UNIVERSITY OF BELGRADE
FACULTY OF TECHNOLOGY AND METALLURGY

Giuma Khalifa Giuma Ayoub

The processing, properties and application of dental inserts based on calcium phosphates and zirconia

Doctoral Dissertation

Belgrade, 2021

UNIVERZITET U BEOGRADU

TEHNOLOŠKO-METALURŠKI FAKULTET

Giuma Khalifa Giuma Ayoub

Procesiranje, svojstva i primena dentalnih inserata na bazi kalcijum-fosfata i cirkonijum(IV)-oksida

Doktorska disertacija

Beograd, 2021.

Supervisor:

____

1. Dr Đorđe Janaćković, Full Professor,
   University of Belgrade, Faculty of Technology and Metallurgy

Committee Members:

____

2. Dr Đorđe Veljović, Associate Professor,
   University of Belgrade, Faculty of Technology and Metallurgy

____

3. Dr Rada Petrović, Full Professor,
   University of Belgrade, Faculty of Technology and Metallurgy

____

4. Dr Vesna Miletic, Full Professor,
   The University of Sydney, School of Dentistry

____

5. Maja Zebić, Research Associate,
   University of Belgrade, Faculty of Dentistry

Date of Defense: ____________________

Acknowledgments

First and foremost, I would like to thank Allah the Almighty for giving me the courage, the willingness, and patience to complete this work. Undertaking this PhD has been a truly life-changing experience for me and it would not have been possible to do without the support and guidance that I received from many people.

I would like to, first of all, express my sincere gratitude to my supervisor, Dr. Đorđe Janaćković, for his endless support and encouragement throughout this dissertation, for patiently sharing his time and knowledge, for his generous guidance and support in my dissertation and in my development to be a more mature researcher. I would have been unable to complete this thesis without his support.

I would like to express the deepest appreciation to my other advisor, Dr. Đorđe Veljović, who has attitude and the substance of a genius: he continually and convincingly conveyed a spirit of adventure in regard to research. Without his guidance and persistent help this dissertation would not have been possible. It has been an honor to be their PhD student.

I cannot begin to express my thanks to thanking the rest of the committee members Dr Rada Petrović and Dr Vesna Miletić my thesis examiners for their interest in my work and for their insightful suggestions and comments on my thesis. They were always willing to help and give me best suggestions.

I would also like to extend my deepest gratitude to Dr. Maja Zebić for her support and help. She has taught me, how good experimental are done. I appreciate all her contributions of time, ideas, and suggestions that helped to make my research skills experience productive and stimulating.

I would like to thank all the participants who took part in the interviews and made this research possible by sharing their stories and experiences.

I would like to thank my wife, who has been by my side throughout this PhD, living every single minute of it, she was always there cheering me up and stood by me through the good times and bad, and for her understanding, wisdom, patience, and encouragement and for pushing me farther than I thought I could go.

I dedicate this work to my lovely family (my wife and my children Doaa, Taqua, Zakaria and Taha) and my dear friends. I would never have reached this point and complete my dissertation without your sustained support; thank you with all my heart.

Giuma Khalifa Ayoub

The processing, properties and application of dental inserts based on calcium phosphates and zirconia

Abstract

The objective of the study was to process nano-structured hydroxyapatite/yttrium stabilized zirconia bioceramic and to investigate the possibilities of its application as dentin replacement in the form of dental inserts. The processing conditions were varied in order to optimize phase composition, microstructure, fracture toughness, hardness, and shear bond strength (SBS) between the obtained inserts and restorative materials, following either the "total-etch" or „self-etch“ clinical protocol. Composite nano-powder, obtained by mixing and homogenization of 80 wt% of stoichiometric hydroxyapatite (HAp) synthesized by modified precipitation method and 20 wt% of yttrium-stabilized ZrO_2 (YSZ) synthesized by plasma method, was isostatically pressed into cylinder-shaped green bodies. After dilatometric analysis, HAp/YSZ inserts were sintered in the temperature range from 1200 °C to 1300 °C. Hardness and fracture toughness of sintered inserts were ranged between 3.90 ± 0.20 – 3.95 ± 0.12 GPa and 1.82 ± 0.04 – 1.88 ± 0.03 $MPam^{1/2}$, respectively. Microstructural analysis of biphasic stoichiometric hydroxyapatite/tetragonal phase of zirconia (HAp/t-ZrO_2) inserts indicated two potential fracture mechanisms for fracture toughness increasing. Sintering temperature and different clinical protocols affected SBS between processed inserts and commercial dental restorative materials. Maximum SBS values of 10.50 ± 4.94 MPa (mean±standard deviation) were reached in inserts sintered at 1300 °C, following the „self-etch“ protocol of adhesive application. It could be concluded that resin-based composites could be strongly bonded to HAp/YSZ inserts, preferably with a „self-etch“ adhesive application. In addition, the values of fracture toughness and hardness of the obtained inserts indicated the possibility of their use as dentin substitutes, which could be a good prerequisite for satisfactory mechanics of restored teeth. One of the aims was also to analyze comparatively physico-chemical and mechanical properties of dental inserts and SBS between dissimilar hydroxyapatite-based dental inserts and different restorative materials, after application of different clinical protocols. Besides HAp/YSZ inserts, monophasic two-step sintered dense HAp (TSSHAp) and biphasic single-step sintered controlled porous (HAp/tricalcium phosphate, TCp) inserts were processed and used in analysis. TSSHAp and HAp/TCp inserts showed comparable and relatively high SBS values, certainly higher compared to HAp/YSZ inserts. Slightly higher SBS values were measured in the case of TSSHAp insert group, and the highest mean SBS value of 18.51 MPa was determined between TSSHAp inserts and Filtek Z250_SBU following the „self-etch“ protocol. Mechanical properties of the three insert types were similar or higher than enamel (hardness) and similar to dentin (fracture toughness) despite differences in insert processing methods. SBS values to HAp-based inserts and various restorative materials varied largely but were found relatable to dentin bonding. Adhesive bonding following either "total-etch" or „self-etch“ protocol is promising to all three types of HAp-based inserts.

Key words: hydroxyapatite, yttrium stabilized zirconia bioceramic, shear bond strength inserts, composites, adhesives, mechanical properties.

Scientific field: Technical engineering

Major in: Materials engineering

Procesiranje, svojstva i primena dentalnih inserata na bazi kalcijum-fosfata i cirkonijum(IV)-oksida

