ceramics

MDPI

Communication

Is a Zirconia Dental Implant Safe When It Is Available on the Market?

Katarina Frigan [1,*], Jérôme Chevalier [2], Fei Zhang [3,4,5] and Benedikt Christopher Spies [1]

[1] Department of Prosthodontics, Geriatric Dentistry and Craniomandibular Disorders, Charité–Universitätsmedizin Berlin, D-14197 Berlin, Germany; benedikt.spies@charite.de
[2] Université de Lyon, INSA-Lyon, MATEIS UMR CNRS 5510, Villeurbanne, CEDEX 69621, France; jerome.chevalier@insa-lyon.fr
[3] Department of Oral Health Sciences, KU Leuven (University of Leuven), Leuven B-3000, Belgium; fei.zhang@kuleuven.be
[4] Department of Materials Engineering, KU Leuven (University of Leuven), Leuven B-3000, Belgium
[5] BIOMAT–Biomaterials Research group, UZ Leuven (University Hospitals Leuven), Dentistry, Leuven B-3000, Belgium
* Correspondence: katarina.frigan@charite.de; Tel.: +49-30-450-662-565

Received: 22 July 2019; Accepted: 10 October 2019; Published: 12 October 2019

Abstract: The market share of zirconia (ZrO_2) dental implants is steadily increasing. This material comprises a polymorphous character with three temperature-dependent crystalline structures, namely monoclinic (m), tetragonal (t) and cubic (c) phases. Special attention is given to the tetragonal phase when maintained in a metastable state at room temperature. Metastable tetragonal grains allow for the beneficial phenomenon of Phase Transformation Toughening (PTT), resulting in a high fracture resistance, but may lead to an undesired surface transformation to the monoclinic phase in a humid environment (low-temperature degradation, LTD, often referred to as 'ageing'). Today, the clinical safety of zirconia dental implants by means of long-term stability is being addressed by two international ISO standards. These standards impose different experimental setups concerning the dynamic fatigue resistance of the final product (ISO 14801) or the ageing behavior of a standardized sample (ISO 13356) separately. However, when evaluating zirconia dental implants pre-clinically, oral environmental conditions should be simulated to the extent possible by combining a hydrothermal treatment and dynamic fatigue. For failure analysis, phase transformation might be quantified by non-destructive techniques, such as X-Ray Diffraction (XRD) or Raman spectroscopy, whereas Scanning Electron Microscopy (SEM) of cross-sections or Focused Ion Beam (FIB) sections might be used for visualization of the monoclinic layer growth in depth. Finally, a minimum load should be defined for static loading to fracture. The purpose of this communication is to contribute to the current discussion on how to optimize the aforementioned standards in order to guarantee clinical safety for the patients.

Keywords: zirconia; ceramics; dental implants

1. Background

1.1. Zirconia, ZrO_2

Zirconia was introduced for medical use several decades ago [1]. Regarding its physical characteristics, it ranges among polymorphous materials. The lattice structure of pure zirconia depends on the temperature, resulting in phase transformations at 1170 °C (< monoclinic, > tetragonal) and 2370 °C (< tetragonal, > cubic), concomitant with changes in density [2]. These phase configurations/modalities are reversible to a certain degree. The doping of zirconia with different

kinds of metal oxides is liable to modifying phase transformation temperatures, potentially resulting in metastable tetragonal or cubic grains at room temperature. The amount of stabilizer used has a major impact on its crystallography and material properties [3]. A precisely adjusted chemical composition, as well as a sintering temperature, defines both phase configuration and grain size, thereby influencing the ceramic material properties, such as fracture resistance, opacity and translucency [4]. In the dental field, the doping process is mostly performed with the transition metal Yttrium, more specifically its oxide (Y_2O_3, Yttria). Therefore, Yttria-stabilized Tetragonal Zirconia Polycrystals (Y-TZP) are synthesized, in reference with a tetragonal crystallography maintained after sintering thanks to the use of Y_2O_3. To date, five generations of Y-TZP are available for medical use. These generations differ from each other in crystallography, mainly by tailoring the volume percentage of the cubic and tetragonal phase. This results in different material properties according to the amount of added Y_2O_3 [mol%]: zirconia stabilized with 3 mol% Y_2O_3 (3Y-TZP) is referred to as biomedical grade and exhibits a flexural strength > 1000 MPa [1]. Increased amounts of Y_2O_3 result in reduced strength (less tetragonal phase content, which is also less transformable due to higher Yttria content) but higher translucency (by increasing the cubic proportion). Zirconia as a raw material was implemented in the dental field decades ago and can be processed in multiple ways. In restorative dentistry, zirconia is mainly available as industrial blank (dyed or non-dyed and pre-sintered or sintered), pressed from zirconium dioxide powder. Subsequent processing of pre-sintered zirconia was initially performed by copying milling units. To date, both pre- and fully-sintered zirconia can be processed by computer-aided design/computer assisted manufacturing (CAD/CAM). Due to its wide application range and biocompatibility, zirconia is worthwhile to be enhanced regarding its material properties. In addition to the aforementioned processing routes, ceramic injection molding (CIM) and additive printing technologies were adapted for zirconia processing as well. The field of zirconia application for dental use ranges from fixed and removable dental prostheses (tooth and implant supported) to dental implants [5,6]. Ceramic dental implants are mostly produced from 3Y-TZP and modified zirconia composites such as alumina-toughened zirconia (ATZ). To date, 3Y-TZP is considered the current standard material for ceramic implants. When used for dental reconstructions, zirconia initially performed as an adequate material for veneered single-crowns (SCs) and multiple unit fixed dental prosthesis (FDPs). Subsequently, after an increasing interest within the dental community, more indications for zirconia were established, such as posts, ceramic orthodontic brackets, monolithic SCs and FDPs, dental implant drills, implant abutments, abutment screws and dental implants. The esthetic appearance of a zirconia dental implant can improve the color of peri-implant soft tissues by avoiding a greyish transgingival discoloration, as opposed to titanium dental implants, in case of a bony recession. Additionally, ceramic dental implants can be considered as an alternative dental implant treatment for patients with hypersensitivity or intolerance to titanium. However, can a ceramic implant available on the market be considered safe, from a mechanical point of view? This communication highlights the drawbacks of currently available standards and aims to discuss potential optimizations.

