4 mm bucco-lingually.^{16,17}

New development of lithium disilicate glass–ceramic was introduced to supplement the product range with high strength and highly esthetics materials for the press technique. This system known as IPS e. max Press[®]. IPS e.max Press are lithium disilicate glass-ceramic ingots for the press technique. It available in two degrees of opacity are medium opacity (MO) are used to fabricate frameworks for vital or slightly discolored teeth and high opacity (HO) are used for non-vital teeth as well as metal core build-ups. The flexural strength of this material is 400 ± 40 MPa and the fracture toughness between 2.5–3.0 MPa/m^{1/2}. This material suitable for crown and FPDs in the anterior to premolar region. This material consist of lithium disilicate needle-like crystals (approx. 70%) which are embedded in a glassy matrix.¹⁸

Glass-infiltrated aluminum oxide ceramic

The In-Ceram[®] Alumina System (Vita Zahnfabrik) is a kind of glass-infiltrated aluminum oxide ceramic in corporate a porous, dry-sintered aluminum oxide substructure that is infiltrated with a low-viscosity lanthanum alumino silica glass to develop a ceramic coping with enhanced strength.^{8,19,20} It was the first restorative system introduced for the fabrication of 3–unit anterior FPDs.^{8,21} The flexural strength of the framework material ranges from 236–600 MPa and the fracture toughness ranges between 3.1–4.6 MPa/m^{1/2}.⁸ To fabricate the framework, can use either the slip–casting technique or

be formed by milling from a dry press presintered block using a CAD/CAM system or with a CAM system and help of the Cerec inLab[®] (Sirona) technology.^{2,8,22} The minimal critical dimension for the connectors are 4 mm occluso–gingival and 3 mm bucco–lingually.⁸ Slip cast technique is a suspension of fine, insoluble particles in a liquid (zirconia/alumina powder is mixed with deionized water and a dispersing agent), then built up with a brush in the special porous gypsum dies and placed in an In-Ceram furnace and the framework fired overnight.²

Glass infiltrated aluminum oxide with 33 % partially stabilized zirconia ceramic

The In-Ceram[®] Zirconia system (Vita Zahnfabrik) is a kind of glass-infiltrated aluminum oxide with 33% partially stabilized zirconia ceramic uses combines glass-infiltrated aluminum with 33% partially stabilized zirconium dioxide to the split composition (33% ZrO2 stabilized by 16% CeO2).^{8,22,23} The addition of this material in order to provide a stronger and tougher framework material.^{2,22} The fracture toughness of the framework material ranges between 6–8 MPa/m^{1/2} and the flexural strength ranges form 600–800 MPa.^{2,8} To fabricate the framework is as same as in the In-Ceram Alumina system.^{8,24} The minimal critical dimension for the connectors are 4-5 mm occluso-gingival and 3-4 mm bucco-lingual. This material is confined to fabricating 3 unit anterior and posterior FPDs,^{2,8} but is not recommended for fabricating anterior all-ceramic FPDs where the translucency is a major factor in enhancing an esthetic result.8

Densely sintered high - purity aluminum oxide ceramic

The Procera[®] All-Ceram system (Nobel Biocare) is a kind of densely sintered high-purity aluminum oxide ceramic uses densely sintered high – purity aluminum oxide as the framework material, consisting of more than 99.9% aluminum oxide particles of 5 μ m grain sizes with a dry pressing technique against the enlarged die of a prepared tooth.^{19,25–27} The framework are fabricated with CAD/CAM technique help of the Procera system, which consists of a computer–controlled scanning and design station located in a dental laboratory that connected via a modem to Procera Sandvik AB in Stockholm, Sweden.²⁷ The flexural strength of the framework material ranges from 487–699 MPa and the fracture toughness ranges between 4.48–6 MPa/m^{1/2}. This material suitable for crown and 3 unit anterior and posterior FPDs.²⁵