Rezime

Cilj ovog istraživanja bio je procesiranje nanostrukturnog hidroksiapatita/itrijumom stabilisanog cirkonijum-dioksida i ispitivanje mogućnosti njihove primene u formi dentalnih inserata kao zamene za dentin. Uslovi procesiranja su varirani sa ciljem optimizacije faznog sastava, mikrostrukture, žilavosti, tvrdoće i jačine veze na smicanje, između dobijenih inserata i restaurativnih materijala prateći protokol totalnog nagrizanja ili samonagrizajući protokol. Kompozitni nanoprah dobijen mešanjem i homogenizacijom 80 % stehiometrijskog hidroksiapatita (HAp), sintetisanog modifikovanom metodom precipitacije i 20 % itrijumom stabilisanog CrO_2 (YSZ), sintetisanog plazma metodom, je izostatski presovan u cilindrični polazni kompakt. Nakon dilatometrijske analize, HAp/YSZ inserti su sinterovani u temperaturnom opsegu od 1200 °C do 1300 °C. Tvrdoća je bila u opsegu 3,90 ± 0,20 – 3,95 ± 0,12 Gpa, a žilavost loma u opsegu 1,82 ± 0,04 – 1,88 ± 0,03 $MPam^{1/2}$. Analiza mikrostruktre dvofaznog stehiometrijskog hidroksiapatita/tetragonalnog cirkonijum dioksida ($HAp/t\text{-}ZrO_2$) je pokazala dva potencijalna mehanizma povećanja žilavosti. Temperatura sinterovanja i različiti klinički protokoli su uticali na jačinu veze na smicanje između procesiranih inserata i komercijalnih restaurativnih materijala. Najveće vrednosti jačine veze na smicanje od 10,50 ± 4,94 MPa su postignute kod inserata koji su sinterovani na 1300 °C, sledeći samonagrizajući protokol primene adheziva. Može se zaključiti da se kompoziti na bazi smole mogu snažno vezati za HAp/YSZ inserte, prevenstveno primenjujući samonagrizajući protokol. Dodatno, vrednosti žilavosti i tvrdoće dobijenih inserata ukazali su na potencijal njihove primene kao supstituenata dentina, što je dobar uslov za zadovoljavajuća mehanička svojstva restauiranih zuba. Jedan od ciljeva je takođe bila komparativna analiza fizičko-hemijskih i mehaničkih osobina dentalnih inserata i jačine veze na smicanje između različitih dentalnih inserata na bazi hidroksiapatita i različitih restaurativnih materijala, nakon primene različitih kliničkih protokola. Pored HAp/YSZ inserata, monofazni, dvostepeno sinterovani gusti HAp (TSSHAp) i dvofazni jednostepeno sinterovani HAp sa kontrolisanom poroznošću (HAp/tricalcium phosphate, TCp) su procesirani i analizirani takođe. TSSHAp i HAp/TCp inserti su pokazali uporedive i relativno velike vrednosti jačine veze na smicanje, više u odnosu na HAp/YSZ inserte. Malo veće vrednosti jačine veze na smicanje su određene kod TSSHAp inserata, a najviša srednja vrednost jačine veze na smicanje, koja je iznosila 18,51 MPa je određena između TSSHAp inserata i Filtek Z250_SBU nakon protokola samonagrizanja. Mehanička svojstva tri tipa inserata su bila slična ili veća u odnosu na gleđ (tvrdoću) i slična dentinu (žilavost) uprkos razlikama u metodama procesiranja inserata. Vrednosti jačine veze na smicanje inserata na bazi HAp-a i različitih restaurativnih materijala su veoma varirale, ali su se pokazale uporedive sa vezom sa dentinom. Adhezivno vezivanje dobijeno protokolom totalnog nagrizanja ili samonagrizajućim portokolom je obećavajuće kod sva tri tipa inserata na bazi HAp-a.

Ključne reči: hidroksiapatit, itrijumom stabilisani cirkonijum-dioksid, jačina veze na smicanje, kompoziti, adhezivi, mehanička svojstva

Naučna oblast: Tehnološko inženjerstvo

Uža naučna oblast: Inženjerstvo materijala

Contents

1. INTRODUCTION 1

2. BIOCERAMICS 7

2.1 Classification of bioceramics 11

2.2 Bioinert and bioactive materials 12

2.3 Hydroxyapatite 13

2.3.1. Apatite in bone 13

2.3.2 Apatite in teeth 15

2.4 Synthetic hydroxyapatite 17

2.4.1 Synthesis methods for HAp powders 20

2.4.2 Mechanical properties 21

2.4.3. Porosity 22

3. ZIRCONIA CERAMICS……………………………………………………….23

3.1 Structure of ZrO_2 Ceramics 23

3.2 Phases transformation of zirconia 24

3.2.1 Monoclinic zirconia 26

3.2.2 Tetragonal zirconia 26

3.2.3 Cubic zirconia 26

3.3 Transformation Toughening of Zirconia 27

3.4 Dispersion-toughened ceramics 28

3.5 The types of zirconia used in dentistry 29

3.5.1 Zirconia for implants and abutments 30

4. DENTAL INSERTS 31

4.1 Current state in the field of dental inserts 34

5. EXPERIMENTAL PART 40

5.1. Synthesis and Processing of Materials 40

5.1.1. Synthesis of powders and inserts preparation 40

5.2. Characterization of Materials 43

5.3. Shear bond strength test 44

6. RESULTS 50

6.1. Characterization of HAp_1, HAp_2 and YSZ powders 50

6.2. Characterization of the HAp/YSZ sintered samples 55

6.3 Shear bond strengths of the composite inserts 59

6.4. Characterization of TSSHAp, HAp/TCp and HAp/YSZ inserts 61

6.5. Shear bond stress 65

7. DISCUSSION 68

8. CONCLUSION 75

9. REFERENCES 77

BIOGRAPHY 97

List of Figures

Figure 1. Diagram illustrating peritubular and interubular dentin....................................3

Figure 2. Interaction of the components of a dental polymer composite 4

Figure 3. Unetched and etched dentin 5

Figure 4. Classification of biomaterials..8

Figure 5. 1.) Glass Ionomer Cements for Primary Teeth. 2.) Resin composites..............9

Figure 6. The construction bridges made of ceramics to restore or replace missing teeth9

Figure 7. The seven hierarchical levels of organization of the zebrafish skeleton bone.14

Figure 8. Apatite in teeth enamel 16

Figure 9. An Illustration of the location of human dentin (hydroxyapatite) 17

Figure 10. 1.) HAp powder, 2.) Granules of HAp, 3.) Porous HAp and Dense HAp.....18

Figure 11. Hydroxyapatite crystal structure 19

Figure 12. Crystal structure of (a) monoclinic, (b) tetragonal, (c) and cubic zirconia....25

Figure 13. Transformation toughening mechanism in zirconia.......................................27

Figure 14. Schematic illustration of dental inserts used in restorative dentistry.............33

Figure 15. Schematic view of the plasma apparatus for plasma processed nanosized-powders of refractory compounds for obtaining fine-grained advanced ceramics. 41

Figure 16. Photographs of 1) The composite powder 2) Insert green samples. 42

Figure 17. Photographs of 1) Inserts etched with phosphoric acid 37% and copiously rinsed with water and mildly air-dried 2) and 3) Negative model of insert; 4) LED light-curing; 5) Composite material was applied on top of the insert.....................................48

Figure 18. Photographs of 1) Universal test machine (Force Gauge PCE-FM200, Southampton, United Kingdom) to measure SBS; 2) Knife-edge shearing blade. 49

Figure 19. SEM micrographs of: a) HAp1 powder, b and c) YSZ powder. 51

Figure 20. FE-SEM micrographs of powders: a) HAp1, b) HAp2, c) YSZ. 52

Figure 21. a) Number and b) volume particle size distribution of yttrium-stabilized ZrO2 and composite powders. 53

Figure 22. XRD patterns of: a) HAp_1 and b) YSZ powders..54

Figure 23. Dilatometric curves of HAp/YSZ of HAp_1 as a control. 55

Figure 24. XRD patterns of sintered HAp/YSZ insert materials....................................56

Figure 25. SEM micrographs of inserts pressed at 100 MPa and sintered at: a) 1200 °C, b) 1250 °C and c) 1300 °C for 2 h..57

Figure 26. SEM micrographs of inserts isostatically pressed at 400 MPa and sintered at: a) 1200 °C, b) 1250 °C and c) 1300 °C for 2 h. 58

Figure 27. SEM micrographs of two randomly selected places on the etched surface of insert sintered at 1250 °C and used in the „total-etch“ protocol of adhesive application.. 60

Figure 28. SBS of HAp/YSZ inserts sintered at different temperatures bonded to dental composite using adhesives applied by „total-etch“ or „self-etch“ protocol. 61

Figure 29. XRD patterns of inserts: a) TSSHAp, b) HAp/TCp......................................62

Figure 30. TSSHAp inserts: a) Fractured surface and b) acid etched surface. 63

Figure 31. HAp/TCp inserts: a) Fractured surface and b) acid etched surface. 64

Figure 32. HAp/YSZ inserts: a) Fractured surface and b) acid etched surface. 64

Figure 33. Box-and-whisker plots of SBS values between the tested groups. 66

List of Tables

Table 1. Type of ceramic materials for various medical applications 10

Table 2. Bioceramic-tissue interactions 11

Table 3. Advantages and disadvantages of some of the synthesis methods for HAp 21