1.1.1. Phase Transformation Toughening, PTT

Due to the metastable character of tetragonal grains stabilized at room temperature, the polymorphous character of zirconia allows for stress-induced phase transformation toughening (PTT) [7,8]. By transformation of metastable tetragonal crystallites to the monoclinic stable state in the stress field of a propagating crack, tetragonal-to-monoclinic (t-m) transformation accompanied by volume expansion induces compressive stress, acting to resist crack propagation. 3Y-TZP comprising a volume percentage of >80% of tetragonal grains is therefore known as ceramic material with comparatively high fracture toughness (> 5 MPa·$m^{1/2}$) and strength (> 1000 MPa) [1]. However, even the as-delivered zirconia dental implant might already have experienced transformation to the monoclinic by means of PTT due to applied stresses during subtractive manufacturing or post-processing procedures in order to create a micro-roughened surface, e.g., sand blasting [9]. To date, it remains unclear to what extent a limited and superficial phase transformation to the

monoclinic due to processing steps can be considered beneficial (inducing an overall compressive stress at the surface tending to close potential advancing cracks and resulting in increased strength) or not (once transformed monoclinic crystallites can no longer exhibit PTT). Subtractive manufacturing and subsequent post-processing are expensive and liable to induce phase composition, which may be beneficial in some cases or not in other situations. Techniques like CIM (ceramic injection molding) might overcome these issues, but more research is necessary on this topic in order to guarantee mechanical reliability.

However, one cannot benefit from PTT without being exposed to the risk of low-temperature degradation (LTD).

1.1.2. Low Temperature Degradation (LTD)

In contrast to stress-induced PTT, LTD refers to spontaneous and progressive transformation from tetragonal to the monoclinic at low temperatures in the presence of water vapor. Once started, LTD continuously and linearly progresses from the implant surface into the bulk in a layer-by-layer manner [10]. This premature degradation is also referred to as 'ageing'. Again, it remains unclear to what extent a limited and superficial phase transformation to the monoclinic due to ageing needs to be considered detrimental, negligible or even beneficial when it comes to the clinical fatigue of a dental implant. However, transformation due to ageing may result in micro-cracking and surface-roughening [11]. The coupled effects of both phenomena were showed to significantly increase wear and, in the most detrimental cases, failure of zirconia-based ball hip joints [12]. PTT and LTD are based on the same phenomenon and using yttria-stabilized zirconia for the fabrication of biomedical implants, one might not exploit the advantage of the former without being exposed to the risk of the latter. Nonetheless, LTD might be less relevant for the application of medical devices without sliding surfaces like dental implants [13]. In addition, current versions of 3Y-TZP powders with small amounts of alumina lead to an improvement of LTD resistance without compromising strength [14]. In other words, not all 3Y-TZP behave the same and there are strategies to improve the balance between LTD and PTT [15–17]. To date, the impact of LTD on the long-term stability of zirconia dental implants is still a point of controversial discussion. The answer may depend on the type of powder used, processing protocols and surface finishing strategies.

Changing sample properties based on post-processing procedures and environmental conditions requires an adequate material testing protocol before a clinical service. To date, evaluation of clinical safety has been addressed by two international ISO standards (ISO 14801 and ISO 13356).

1.2. Available ISO Standards for Dental Implants Made from Y-TZP

Today, interest of both dentists and patients in offering or demanding metal-free dentistry seems to be steadily increasing. However, for supporting implant-borne reconstructions, titanium-based dental implants are still referred to as the gold standard material. Even if the market share of zirconia dental implants increases, concerns regarding the fracture resistance are still present. Can a ceramic implant available for purchase be considered safe? From the authors' point of view, it is crucial to evaluate each newly developed zirconia dental implant in a reliable way and preclinical testing procedures mimicking intraoral conditions to the extent possible should be considered mandatory prior to market-release. However, adequate standardized testing protocols for market-ready ceramic implants adequately addressing 3Y-TZPs hydrothermal ageing behavior in terms of t-m phase transformation are still lacking. In the following section, both available ISO standards are described, and their drawbacks are considered.