Yttrium tetragonal zirconia polycrystals (y-tzp) based ceramic

There are several system uses yttrium tetragonal zirconium polycrystals (Y-TZP) as the framework materials, such as Procera[®]All-Zirkon system (Nobel Biocare),^{26–28} In-Ceram[®] YZ Cubes (Vita Zahnfabrik),^{29,30} IPS e.max[®] Zir CAD (Ivoclar Vivadent),³¹ LavaTM system (3M ESPE),^{26,32,33} Cercon[®] system (Dentsply Ceramco),²⁶ DCS–Precident[®] sytem (DCS Dental)^{32,34,35} etc. Dental restorations using prefabricated Y-TZP ceramic blanks are

manufactured in two ways, the first is by milling enlarged restorations out of homogenous ceramic green body blanks of zirconia which are then sintered and shrunk to the desired final dimension, and the second is by milling the restorations directly with the final dimensions or complete sintering of highly densed sintered prefabricated zirconia blanks and known as hot isostatic pressure (HIP).^{1,32,35} Laboratory–based systems incorporate a variation of the digital scanning technique to custom framework design using virtual waxing on the computer monitor, such as Lava system, Procera system and Cerec system or using information obtained from a wax model of the framework produced by the technician and known as CAM system (semi CAD/CAM) such as Cercon system.²⁶

The fracture toughness of the framework material ranges between 9–10 MPa/m^{1/2} and the flexural strength ranges from 900–1200 MPa.⁸ Recommended connector surface is 7–11 mm² for Cercon system,²⁶ 9 mm² for Lava system and 16 mm² for DCS– Precident system.⁸ The indication for IPS e.max Zir CAD are for crown and 3–4 unit FPDs frameworks for anterior and posterior design,³¹ Procera All-Zirkon system for crown and 2–4 unit FPDs for anterior and posterior,³⁶ Lava system for crown and 4 unit FPDs with 2 pontics for the anterior and posterior, ³² In-Ceram YZ for crown and 5 unit FPDs with 2 pontics for the anterior and posterior.³⁷

DISCUSSION

Indication for all-ceramic restorations have been extended as their mechanical properties have been developed and now it is possible to use high-strength ceramic materials for the anterior and posterior FPDs, as their strength seem to be sufficient enough to resist the occlusal forces.²⁶ The longevity of dental restorations is an important health concern. A prosthetic restorative system can be considered successful if it demonstrates a survival rate of 95% after 5 years and 85% after 10 years.²⁷ For interim all-ceramic FPDs, an adequate clinical fracture resistance is required to avoid the fracture of the FPDs under function and Dr. McLean's warning that all-ceramic system age, and that all data regarding their performance should at least provide for a 5 year period before they become routine modalities of therapy.¹⁹ The clinical failure of all-ceramic restorations is very often associated with their brittleness and low fracture toughness.³⁸ The lack of sufficient clinical studies regarding the latest generation of materials has led the clinician to place great emphasis on mechanical properties to define the clinical indication of these materials. In this regard, the most relevant mechanical properties are flexural strength and fracture toughness.^{13,38} The strength is related to the flaw-size distribution and toughening mechanism.³⁹ The toughening mechanism have been describe by Swain and subsequently by Evans, can be classified by: crack deflection, zone shielding, contact shielding and crack bridging.^{38,40} According to Davenport and Lawn et al., it has recently been advocated that stronger and tougher framework material would improve the reliability and therefore the lifetime of an all-ceramic FPDs.^{33,41} Some authors indicated that, in order to fabricated an all-ceramic FPDs, a material would be required with fracture toughness 3 MPa/m^{1/2} and flexural strength in excess of 300 MPa.¹⁵ Shiratsuchi *et al.*⁴² indicated that marginal adaptation is one of the most important elements for long-term clinical success of restorations, because poor marginal adaptation increases the potential for micro leakage and plaque retention, which in turn raises the risk of recurrent caries and periodontal disease. Marginal discrepancies in the range of 100 μ m have been reported to be clinically acceptable with regard to longevity of a restoration.