Table 4. Details on the tested materials 45

Table 5. Preparation procedure in each group 50

Table 7. Mechanical properties of sintered inserts pressed at 100 MPa 57

Table 8. Mechanical properties of sintered inserts isostatically pressed at 400 MPa 59

Table 9. Hardness and fracture toughness of used inserts 65

Table 10. Summary of the GLM statistics…………………………………………...67

1. Introduction

Due to an increase in the amount of trauma and accidents and inherent bone defects caused by age and diseases in recent decades, there has been an increase in the market for synthetic bone and hard tissue replacements, especially in the areas of cranial, orthopedic, maxillofacial, dental, and spinal applications, caused by high demand from hospitals for the replacements. Many patients around the world have benefited from recent advancements in materials and cell engineering, as well as surgical bone grafting techniques. Continuous advances in biomaterials, artificial organs, and stem cells, as well as their latest achievements, indicate a strong progression in human biological sciences. Despite the fact that existing technologies are advanced, many more advances and enhancements are needed to accurately mimic the biological properties of humans [1]. Though, must be manufactured from a particular class of tolerable materials known as biomedical materials or biomaterials, in order to be tolerated by the living body without suffering any unnecessary side effects [2,3].

Biomaterials designing, developing, and manufacturing are based on four main types of materials: ceramics, metals, polymers, composites, and various blends thereof. The biomaterials could also have a natural origin (human or animal) and could be used with artificial materials [4].

Ceramic materials for medical uses were initiated in the 1970s, when some failures and undesired effects of the biomaterials used in that period, such as cobalt alloys, steel, and poly-(methyl methacrylate), started to be detected. In order to find successful bone integration features, the research was concentrated on ceramic materials [5].

Calcium phosphate materials are a class of ceramic materials, and are preferable materials for dental repairs as a result of typical biocompatibility, chemical similarity with human bones and teeth, accompanying bioactivity, and possible forming of strong bonds with hard tissues [6-8].

One of the most researched calcium phosphates for use in the dental field is hydroxyapatite (HAp), which is the primary inorganic constituents of bones and teeth and is occasionally tracked with more bioactive calcium phosphates or fortified with several powerful nanosized particles such as stabilized zirconia-alumina composite [9].

For dental application and purpose, bioactive HAp and other biocompatible calcium phosphates are developed as dental cement, thin films at the surface of metal implants, filler in dental composites and adhesives, pulp capping material essential in pulp therapy, etc. [10,11].

Recently, various materials have been investigated as dental materials for restoring large cavities [12,13]. A potential role of HAp as dentin substitute in the future can be in the form of dental inserts [14,15]. As dental insert has mechanical features similar to the properties of dentin it can be used as dentin substitute. Furthermore, the esthetical appearance of HAp inserts is not satisfactory so they must be covered with a layer of composite material. The thickness of that layer should be at least 2 mm [15]. The application of dental bioceramic inserts in large cavities during restoration could reduce amount of composite dental filling material and therefore reduce polymerization shrinkage. In that way, use of inserts during cavities restoration can simplify the procedure, reduce the steps in the clinical protocol, and potentially reduce polymerization shrinkage stress due to the insert's central position in the cavity [9]. The main advantages of HAp based inserts are: the similar mechanical properties to human dentin, possible chemical interaction with functional monomer groups of commercial adhesives and bonding with resin-based commercial composites or glass-ionomers, which can lead to acceptable values of bond strength between insert and composite materials.

Dentin is specialized mineralized tissue that has a higher hardness and density than bone. When compared to enamel, HAp in dentin has smaller crystals with a needle-like form. The majority of these crystals are integrated into the collagen network. That is why, when compared to enamel, dentin can be more elastically distorted during function [16].

Dentin structure comprises dentin tubules, canals within dentin which are filled with odontoblast and dentin liquid. The direction and diameter of these tubules vary in different parts of the tooth, and it is shown in Figure 1. When applied, dental adhesive systems should reach into those spaces and contribute to bonding dental restoration. Acid etching of dentin, among other reasons, serves as cleaner of these tubules from debris created during tooth drilling and caries removal, making them available for adhesive. Adhesive, unlike composite, has low viscosity, lower surface tension and that is one of the reasons why it is used as first material to contact with dentin. Because of the same reasons, it was used as first material to contact with HAp inserts. Entering dentin tubules surface of contact for chemical bonding between dental adhesive and dentin is also enlarged. Dentin around these tubules is called peritubular dentin and it contains the highest mineral percentage, and thus had the strongest mechanical features. Between these dentinal tubules is intertubular dentin, with average features. Diameter of tubules is about 3,5 micrometers, and their density is about 40 000 tubules/mm^2 [17].

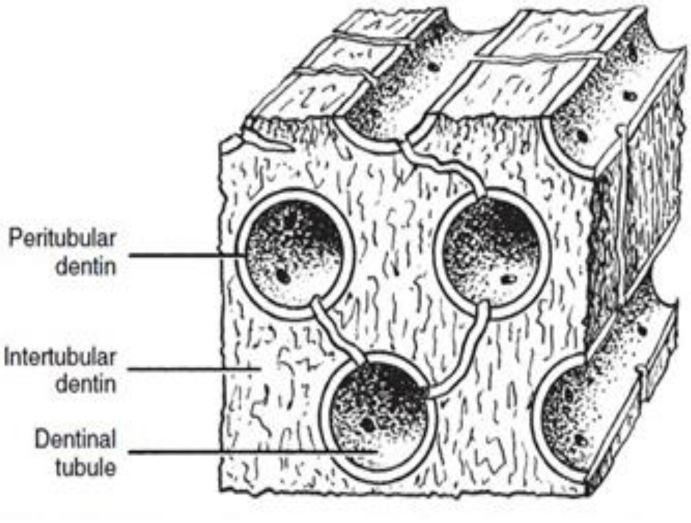

Figure 1. Diagram illustrating peritubular and intertubular dentin. [18]

Dental composites in combination with dental adhesives are the most used restorative materials nowadays. Three basic components of dental composites are 1) organic matrix, 2) inorganic filler and 3) organic-inorganic coupling agent. Organic matrix forms the continuous phase and binds filler particles. It also contains initiator system for polymerization, standardly excited by blue light, and many other ingredients in a small proportion. Inorganic fillers are the component responsible for increase in mechanical properties. Dental adhesives comprise less of the fillers, or none of them, thus having poor mechanical strength, but have some other desirable features. A simplified graphic representation of some of these interactions between components is shown in Figure 2.

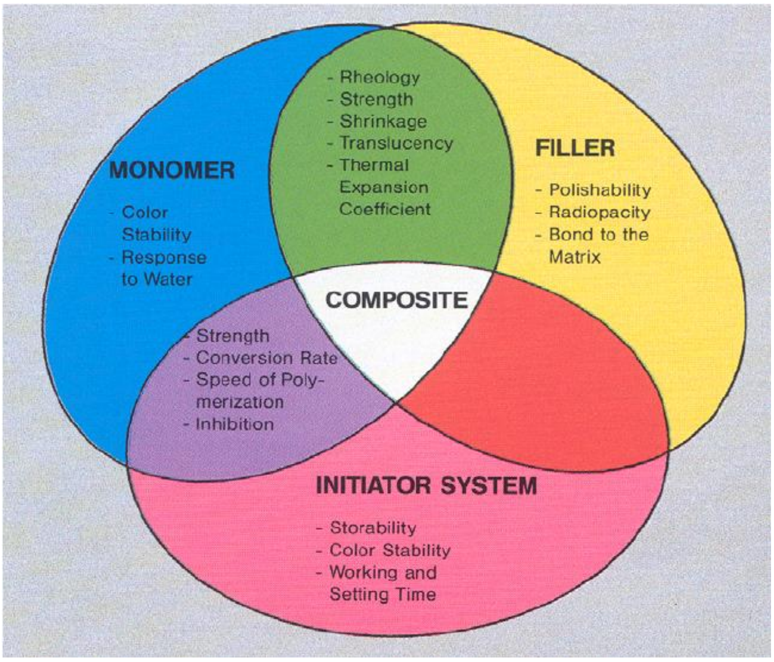

Figure 2. Interaction of the components of a dental polymer composite. [19]

Dental adhesives are used in a thin layer and should constitute the bond among restoration and teeth tissues. There are several classifications of dental adhesives, and the one suitable for this thesis is:

- Acid etching systems. They require acid etching of enamel (30 s) and dentin (15 s) prior to adhesive use.
- Self-etching systems. They can be used on dentin without acid etching. For enamel, it is still recommended 15 s acid etching but not obligatory.
- Universal adhesives. They can be applied with either prior acid etching or without it.