1.2.1. ISO 14801

Dentistry–Implants–Dynamic Fatigue Test for Endosseous Dental Implants

To date, the ISO 14801 standard test [18], mostly referring to titanium implants, is the only laboratory test to evaluate the safety of dental implants that is accepted by the US Food and Drug Administration. Here, market-ready implants with micro-roughened surfaces are examined and standardized embedding of the implants is clearly defined, with the aim to simulate a "worst case scenario" by requiring an angulation of 30° to the vertical and a simulated bony recession of 3 mm. This embedding procedure, along with an individualized loading hemisphere attached to the abutment, guarantees identical leverage (5.5 mm) during dynamic loading for all different types of implants and allows for a direct comparison of the outcome. Finally, ISO 14801 imposes a dynamic loading procedure, submitting the implants to different loads in order to obtain a fatigue resistance curve (Wöhler curve). However, from the authors' point of view, intraoral conditions are not simulated adequately, neither environmentally (a humid atmosphere thermally accelerating ageing and crack propagation kinetics) nor motorically (the described loading procedure does not account for shear stresses due to horizontal forces such as those resulting from lateral movements of the mandible during mastication or bruxism). Furthermore, ISO 14801 does not require a minimum load of the investigated specimen. Thereby, the data acquired by applying this experimental setup might result in a limited validity concerning the lifetime prediction of market-ready zirconia implants.

1.2.2. ISO 13356

Implants for Surgery—Ceramic Materials Based on Yttria-Stabilized Tetragonal Zirconia (Y-TZP)

ISO 13356 imposes that a maximum of 25 vol% of monoclinic phase be present in test specimens after an accelerated ageing test (5h at 134 °C and 0.2 MPa) [19]. However, specimens with a polished surface and a simplified geometry (bending bars) have been used. It was shown that complex implant geometries and surface modifications with micro-roughening to enhance osseointegration can significantly compromise fracture strength and ageing kinetics [20,21]. Roughened or porous implant surfaces presented an up to 60% higher transformation rate compared to specimen with polished surfaces [13]. Regrettably, roughened and porous specimens are disregarded in ISO 13356. As a consequence, ISO 13356 does not account for the real transformation rate of the final product to be installed in the patients' mouths [13]. When evaluating the fatigue resistance and ageing susceptibility of zirconia implants in two different procedures using different sample geometries processed in different ways, the impact of both phenomena on the reliability of the final product cannot be evaluated.

1.3. Methods for Quantification and Visualization of Crystallography

Several techniques are available for quantifying and visualizing the phase transformation before and after dynamic loading or hydrothermal treatment of a zirconia specimen. While visualization by scanning electron microscopy is mostly destructive in nature, non-destructive techniques such as X-ray diffraction (XRD) and Raman spectroscopy can be applied for quantification of the monoclinic phase to a certain degree, depending on the penetration depth, the thickness of the aged layer, and the surface topography.

1.3.1. X-ray Diffraction (XRD)

Diffraction of X-rays by crystal planes allows one to derive crystal lattice spacings by using Bragg's law. Thus, XRD is liable to distinguish between the t- and m-polymorphs of Y-TZP, since they exhibit different lattice parameters [11]. To determine the volume fraction of the monoclinic phase, an equation provided by Garvie and Nicholson has been mostly applied [22] in combination with the formula of Toraya et al. [23]. This calculation based on the gathered XRD patterns (Figure 1) results in an integrated average monoclinic volume percentage over the penetration depth of the

X-rays and has been successfully applied in laboratory studies evaluation zirconia dental implants [13]. Although the latter equation was calibrated for homogeneous mixtures of zirconia powders of a known monoclinic-tetragonal ratio (contrasting aged surfaces of roughened implants comprising a superficial layer of fully transformed grains with an underlying tetragonal layer of virtually infinite thickness), it proved to be accurate for the evaluation of zirconia implants. However, the characteristic maximum inferred information depth of the X-ray depends on the wavelength and boundary conditions. This results in a given upper limit of attainable monoclinic phase in a volume. For instance, a maximum information depth of roughly 5 and 7 μm was found when evaluating aged Y-TZP samples with Co-Kα or Cu-Kα radiation, respectively (10° incidence angle, reflective mode) [24].