The IPS Empress 2 in composed of densely arranged lithium disilicate crystals (\pm 70% volume) with a length of $4 \,\mu\text{m}$ and a diameter of 0.5 μm uniformly bounded in a glassy matrix. The interlocking structure of the ceramic hinders crack propagation and elevates flexural strength to 300–400 MPa.^{27,43} The evolution of IPS technology continued with the introduction of IPS e.max[®] Press technique which used lithium disilicate glass-ceramic ingots for the press technique. This material as same as with the IPS Empress 2, but stronger and tougher because the ingots are produced by bulk casting. A continuous manufacturing process based on glass technology (casting/ pressing procedure) is utilized in the manufacture of the ingots. This new technology, which largely differs from sintering process employed in the production of Empress 2 ingots. Uses optimized processing parameters, which prevent the formation of defects (pores, pigments etc) in the bulk of ingots.¹⁸ This is corroborated by the study of Guazzato et al.³⁸ who found that the porosity, grain size, shape and orientation are important in determining the mechanical properties of glass-ceramic. The advantages of the IPS e.max Press is more widely clinical use than IPS Empress 2 because it available in two different levels of opacity are used to fabricate frameworks for vital, non-vital or discoloration teeth³¹ and the material has the flexural strength 400 ± 40 MPa.^{18,44} This flexural strength is similar with the In-Ceram Alumina (446 MPa),^{20,45} a strength that exceeds maximal occlusal loads recorded intraorally on anterior teeth.^{46,47} This is show clearly about the clinical indication of that two all-ceramic systems only for the use of anterior FPDs as the manufacture's suggestion.

The IPS e.max Press and In-Ceram Alumina have similar strength, but different binders crack propagation. McLaren and White revealed that the strength of In-Ceram system used the reinforcing compound form a continuous skeleton–like meshwork capable of stopping crack growth. This differed from glass-ceramic where each reinforcing particle is completely surround by their glassy matrices.² It is corroborated by the revealed of Guazzato *et al.*³⁸ that the major difference between the pressable and the infiltrated ceramics is that the latter consist of two penetrating networks that are both the ceramic and the glass phase, whereas in the press sable materials only the glass phase is continuous. The toughening mechanism of the In-Ceram Alumina is the crack bridging mechanism wherein the crack propagation is deflected along the grain boundaries, causing friction between the separated fragments. The longer path of the crack and the friction between the parts are responsible for dissipating the initial energy.⁴⁸ The IPS e.max Press system used the interlocking structure of multielongated needle-like crystals and the technology of bulk casting in the manufacture of the ingots capable of stopping crack growth.¹⁸ The toughening mechanism for lithium disilicate glass-ceramic are thermally induced micro cracking and crack deflection.³⁸

For the marginal discrepancy, Kelly et al. and Sorensen reported that vertical marginal discrepancy of FPDs In-Ceram Alumina is $58 \pm 38 \,\mu$ m,^{32,49} and Stappert⁵⁰ showed that marginal discrepancy of FPDs Empress 2 is $58-68 \,\mu$ m, and e.max Press is similar with the Empress 2. This is suggestion that In-Ceram Alumina and IPS e.max Press are within the range of clinically acceptable value.

For the survival rate, Vult von Steyern et al. reported a 90% success rate after 5 years in an treatment for three unit FPDs In-Ceram Alumina,⁵¹ Marquardt and Strub⁵² reported that survival rate after 5 years of the three unit FPDs Empress 2 was 70% and the 5 year clinical performance failure rate of IPS e.max Press is 3.3% if the manufacture's direction were followed.¹⁸ This is suggestion that In-Ceram Alumina and IPS e.max Press are within the range of successful longevity of dental restorations, and need more attention if use IPS Empress 2.

For the flexural strength of the two forms material of In-Ceram Alumina, in uniaxial flexural test by Guazzato et al. shown the contradictory result with the manufacturer's suggestion that dry-pressed material is thought to possess better mechanical properties on the basis of a more consistent sintering process. This suggestion is corroborated by the suggest of Sailer *et al.* that the stability of ceramic is highly dependent on the quality (density) of the material and this in turn is dependent on the production technology.⁵³ The study of Guazzato et al. showed that however the toughening mechanism such as crack deflection, contact shielding and micro crack toughening operate in In-Ceram Alumina dry-press and slip, the microstructure of the two materials is somewhat diverse. In-Ceram Alumina drypress consist of equi-axed particles embedded in a glassy phase and the crack pattern is constantly intergranular. Conversely, In-Ceram Alumina slip mainly consist of elongated grains and induced the crack propagate through (transgranular crack pattern) and/or around (intergranular crack pattern) the alumina grains according to their orientation, generating asymmetric cracks and dissipating a greater amount of energy.³⁸ Other study by Tan et al. found that a material with greater fracture toughness should be expected when the crack is perpendicular oriented to the elongated grains.54

Another aluminum oxide ceramic is Procera All-Ceram system. The difference with In-Ceram Alumina are about the composition, crystal volume and fabrication technique.