The protocol which comprises acid etching of dentin for 10-15 s and enamel for 30 s is called **total-etch** protocol, and protocol without using etchant (37% phosphoric acid), when acid monomers from the adhesive itself do certain etching is called **self-etch.** Controlled porous dental inserts made of hydroxyapatite are supposed to be treated as dentin to a certain extent as they exhibit pores that may serve as dentinal tubules [14], but the inserts do not contain organic collagen network or water which would make them a similarly challenging bonding substrate as dentin is. After tooth preparation dentin is covered with a smear layer, and the etching protocol removes it, as can be seen in Figure 3.

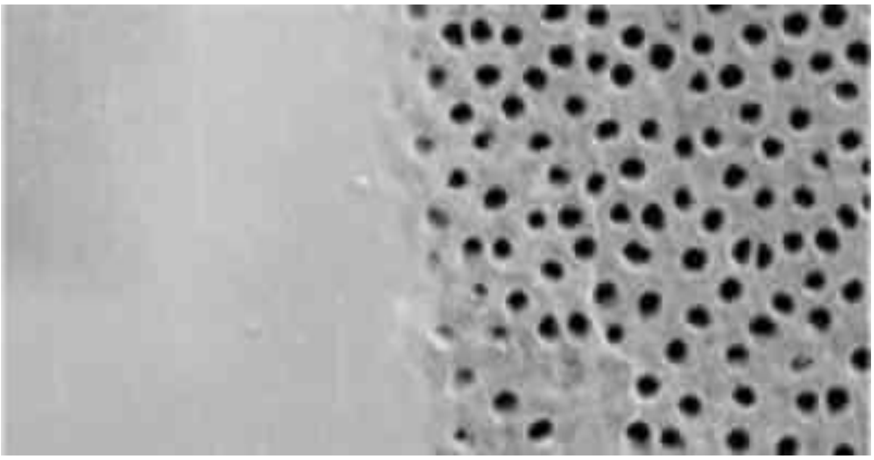

Figure 3. Unetched and etched dentin [20].

Some of the main reasons for composite restoration failure is secondary caries, because of micro-gap formation between the bond and dental tissues and due to polymerization contraction, and also fracture in stress bearing areas due to limited mechanical properties [21]. Large restorations are more susceptible to failure due to fracture [22]. The use of dental inserts stems could improve restoration stability and durability due to minimizing polymerization contraction because the amount of dental composite is reduced, and also due to strengthening the complete restoration with the use of sintered HAp blocks - inserts.

The aim of this dissertation was to investigate the sintering conditions of composite nano-powder based on hydroxyapatite and yttrium-stabilized zirconia (YSZ) in order to optimize microstructure, to increase fracture toughness and shear bond strength (SBS) between the composite inserts and restorative materials, as well as analyse comparatively the microstructure, phase composition, fracture toughness and hardness of the optimized sample with two other types of dental inserts based on HAP. In order to achieve these requirements, two-step sintered HAp inserts, single-step sintered HAp/TCp inserts and single-step sintered composite HAp/YSZ inserts were used in the investigation.

Further, the influence of different clinical protocols on the SBS between the inserts as potential dentin substitutes and commercial restorative materials for potential use with inserts were also investigated.

The results from this study indicate potential application of different sintered monophasic HAp based dental inserts as dentin replacement.

2. Bioceramics

There is a broad range of substances that are used in the construction of medical equipment and every substance can react in some path with the biological environment. A biomaterial is an artificial material to be used in intimate connection with living tissue.

Definition of a biomaterial was given in 1986, at the Consensus Conference of the European Society for Biomaterials, as a “nonviable material used in a medical device, intended to react with biological systems” [23].

Biomaterials engineering includes a wide range of scientific disciplines, such as chemistry, materials engineering, biology, physics, biotechnology, medicine, human genetics, and dentistry. Regardless of rapid advances in fields such as tissue engineering during the last two or three decades, biomaterials are still currently used as implants to replace diseased or weakened tissues. Biomaterials enclose a broad spectrum of materials involving natural such as collagen, chitin, elastin, or artificial, such as metals, ceramics, polymers, or composites, as shown in Figure 4. [24]. One of the most important usages of biomaterials is in the alteration of the hard tissues of the body, like hip joint prostheses, knee, bones from maxillofacial region, etc. Further, the most comprehensive use of biomaterials is also in the replacement of the oral hard tissues, called dentine and enamel. Although many various types of biomaterials have been developed over the past two decades, they still require a great deal of control over their functional properties. For example, materials can degrade significantly in demanding situations such as joint replacements due to erosion and wear (e.g., metals may corrode at a rate of 0.05 mm/year, while polymers can wear out at a rate of 0.1–0.2 mm/year). Ceramics that are utilized for reconstructive purposes as a bone substitute are called “Bioceramics”.

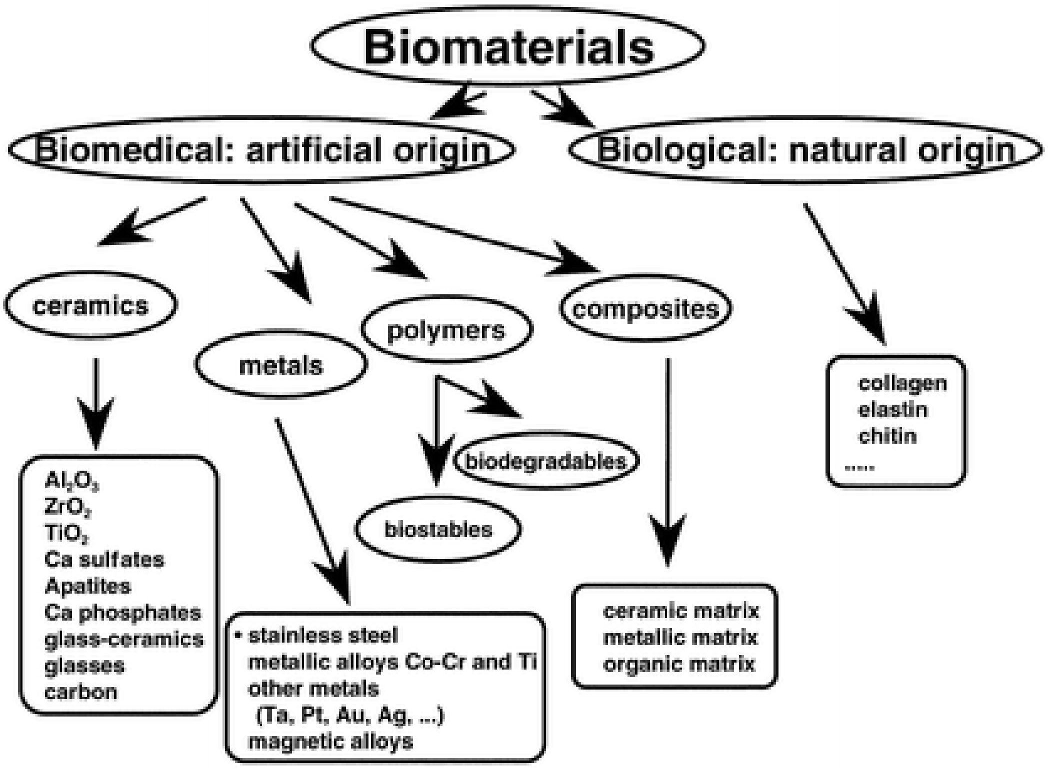

Figure 4. Classification of biomaterials. [24]

Bioceramics are ceramics that are mostly used as a bone replacement in the reconstruction process and represent a subset of biomaterials that accounts for nearly half of global biomaterial use. Besides the facts that are widely used as a material for skeletal rebuilding, bioceramics are often used for dental treatment. Teeth are made from dentine and enamel and these tissues do not have the ability to be naturally reconstructed if they get harmed or destroyed due to dental diseases like caries or trauma. There are millions of people who require dental treatment every year. Also, the request for esthetic tooth-like restorations is growing. Dental materials are one of the fastest-growing applications of bioceramics [25], and ceramics are well suited to satisfy this need.