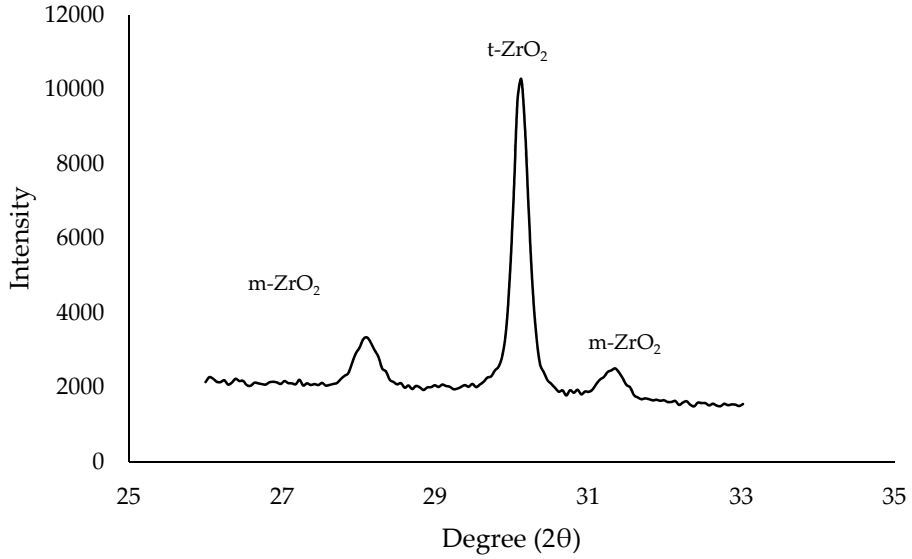

Figure 1. Exemplary X-Ray Diffraction (XRD) pattern acquired at the surface of a zirconia implant showing tetragonal (region of 30° 2θ) and monoclinic peaks (in the region of 28.2° 2θ and 31.4° 2θ). Quantification of monoclinic and tetragonal fractions is based on the respective intensity (area) of the peaks.

1.3.2. Raman Spectroscopy

Raman spectroscopy relies on inelastic scattering of monochromatic light, usually from a laser. In contrast to XRD requiring minutes for measurements, Raman spectroscopy can be acquired in a few seconds [25]. The Raman sampling depth in zirconia ceramics can reach 5 μm to more than 50 μm, among other variables, depending on laser intensity, wavelength and objective lens [26]. The monoclinic phase content within the penetration depth of the laser can be calculated from the spectra (Figure 2) according to the formula by Tabares et al. [27].

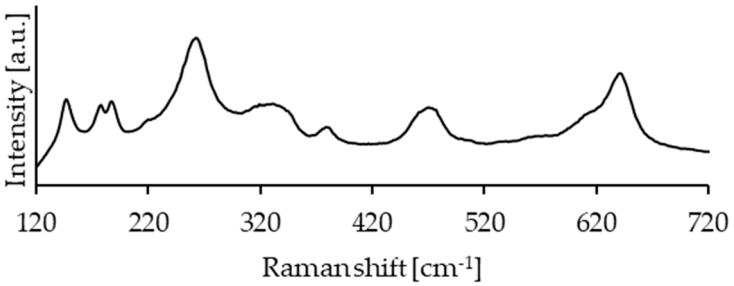

Figure 2. Representative Raman spectrum (phase transformation to the monoclinic is evident from the appearance of the Raman twin band in the frequency range between 170 and 200 cm^{-1}).

1.3.3. Scanning Electron Microscopy (SEM)

When used for the visualization of transformed grains under the surface, SEM has to be considered a destructive quantification technique. Two methods, namely cross sectioning (Figure 3) and focused ion beam (FIB, Figure 4) sectioning, have mostly been applied to prepare samples from zirconia implants for SEM analyses (Figure 5). For cross sectioning, the implant needs to be embedded and cut [28]. After precision sectioning with a diamond sawing blade, the sectioned surface requires thorough polishing to avoid falsification of the results due to transformation as a consequence of applied stress during sample preparation. However, this procedure allows for a rather huge field of view available for SEM imaging or even Raman mapping. Moreover, a focused ion beam (FIB) can be used for sectioning the specimen at specific desired locations [13]. This procedure has to be considered a local and site-specific analysis. During the application of the beam, two-dimensional SEM images as datasets can be taken simultaneously. This implementation shows less falsification or structural damages of the specimen surface after the specimen slicing/cutting procedure. Based on both sectioning procedures, SEM is able to reveal a surface layer of monoclinic grains and intergranular micro cracks for very small depths (1–2 µm) at the onset of transformation. At the other bound, the width of a monoclinic surface layer can be measured in depth, even if it exceeds the penetration depth of XRD or Raman spectroscopy, i.e., at distances higher than 20–50 microns, where XRD and Raman are no longer relevant. Finally, SEM of the fractured surface of an implant that failed during dynamic loading or fractured at the static loading test can be used for fracture analyses.