The framework of Procera All-Ceram manufactured by densely sintered high-purity aluminum oxide and does not contain any silica,^{20,27} while In-Ceram Alumina is not a dense aluminum oxide because it used infiltrated with a special lanthanum glass and the resultant interpenetratingphase composite ceramic contained 85 % alumina and 15% glass.² So, the strength of In-Ceram Alumina depends on the strength of the fired bond between the aluminum oxide particles and the complete wetting of the openpore microstructure by lanthanum glass infiltration.55 Different framework meshwork materials result in different properties,² and an increase in crystalline content to achieve greater strength.⁵⁶ However, this differed from glass ceramic, where each reinforcing particle is completely surround by their glassy matrices and glasses undergo brittle fracture by rapid crack proportion at low critical strains.² These condition can explain about the mechanical properties of Procera All-Ceram higher than In-Ceram Alumina and Empress 2. This is corroborated by the study of Pallis *et al.*¹² who found that Procera All-Ceram had higher Weibull modulus than Empress 2, and Wagner and Chu who found Procera All-Ceram to have higher flexural strength than In-Ceram Alumina.⁵⁷ Weibull modulus is related to the flaw-size distribution and reported to relate to the probability of failure.³⁹ The enlarged die of a prepared tooth must be done because the problem with aluminum oxide was large amount of sintering shrinkage during processing.¹⁹ The marginal discrepancy of Procera All-Ceram is 50-60 µm is within the range of clinically acceptable value.¹⁹

Several authors reported that In-Ceram Zirconia has a better mechanical properties than In-Ceram Alumina, because attributed to the phase transformation toughening mechanism that takes place in the mass of the material.^{2,8} Transformation toughening can occur when zirconia particles are in the metastable tetragonal form, and on the verge of transformation the metastability of the transformation is dependent on the composition, size, shape of the zirconia particles, the type and amount of the stabilizing oxides, the interaction of zirconia with other phases and the processing.²² When an internal stress is applied to the tetragonal zirconia, it can undergo a phase transformation to a different monoclinic crystals configuration. The monoclinic crystal is 3% to 5% larger than the tetragonal crystal it replaced. This phase transformation increases local compressive stresses, which increase the resistance to crack propagation.² A different result reported by Guazzato et al. in a uniaxial flexural strength test, however the toughening mechanism operating in In-Ceram Zirconia as a combination of several mechanism such as crack deflection and contact shielding attributed to the alumina grains and the phase transformation and micro crack nucleation mainly related to the zirconia particles, there's no statistically significant difference was found between the strength of In-Ceram Zirconia and In-Ceram Alumina disks.²² The similarities in strength values between In-Ceram Alumina slip with In-Ceram Zirconia

slip and In-Ceram Alumina dry-pressed with In-Ceram Zirconia dry-pressed blocks seem not to be related to the processing, but more likely to the coincident effect of the porosity. The porosity in In-Ceram Zirconia was greater than In-Ceram Alumina. This may be explained by the poor distribution of alumina and zirconia particles and by their poor solubility with each other and the glass phase.²² Other study found that the poor solubility of coarse grain aluminazirconia-glass compound was due to the low coefficients of diffusion of AL₂O₃ and ZrO₂ within the glassy phase.⁵⁸ Guazzato et al. also suggested that the fracture behavior of In-Ceram Zirconia slip and dry-pressed is comparable, where the crack propagation is generally transgranular for the zirconia particles and intergranular or occasionally transgranular, depending on the orientation of the crack in respect of the elongated alumina grains.²² However, Sailer et al. suggested that zirconia framework demonstrated sufficient stability for replacement of posterior teeth.53 Study by Luthy et al. in a static load bearing capacity test of four-unit frameworks, showed that In-Ceram Zirconia are not recommended for four-unit FPDs in the molar region, it's confirmed the indication of In-Ceram Zirconia as manufacturer's suggestion.59