Ceramics are used in a variety of dental filling materials, including glass fillers in glass ionomer cements and resin composites (Figure 5.) [26] and are also extensively used in the construction of bridges and crowns to restore or replace missing teeth as shown in Figure 6. [27].

Figure 5. 1.) Glass Ionomer Cements for Primary Teeth. 2.) Resin composites. [26]

Figure 6. The construction bridges made of ceramics to restore or replace missing teeth [27].

Bioceramics are primarily focused on the processing of synthetic phases with controlled properties and their long-term application. As a result, we can say that bioceramics are synthetic inorganic phases that could replace the natural tissue with similar properties. In Table 1, the various type of bioceramics used for the production of implants for different applications, are presented [28].

Table 1. Type of ceramic materials for various medical applications [28].

Application	Ceramic materials
Orthopedic load bearing	Alumina, partially stabilized zirconia
Dental orthopedic	Bioactive glasses, glass ceramics, alumina, partially stabilized zirconia
Dental implants	Alumina, hydroxyapatite, bioactive glasses
Temporary bone space fillers	Tricalcium phosphate
Alveolar ridge	Bioactive glass ceramics, alumina
Spinal surgery	Bioactive glass ceramics, hydroxyapatite
Maxillofacial reconstruction	Bioactive glasses, glass ceramics

2.1 Classification of bioceramics

Classification of bioceramics could be based on the type of materials, but classification based on their interaction with the biological environment is the most suitable. The bioactive ceramics are suitable for the character of osteoconduction and the capability of chemical bonding with living bone tissue. In other words, when bioactive ceramics are implanted in living bone, they are incorporated into the bone tissue in accordance with the template of "bonding osteogenesis". The template of their incorporation into the bone tissue is considered similar to contact osteogenesis [29]. When the bioceramic is implanted in the human body, the tissue responds in many ways, depending on the type and material form [30]. It is obvious that foreign substances can not be fully compatible with a living organism. The only materials that are completely identical are those made by the body itself. Synthetic material will create some kind of response from living tissue, also these substances may be identified as foreign and can cause a variety of tissue responses. The mechanism of tissue reaction depends on the tissue response to the implant surface [31]. Table 2 shows four different varieties of bioceramic-tissue interactions [31].

Table 2. Bioceramic-tissue interactions [31].

1. If the material is toxic, the surrounding tissue dies.
2. If the material is nontoxic and biologically passive, it is encapsulated with fibrous tissue or bone.
3. If the material is nontoxic and bioactive, an interfacial bond forms.
4. If the material is nontoxic and dissolves, the surrounding tissue replaces it.

The challenge for the materials scientists is to improve new ceramics that produce the most suitable response that the clinical situation requires. In general, bioceramic is classified as bioactive, bioinert, or bioresorbable based on their interaction with tissue [32].

2.2 Bioinert and bioactive materials

Biomaterials have historically been used to repair diseased or weakened tissues. The first generation of biomaterials was chosen to be as bioinert as possible, reducing the creation of fibrous tissue at the interface with host tissues. Such biomaterials cause damage of surrounding tissues, resulting in fibrous encapsulation of the implant or, in more toxic cases, worse sequelae such as necrosis and implant sequestration. Fibrous encapsulation is a host's defense system that tries to prevent the implant from interacting with the host. Usually, this is a reaction to biomaterials that are moderately irritating. Where an implant is in nearby proximity to bone and if there is a shortage of a fibrous tissue layer, that is, nearby apposition of new bone to the surface of the implant, this is described as osseointegration. [33].

Biologically active materials catalyse a specific biological reaction at the material-tissue interface, such as the formation of biochemical bonds between living tissues and material [34].

Significant developments from first to third generation bioceramics have occurred in the field over the last four decades [35]:

- 1st generation Bioceramics: “bioinert” such as zirconia and alumina.
- 2nd generation Bioceramics: “bioactive” and “bioresorbable” such as bioglass and calcium phosphates (HAp, and β-TCp’s).
- 3rd generation Bioceramics: Porous 2nd generation bioceramics and composites containing biologically active substances such as cells, growth factors, proteins capable of regenerating new tissue.

2.3 Hydroxyapatite

Many experiments have shown that the biological apatite in calcified tissues is often in the range of a few to hundreds of nanometers, with the tiniest building blocks on the nanometer scale [36-40]. During tooth and bone development, nanometer sized apatite crystals grow in a collagen matrix creating self-assembled structures [36-38]. Synthetic nanodimensional and nanocrystalline types of calcium orthophosphates can be constituent components of calcified tissues and imitate the structure of natural bone. Because of their high biocompatibility, they can be used in biomineralization and as biomaterials [41, 42].

Calcium orthophosphate-based biomaterials could be improved using nanotechnology [43]. In 1987 Karch et al. stated that a brittle ceramic with nanodimensional grains could make a large plastic strain of up to 100 % [44]. Furthermore, nanostructured ceramics can be sintered at lower temperatures, reducing the main issues associated with high-temperature sintering. As a result, bioceramics in nanodimensional and nanocrystalline forms represent a promising class of implant formulations for orthopedic and dental application with enhanced biological and biomechanical properties [45, 46].

2.3.1. Apatite in bone

Bones are the most common calcified tissue in mammals and they come in all kinds of sizes and shapes in order to fulfill various functions of protection and mechanical support of the body. The main inorganic component of bone is a biological apatite, which can be characterized as non-stoichiometric, poorly crystalline, and ion substituted calcium deficient hydroxyapatite (CDHA) [47-52] from a material standpoint. Bone can be thought of as a set of distinct levels of seven hierarchical structural units that span the macro-, micro-, and nanoscales (Figure 7.) to fulfill a variety of functions [47, 49,52-54]. Moreover, cells and biological macromolecules interact with all of these levels of bones perpetually.