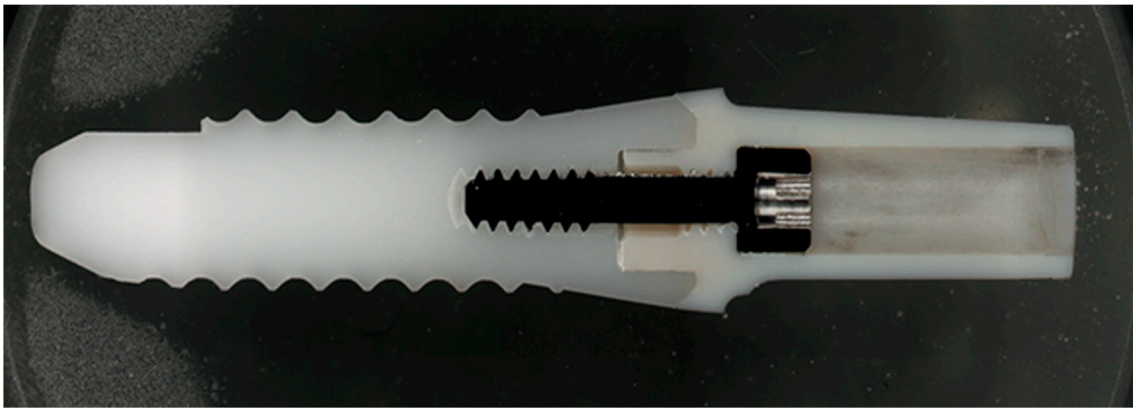

Figure 3. Exemplary cross-section of a two-piece zirconia implant.

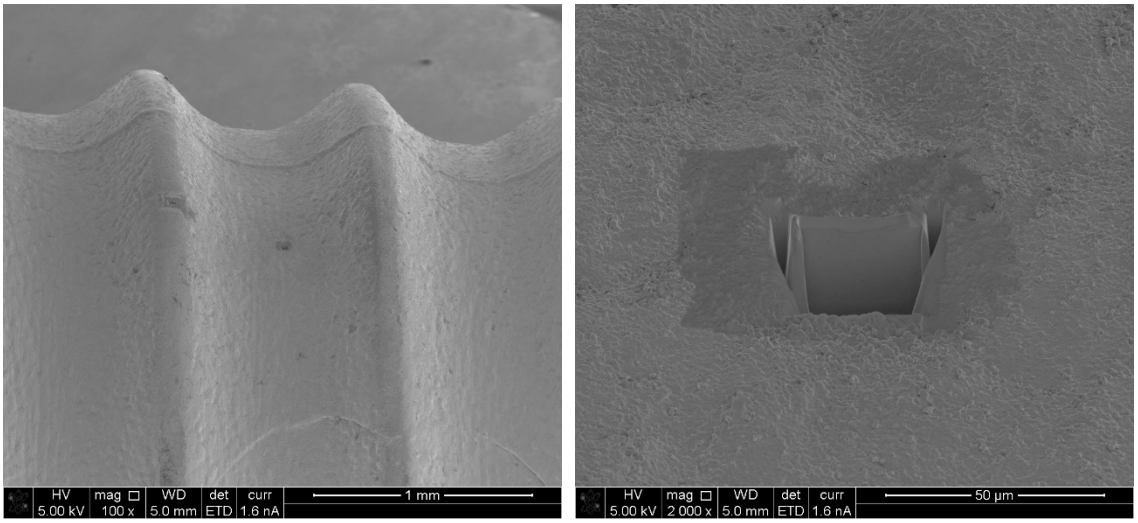

Figure 4. Exemplary Focused Ion Beam (FIB)-sections on the endosseous part of a zirconia dental implants.

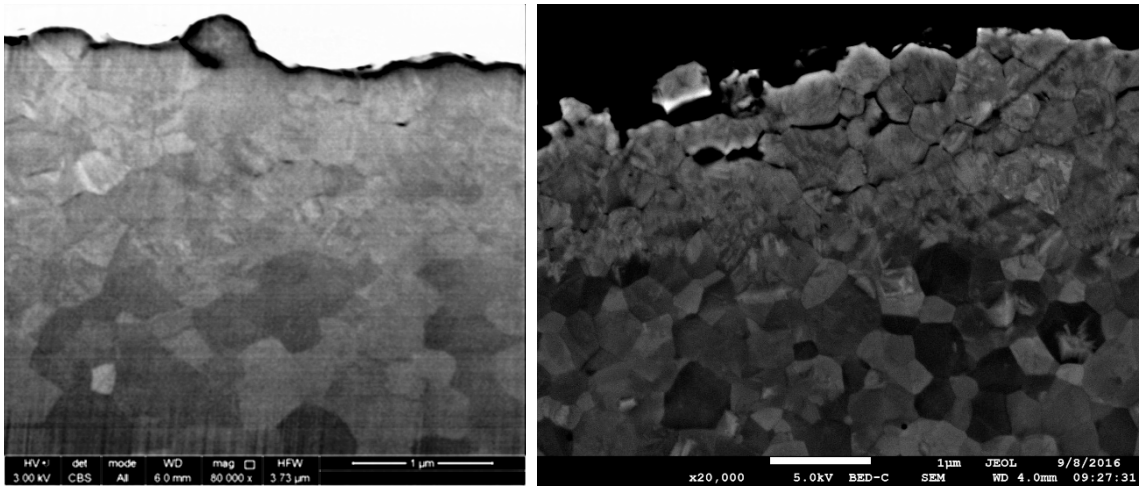

Figure 5. Scanning Electron Microscopy (SEM) images showing a transformed layer after ageing for 60 days in water set at 85 °C (left: FIB section, right: cross-section).