The recent framework material are Y-TZP - based materials. Conversely to In-Ceram Zirconia, Y-TZP are fully sintered zirconia, therefore better mechanical properties.^{22,32} Yttrium oxide is a stabilizing oxide added to pure zirconia to stabilize it at room temperature and to generate a multiphase material known as partially stabilized zirconia. The high flexural strength and fracture toughness of Y-TZP result from the physical property (transformation toughening) of partially stabilized zirconia,⁸ free of glass phase and polycrystalline microstructure with minimal voids, flaws and cracks,⁶⁰ they do not exhibit the phenomenon of sub critical crack propagation and stress corrosion.⁸ The longterm stability of ceramic is closely related to sub critical crack propagation and stress corrosion caused by water in the saliva reacting with the glass, resulting in decomposition of glass structure and increased crack propagation in glasscontaining system.^{8,61} An in-vitro study evaluating Y-TZP FPDs under static load demonstrated fracture resistance of more than 2000 MPa,²³ and other investigators showed that strength ranging from 1000–1500 MPa.⁶² The framework can be fabricated mainly with the help of a CAD/CAM system by means of milling of a ZrO₂ block.²⁷ Sailer et al. showed that zirconia framework exhibit sufficient stability to be used for the replacement of molars and premolars.⁵³ In biaxial disk flexural strength of ceramics under different storage condition, Sorensen revealed that zirconia ceramics particularly attractive for posterior FPDs.³² Other study by Luthy et al. showed that Y-TZP recommended for four unit posterior FPDs and the connector size recommended to be larger than 7.3 mm² for clinical application.⁵⁹ In a recent in-vitro study, the failure probability of FPDs with zirconia framework after a simulated 10 year clinical service was nearly zero and 100% after 3 years. Furthermore, the FPDs included not only 3 unit but also longer span, as large as

5 units.⁵³ However, more clinical long-term follow-up studies are needed.

The marginal discrepancy of FPDs Y-TZP with CAD/CAM system, Sorensen reported that Lava was $87 \pm 43 \ \mu$,³² and Riech *et al.* reported that was $65 \ \mu$.⁶⁴ For Cercon system, Tsumita *et al.* reported that was $86,9 \ \mu$.⁶⁵ Tinscherd *et al.* reported that DCS-Precident was $61-74 \ \mu$.⁶³ It is seems that all of the CAD/CAM system which are a clinically acceptable value and had similar value with the slip cast fabricated In-Ceram Alumina system as the most accurate all-ceramic FPDs with a mean marginal discrepancy $58 \pm 38 \ \mu$.^{32,49}

Another important factor for the framework material is the translucency. The framework's translucency as one of the primary factors in controlling esthetics and a critical consideration in the selection of materials.⁵⁶ Some investigators reported that an increase in crystalline content to achieve greater strength generally results in greater opacity, such as Empress 2 have a lower crystal content within the matrix than In-Ceram and Procera materials.¹⁷ In-vitro study by Heffernan et al. showed that Procera and Empress 2 more translucent than In-Ceram Alumina and In-Ceram Alumina more translucent than In-Ceram Zirconia.56 However, In-Ceram Alumina and Procera may be exception. The crystal content of Procera is higher than In-Ceram Alumina but the translucency of Procera is higher than In-Ceram Alumina.⁵⁶ It can explain by the suggestion from van Noort that the pure alumina framework has a better translucency than the glass-alumina composite structure.²¹ Zirconium-based ceramic is more whitish than aluminumbased ceramic and lithium disilicate glass-ceramic because zirconium oxide has refractive index higher than that two materials.56

It is concluded that the all-ceramic FPDs are seems to be an acceptable clinically prosthodontic treatment according to the short-term studies and the lithium disilicate and alumina-based ceramic materials are acceptable for 3 units anterior FPDs, whereas zirconia-based ceramic are acceptable for 3–5 units anterior and posterior FPDs with 2 pontics. However, further investigation and more clinical long-term follow-up studies are needed.

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