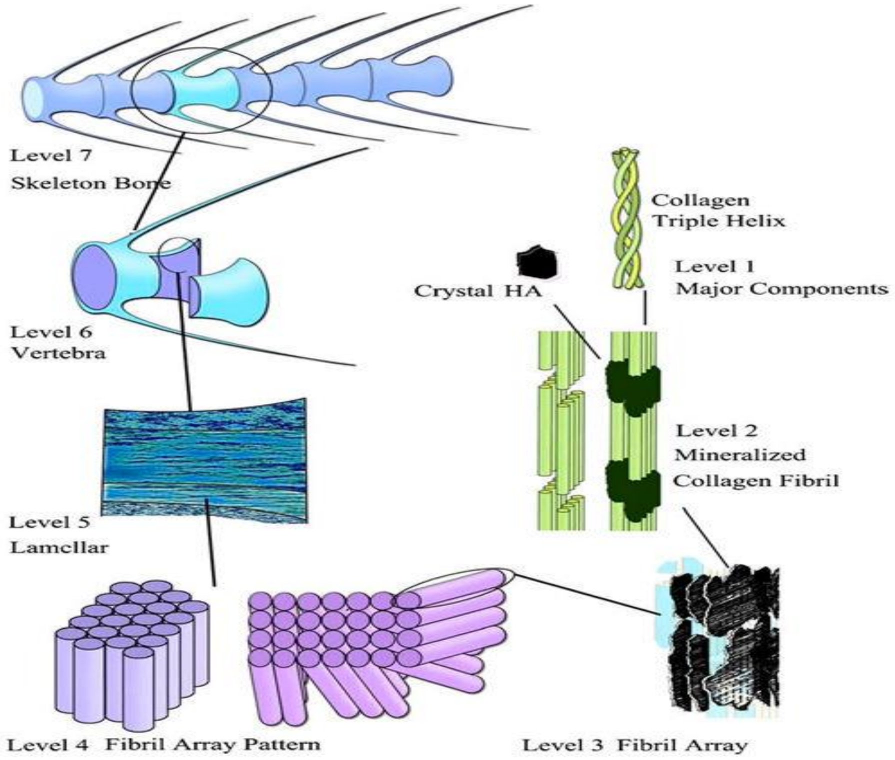

Figure 7. The seven hierarchical levels of organization of the zebrafish skeleton bone (Level 1: Isolated crystals and part of a collagen fibril with the triple helix structure. Level 2: Mineralized collagen fibrils. Level 3: The array of mineralized collagen fibrils with a cross-striation periodicity of nearly 60-70 nm. Level 4: Two fibril array patterns of organization as found in the zebrafish skeleton bone. Level 5: The lamellar structure in one vertebra. Level 6: A vertebra. Level 7: Skeleton bone. Reprinted from Ref. [55])

At the nanostructural level, small plate-like crystals of biological apatite in bone occur inside the discrete spaces inside the collagen fibrils and develop with specified crystalline orientation along the c-axes, which are approximately parallel to the collagen fibrils' long axes [56]. Type I collagen molecules are self-assembled into fibrils with a periodicity of ~ 67 nm and ~ 40 nm holes between the ends of their molecules, into which the apatite nano-sized crystals are sited. A biocomposite of these two components forms mineral fibers. The fibers also may be cross-linked, which offers a highly dynamic system able adjustment through the election of various amino acids to permit various mechanical properties for diverse biomaterial applications [57]. This is the reason why bones are commonly called a fiber-reinforced composite of biological origin, in which solid nanometer-sized inclusions are embedded in a smooth protein matrix [58]. Although biological apatite crystals have different dimensions, they are usually around in the nano-level with values in the ranges of widths of 15–30 nm, lengths of 30–50 nm, and thicknesses of 2–10 nm [59].

It has recently been shown that natural biocomposites exhibit such mechanical structure in which nanometer sizes of particles ensure optimum strength [60,61]. Besides, nanodimensional apatite has another important role in organism. It is a large reservoir of orthophosphate ions and calcium needed for a broad range of metabolic functions, which give or consume orthophosphate ions and calcium through a so-called "remodeling" process because of the continuous resorption and formation of nanodimensional apatite by osteoblasts and osteoclasts in a delicate balance [47, 49].

2.3.2 Apatite in teeth

Besides the bone, teeth are another calcified organ in vertebrates that is made up of calcium orthophosphate. Teeth, having different structure compared with bone, are made of two different biominerals: enamel and dentin [62,63]. Up to 98 percent of biological apatite, 1 % of bioorganic compounds, and up to 2 % of water are present in dental enamel. Rod-like apatite crystals measuring 25-100 nm with an undefined length of 100 nm to 100 μm or longer along the c-axis [64-67] represent standard rods in enamel, presented in Figure 8. On the other hand, it has been discovered that the apatite crystals in enamel have natural sub-domains or subunits with distinct chemical properties [67,68].

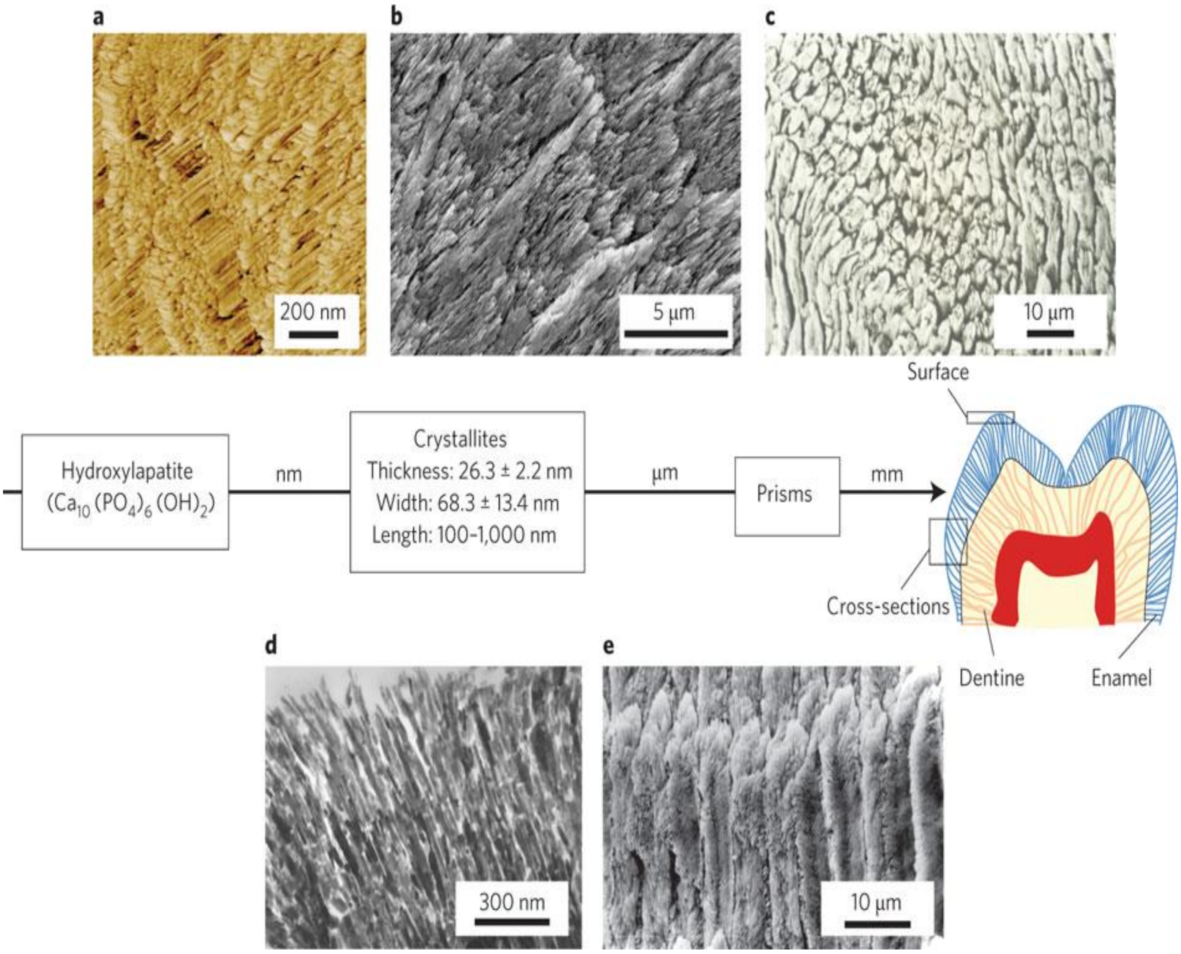

Figure 8. Apatite in teeth enamel. The enamel is composed of three-dimensionally organized nanosized hydroxyapatite crystallites (a,b,d) that are arranged into micrometer-sized prisms (c,e). a, Atomic force microscope and b,c, scanning electron microscope images of the enamel surface. d, Transmission electron microscope and e, scanning electron microscope images of a cross-section of the enamel [67].

Dentin (Figure 9) contains ~ 50 vol % of biological apatite, ~ 30 vol % of bioorganic compounds and ~ 20 vol % of water. In dentin, the nanodimensional building blocks (~ 25 nm width, ~ 4 nm thickness and ~ 35 nm length) of biological apatite are smaller than those of enamel [69].