2. Discussion

From the authors' point of view, an adequate testing procedure should simulate intraoral conditions to the extent possible, and therefore include (1) environmental conditions inducing phase transformation during dynamic loading or load zirconia implants subjected to an accelerated ageing procedure prior to loading; (2) horizontal shear forces should be applied; (3) the applied load as well as the amount of loading cycles need to be tailored to simulate a clinical service of at least 40 years; (4) a minimum requirement for final loading to fracture needs to be defined. In the case of non-success mentioned above, (5) destructive and non-destructive techniques for determining the amount of phase transformation might be used for failure analyses.

2.1. Environmental Conditions—Ageing of the Final Product

Since it is evident that surface modifications processed to enhance osseointegration may play a major role in phase transformation, it is strongly recommended to artificially age the final product instead of a standardized sample with a polished surface, as presented in [29]. Two scenarios have been presented to realize this procedure: accelerated ageing during dynamic loading or prior to dynamic loading. Both methods were successfully applied in laboratory studies [13,28]. Loading and ageing might be advantageous simultaneously for the evaluation of two-piece zirconia implants, since it was shown that even internal parts of the implant-abutment connection were exposed to water, finally resulting in LTD at the exposed surface [28]. When ageing the sample without a load, penetration of water in that area might not occur, thereby sophisticating the outcome. However, tailoring the material-specific water temperature during dynamic loading depending on the activation energy in relation to the amount of chewing cycles and chewing frequency might be not practicable for a standardized procedure. Furthermore, no escalating effect of loading and ageing at the same time has been shown to date. Therefore, ageing prior to loading in the artificial mouth might be more feasible and could be standardized more easily. Whether the conditions described in ISO 13356 might be suitable for an ageing procedure of the final product prior to dynamic loading still needs to be evaluated.

2.2. Horizontal Shear Forces

Even if the embedding procedure mentioned in ISO 14801 prescribes an angulation of the implant of 30° to the vertical, the application of horizontal shear forces to the implant might be reasonable. It was already demonstrated in clinical studies that mastication does not solely result in axial but also in horizontal forces applied to dental implants. In ISO 14801, loading a vertically angulated

implant with a bony recession of 3 mm was claimed to simulate a clinical worst-case scenario and not for mimicking horizontal forces by applying a unidimensional loading procedure to the angulated implant. In studies available today, a lateral movement of 0.5 mm per cycle under load was suggested to simulate mastication movements in a proper way.

2.3. Applied Load and Amount of Loading Cycles

There is an ongoing discussion in the literature on how to set the load dynamically applied to the implant during dynamic loading. Several clinical studies using intraoral strain gauge abutments to determine forces applied to dental implants during chewing and clenching were conducted [30]. The highest bending moment measured once in these trials was 95 Ncm. Embedding the implants according to ISO 14801, this would correspond to an axial load of 174 N. In combination with a lateral movement applied to the angulated implant, it needs to be discussed whether this maximum load or a reduced load, e.g., in the range of 100 N, should be considered sufficient for dynamic loading in the artificial mouth. Another point of discussion represents the amount of loading cycles. In most of the available laboratory studies using a chewing simulator, clinical correlation is derived from findings by DeLong et al. [31,32]. In their study, a correlation of wear data obtained in a chewing simulator was correlated with 18-month and 4-year in vivo data of three composite materials and one amalgam material using a stereomicroscope with a measuring device to quantify wear, resulting in 240,000 chewing cycles per year. However, this method may be inadequate to conclude the cycles to the number of chewing cycles in human beings from the wear of a dental material. With regard to the number of chewing cycles and tooth contacts in relation to time, no systematic research has been carried out so far. There are hints that a subject performs about 330,000 chewing cycles per year on average. This estimate derives from a small clinical trial on subjects whose chewing frequency was recorded with portable EMG devices in their home environment [33]. However, it was already claimed elsewhere that up to 1,000,000 chewing cycles per year may be possible [34]. Therefore, it is strongly encouraged to generate more profound clinical data on the chewing frequency of humans in order to obtain a more precise estimate of how many cycles should be sufficient to simulate at least 40 years of clinical service.

2.4. Final Static Loading to Fracture

After ageing and dynamic loading, all specimens should be subjected to static loading until fracture, followed by fracture analyses. Regrettably, ISO 14801 does not require an indication-specific minimum value for fracture strength, e.g., as defined in detail in ISO 6872 for reconstructive ceramic materials used in dentistry [35]. Taking the highest clinically measured bending moment of 95 Ncm into account [30] and applying a safety buffer of 100%, the authors suggest that a minimum static moment to fracture of 200 Ncm for all the tested specimen, roughly corresponding to a load of 400 N when embedding the implants according to ISO 14801, might result in clinical safety.