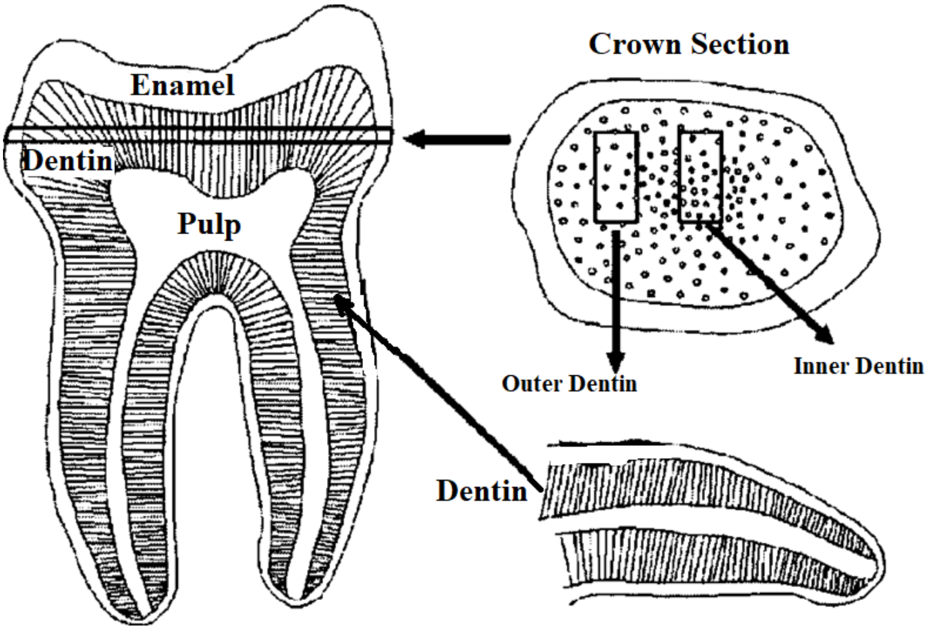

Figure 9. An Illustration of the location of human dentin [69].

2.4 Synthetic hydroxyapatite

For scientists, research in novel biomaterials in order to improve human life, quality remains a major priority. They began implanting artificial or man-made materials in the body centuries earlier to help and preserve organ or tissue function. One of the most important developments in orthopedics over the past 40 years has been the use of hydroxyapatite based materials to replace, regenerate and restore bones.

Biocompatible ceramics are mostly based on calcium phosphates (such as HAp and β-TCp), bioglass, and biphasic calcium phosphates. Originally used as a biocompatible alternative to mineral bone implants, due to its superior performance, it has now become one of the most used biomaterials for orthopaedic clinical applications.

HAp is the most utilized for orthopedic since it is the dominant component of human bone mineral and teeth enamel and dentin. As appeared in Figure 10 HAp has been utilized clinically within the shape of powders, cements, granules, dense and porous blocks, coatings, biphasic and composites [70].

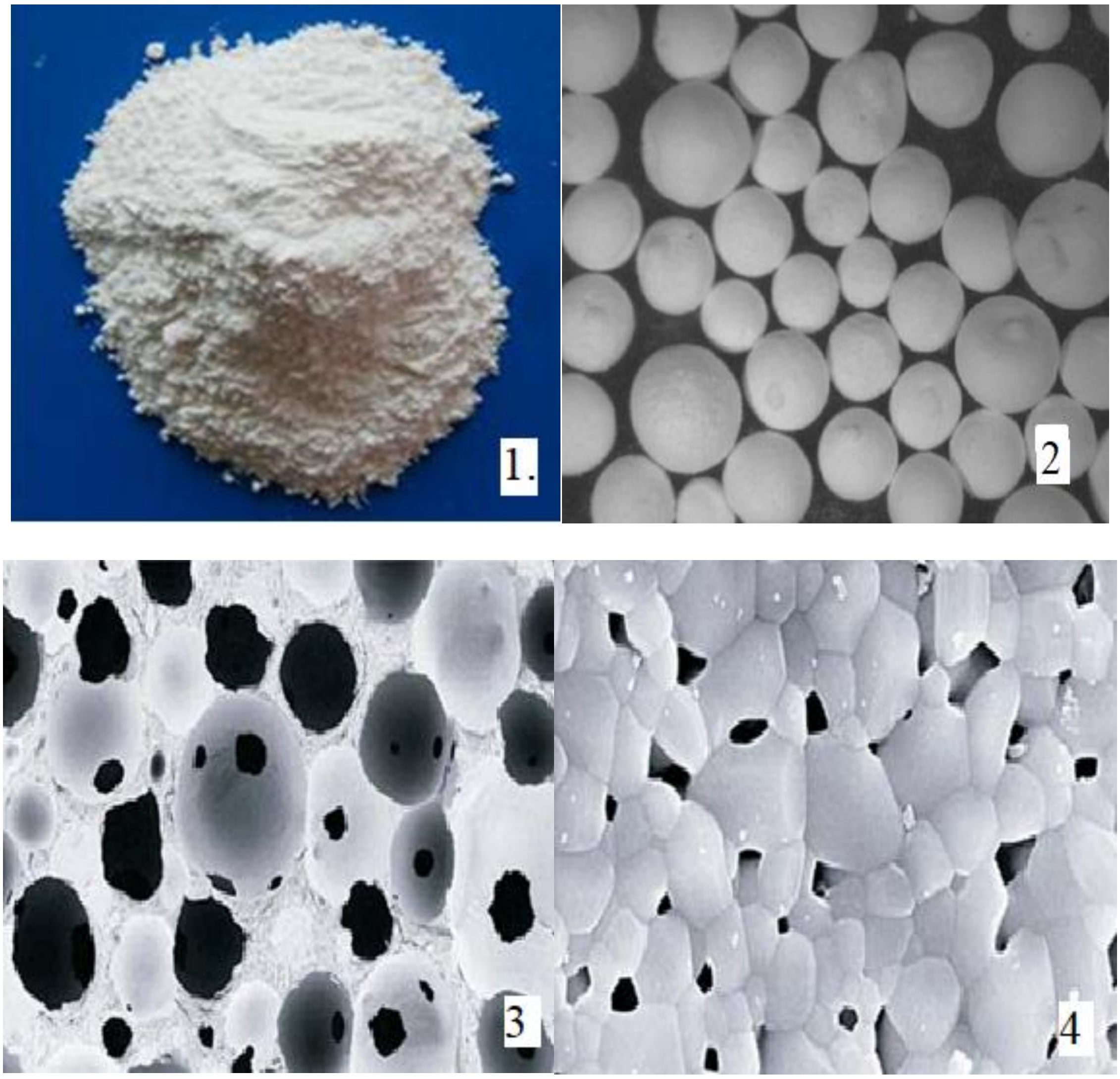

Figure 10. 1.) HAp powder, 2.) Granules of HAp, 3.) Porous HAp and Dense HAp [71].

Biocompatibility, lack of an immunogenic reaction, and gradual resorption are some of the advantages of HAp as a choice for bone repair.

While the bioinert bioceramics influenced the undesired fibrous encapsulation, which resulted in problems with implant fixation and complications, the bioactive ceramics such as HAp or bioglass, were able to form direct bonds with native tissue and in that way enhance the material's bonding and fixation. Ion-exchange occurred in interaction of bioactive materials with the encompassing tissue. Implanted bioactive materials release chemicals in the form of ionic dissolution products at controlled rates to stimulate native cells, which then triggers a cascade of biological reactions that result in new tissue growth [72]. On the surface of the bioactive implants, a biologically active carbonate apatite coating forms, which is chemically similar to the mineral process of bone [73].