3. Conclusions

The application of available ISO standards (ISO 14801 and ISO 13356) does not guarantee the clinical safety of zirconia dental implants. It is strongly recommended to adapt and combine these standards, mainly due to the insufficient testing of ageing susceptibility and the missing minimum requirement regarding fracture strength. Instead of a polished sample, the final and later on market-available products should be hydrothermally aged and loaded, either simultaneously or subsequently.

Author Contributions: K.F., J.C., F.Z. and B.C.S. contributed to drafting and approval of the article.

Funding: This commentary received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Piconi, C.; Maccauro, G. Zirconia as a ceramic biomaterial. *Biomaterials* **1999**, *20*, 1–25. [CrossRef]
2. Kisi, E.H.; Howard, C. Crystal Structures of Zirconia Phases and their Inter-Relation. *Key Eng. Mater.* **1998**, *153*, 1–36. [CrossRef]
3. Zhang, F.; Reveron, H.; Spies, B.C.; Van Meerbeek, B.; Chevalier, J. Trade-off between fracture resistance and translucency of zirconia and lithium-disilicate glass ceramics for monolithic restorations. *Acta Biomater.* **2019**, *91*, 24–34. [CrossRef] [PubMed]
4. Camposilvan, E.; Leone, R.; Gremillard, L.; Sorrentino, R.; Zarone, F.; Ferrari, M.; Chevalier, J. Aging resistance, mechanical properties and translucency of different yttria-stabilized zirconia ceramics for monolithic dental crown applications. *Dent. Mater.* **2018**, *34*, 879–890. [CrossRef] [PubMed]
5. Pieralli, S.; Kohal, R.J.; Jung, R.E.; Vach, K.; Spies, B.C. Clinical Outcomes of Zirconia Dental Implants: A Systematic Review. *J. Dent. Res.* **2017**, *96*, 38–46. [CrossRef] [PubMed]
6. Pieralli, S.; Kohal, R.J.; Rabel, K.; von Stein-Lausnitz, M.; Vach, K.; Spies, B.C. Clinical outcomes of partial and full-arch all-ceramic implant-supported fixed dental prostheses. A systematic review and meta-analysis. *Clin. Oral. Implant. Res.* **2018**, *29*, 224–236. [CrossRef]
7. Garvie, R.C.; Hannink, R.H.; Pascoe, R.T. Ceramic steel? *Nature* **1975**, *258*, 703–704. [CrossRef]
8. Gupta, T.K.; Lange, F.F.; Bechtold, J.H. Effect of stress-induced phase transformation on the properties of polycrystalline zirconia containing metastable tetragonal phase. *J. Mater. Sci.* **1978**, *13*, 1464–1470. [CrossRef]
9. Deville, S.; Chevalier, J.; Gremillard, L. Influence of surface finish and residual stresses on the ageing sensitivity of biomedical grade zirconia. *Biomaterials* **2006**, *27*, 2186–2192. [CrossRef]
10. Keuper, M.; Eder, K.; Berthold, C.; Nickel, K. Direct evidence for continuous linear kinetics in the low-temperature degradation of Y-TZP. *Acta Biomater.* **2013**, *9*, 4826–4835. [CrossRef]
11. Lughi, V.; Sergo, V. Low temperature degradation -aging- of zirconia: A critical review of the relevant aspects in dentistry. *Dent. Mater.* **2010**, *26*, 807–820. [CrossRef] [PubMed]
12. Clarke, I.C.; Manaka, M.; Green, D.D.; Williams, P.; Pezzotti, G.; Kim, Y.-H.; Ries, M.; Sugano, N.; Sedel, L.; Delauney, C.; et al. Current status of zirconia used in total hip implants. *JBJS* **2003**, *85*, 73–84. [CrossRef] [PubMed]
13. Sanon, C.; Chevalier, J.; Douillard, T.; Cattani-Lorente, M.; Scherrer, S.S.; Gremillard, L. A new testing protocol for zirconia dental implants. *Dent. Mater.* **2015**, *31*, 15–25. [CrossRef] [PubMed]
14. Zhang, F.; Inokoshi, M.; Batuk, M.; Hadermann, J.; Naert, I.; Van Meerbeek, B.; Vleugels, J. Strength, toughness and aging stability of highly-translucent Y-TZP ceramics for dental restorations. *Dent. Mater.* **2016**, *32*, e327–e337. [CrossRef] [PubMed]
15. Matsui, K.; Yoshida, H.; Ikuhara, Y. Nanocrystalline, Ultra-Degradation-Resistant Zirconia: Its Grain Boundary Nanostructure and Nanochemistry. *Sci. Rep.* **2014**, *4*, 4758. [CrossRef] [PubMed]
16. Nogiwa-Valdez, A.; Rainforth, W.; Zeng, P.; Ross, I.; Rainforth, W. Deceleration of hydrothermal degradation of 3Y-TZP by alumina and lanthana co-doping. *Acta Biomater.* **2013**, *9*, 6226–6235. [CrossRef] [PubMed]
17. Batuk, M.; Hadermann, J.; Vleugels, J.; Chevalier, J.; Olagnon, C.; Van Meerbeek, B.; Zhang, F. Grain-Boundary Engineering for Aging and Slow-Crack-Growth Resistant Zirconia. *J. Dent. Res.* **2017**, *96*, 774–779.
18. ISO 14801: Dentistry-Implants—Dynamic Fatigue Test for Endosseous Dental Implants. Volume DIN EN ISO 14801:2008-02. Available online: https://www.iso.org/obp/ui/#iso:std:iso:14801:ed-2:v1:en (accessed on 23 October 2019).
19. ISO 13356: Implants for Surgery—Ceramic Materials Based on Yttria-Stabilized Tetragonal Zirconia (Y-TZP). Volume ISO 13356:2008(E) 2nd Edition. Available online: https://www.iso.org/standard/40166.html (accessed on 23 October 2019).
20. Cattani-Lorente, M.; Scherrer, S.; Durual, S.; Sanon, C.; Douillard, T.; Gremillard, L.; Chevalier, J.; Wiskott, A. Effect of different surface treatments on the hydrothermal degradation of a 3Y-TZP ceramic for dental implants. *Dent. Mater.* **2014**, *30*, 1136–1146. [CrossRef]
21. Chevalier, J.; Loh, J.; Gremillard, L.; Meille, S.; Adolfson, E. Low-temperature degradation in zirconia with a porous surface. *Acta Biomater.* **2011**, *7*, 2986–2993. [CrossRef]
22. Garvie, R.C.; Nicholson, P.S. Phase analysis in zirconia systems. *J. Am. Ceram. Soc.* **1972**, *55*, 303–305. [CrossRef]

23. Toraya, H.; Yoshimura, M.; Somiya, S. Calibration Curve for Quantitative Analysis of the Monoclinic-Tetragonal ZrO2System by X-Ray Diffraction. *J. Am. Ceram. Soc.* **1984**, *67*, C-119–C-121. [CrossRef]
24. Keuper, M.; Berthold, C.; Nickel, K.G. Long-time aging in 3mol.% yttria-stabilized tetragonal zirconia polycrystals at human body temperature. *Acta Biomater.* **2014**, *10*, 951–959. [CrossRef] [PubMed]
25. Chevalier, J.; Gremillard, L.; Deville, S. Low-Temperature Degradation of Zirconia and Implications for Biomedical Implants. *Annu. Rev. Mater. Res.* **2007**, *37*, 1–32. [CrossRef]
26. Presser, V.; Keuper, M.; Berthold, C.; Nickel, K.G. Experimental Determination of the Raman Sampling Depth in Zirconia Ceramics. *Appl. Spectrosc.* **2009**, *63*, 1288–1292. [CrossRef] [PubMed]
27. Tabares, J.A.M.; Anglada, M.J. Quantitative Analysis of Monoclinic Phase in 3Y-TZP by Raman Spectroscopy. *J. Am. Ceram. Soc.* **2010**, *93*, 1790–1795.
28. Spies, B.C.; Maass, M.E.; Adolfsson, E.; Sergo, V.; Kiemle, T.; Berthold, C.; Gurian, E.; Fornasaro, S.; Vach, K.; Kohal, R.-J. Long-term stability of an injection-molded zirconia bone-level implant: A testing protocol considering aging kinetics and dynamic fatigue. *Dent. Mater.* **2017**, *33*, 954–965. [CrossRef] [PubMed]
29. Sanon, C.; Chevalier, J.; Douillard, T.; Kohal, R.J.; Coelho, P.G.; Hjerppe, J.; Silva, N.R. Low temperature degradation and reliability of one-piece ceramic oral implants with a porous surface. *Dent. Mater.* **2013**, *29*, 389–397. [CrossRef] [PubMed]
30. Morneburg, T.R.; A Pröschel, P. In vivo forces on implants influenced by occlusal scheme and food consistency. *Int. J. Prosthodont.* **2003**, *16*, 481–486.
31. Delong, R.; Sakaguchi, R.; Douglas, W.; Pintado, M. The wear of dental amalgam in an artificial mouth: A clinical correlation. *Dent. Mater.* **1985**, *1*, 238–242. [CrossRef]
32. Sakaguchi, R.L.; Douglas, W.H.; DeLong, R.; Pintado, M.R. The wear of a posterior composite in an artificial mouth: A clinical correlation. *Dent. Mater.* **1986**, *2*, 235–340. [CrossRef]
33. Po, J.; Kieser, J.; Gallo, L.; Tésenyi, A.; Herbison, P.; Farella, M. Time-Frequency Analysis of Chewing Activity in the Natural Environment. *J. Dent. Res.* **2011**, *90*, 1206–1210. [CrossRef] [PubMed]
34. Rosentritt, M.; Behr, M.; Gebhard, R.; Handel, G. Influence of stress simulation parameters on the fracture strength of all-ceramic fixed-partial dentures. *Dent. Mater.* **2006**, *22*, 176–182. [CrossRef] [PubMed]
35. ISO 6872:2015(E). Dentistry—Ceramic materials. Available online: https://www.iso.org/obp/ui/#iso:std:iso:6872:ed-4:v1:en (accessed on 23 October 2019).