There are several natural sources for HAp which include human bone, coral [74,75], bovine bone [76,77], fish bone [78], chitosan [79,80], and egg shell [81], among others. Though, where adequate preparation is not practiced to extract all protein, transfer of diseases is a problem with natural HAp [82]. Synthetic HAp is more widely used because it can be easily synthesised and does not spread disease.

Synthetic HAp is frequently stoichiometric with a chemical formula of $Ca_{10}(PO_4)_6(OH)_2$ and has an atomic Ca/P ratio of 1.67, which could, in general, vary from 1.5 to 1.67. Crystal structure of HAp is shown in Figure 11. HAp is highly crystalline, with lattice parameters of (a= 0:95 nm and c = 0:68 nm) and hexagonal symmetry (S.G. P63/m) with a preferred orientation along the c axis [83]. The needle-like morphology of HAp crystals is normal.

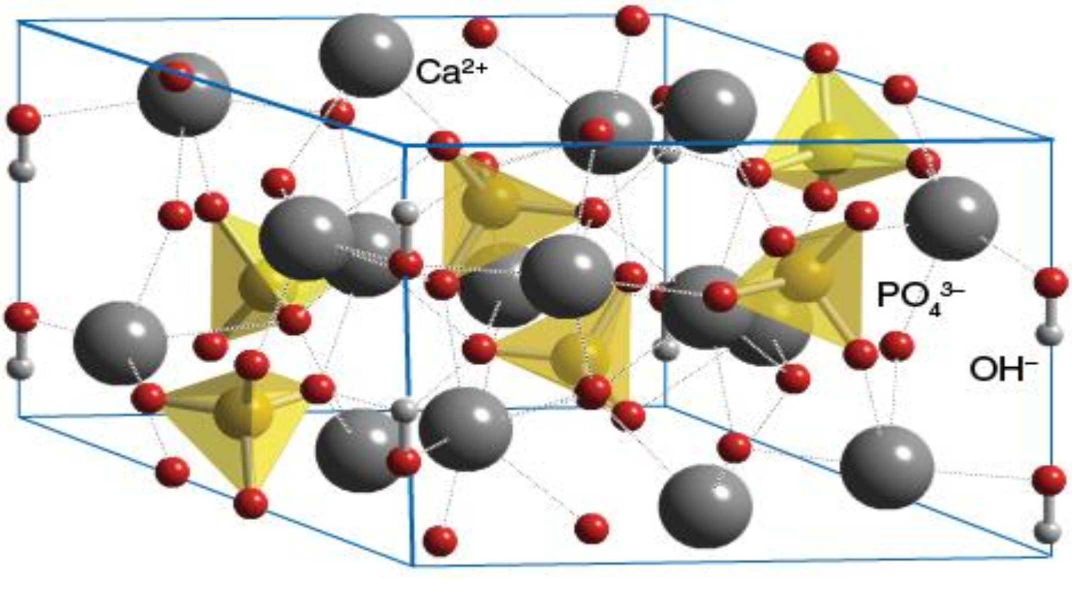

Figure 11. Hydroxyapatite crystal structure [84].

Synthetic HAp could be similar to that of natural bone, but there are some variations in chemical composition, structure and stoichiometry. The bone that consists of biological apatite, is characterized by being non-stoichiometric, amorphous, ion-substituted, carbonized, with lack of calcium. HAp exists in the form of nanocrystals with dimensions of 4 x 50 x 50 nm in which the nanocrystals are incorporated into the matrix of organic collagen fibers comprising 90 % of the protein content [85].

The chemical formula for the human bone mineral is ion substituted HAp: $Ca_{8.3}(PO_4)_{4.3}(HPO_4,CO_3)_{1.7}(OH,CO_3)_{0.3}$ [85,86]. When CO_3^{2-} and HPO_4^{2-} ions are incorporated in the structure, the Ca/P ratio varies between 1.50 to 1.70 depending on the age and bone site [85]. The calcium/phosphorus ratio rises as the bones age, which means that the amounts of carbonates also rise.

Besides the fact that HAp has good biocompatibility, due to the relatively poor mechanical properties, specifically brittleness, impact resistance, and low tensile strength, HAp usually has restricted use in load-bearing applications [87]. As a consequence, HAp is usually used in non-critical load-bearing applications such as orthopaedic bone grafting, the ossicles of the middle ear, etc.

2.4.1 Synthesis methods for HAp powders

The properties and features of the starting HAp powder influence the processing parameters and properties of obtained HAp ceramics. By controlling the homogeneity and stoichiometry, phase composition, particle shape and size distribution, grain size, crystallinity, and the agglomeration of the powder, the properties of the obtained final product could be controlled [88], since these powders are further processed into HAp implants by mixing it with polymers into biocomposites, applied as coatings for implants, or sintered into porous or dense bodies [88].

HAp has been synthesized using a variety of methods, including precipitation, hydrothermal, sol-gel, electrodeposition, emulsion, biomimetic deposition, solid state reaction methods [89-98], etc. Table 3 provides an outline of the advantages and disadvantages of some mentioned methods. [99]

Table 3. Advantages and disadvantages of some of the synthesis methods for HAp [100].

Categories	Advantages	Disadvantages	References
Solid-state	Easy to perform; inexpensive; stoichiometric HAp formed	Needs high sintering temperature; long treatment times	[98]; [100]; [101]; [102]
Precipitation	Can produce nano HAp particles; industrial production possible; water is the only by-product	Difficulty to obtain stoichiometric HAp; need high pH to prevent formation of Ca deficient HAp; need high sintering temperature to form crystalline HAp; product very sensitive to reaction conditions such as pH, stirring rate, drying temperature, etc.	[103]; [104]
Sol-gel	Can produce nano-HAp particles; homogenous: molecular mixing occurs; low processing temperature's required; increased control over phase purity	Difficulty to hydrolyse phosphate; expensive starting chemicals	[105]; [106]; [107]
Hydrothermal	Well crystallised and homogenous powder; nano-HAp has been prepared	Agglomeration of HAp powders is common; high pressures required for processing.	[108-111]

2.4.2 Mechanical properties

Calcium phosphates (CaPs) are fragile due to their high strength ionic bonds [112]. The mechanical properties of CaPs depend on crystallinity, grain boundary, and size, stoichiometry and porosity. The decreases in grain size within the microstructure results in increase in mechanical strength. According to the literature, HAp ceramics have fracture toughness of around 1.2 $\mathrm{MPa\cdot m^{1/2}}$ [113]. It was found that the fracture toughness of hot pressed HAp with micrometric grain sizes varies with grain size [114]. Tensile strength, compressive strength and bending strength of dense HAp ceramics are in the range of 38–300 MPa, 120–900 MPa and 38–250 MPa, respectively. Dense bioceramics have Young's modulus of 35–120 GPa, which is similar to calcified tissues. Dense HAp has a mechanical resistance three times higher that of natural human bone [115]. Dense HAp has a Vickers hardness of 3–7 GPa and a Poisson's ratio similar to natural bone. In the temperature range of 1000–1100 °C, a superplastic deformation [89] with grain boundary sliding has been recorded. It has also been reported that the polymeric coating of HAp ceramics increases the mechanical properties of HAp [116]. Further, introduction of reinforcing agents in forms such as platelets, fibers and whiskers could also improve some mechanical properties [117–119].

2.4.3. Porosity

Another important factor that contributes to good mechanical fixation and biochemical bonding between bioceramics and bones is porosity [120,121]. The surface and space for cell attachment, tissue proliferation and bone ingrowth are provided by open porosity, which is directly connected to bone formation. Pore interconnection enables migration of cells and development of blood vessels needed for bone tissue remodeling [120–122]. Porous HAp materials could be produced using various methods, such as ceramic foaming, sintering with porogens, starch consolidation, microwave processing, slip casting and electrophoretic deposition [123]. Interconnecting macro-pores size bigger than 100 μm could be formed by the gaseous porogen [124], or by using water-filled microemulsion or a combination of slurry dipping and electrospraying to produce HAp foams as potential matrices [125,126].

It is very important to emphasize that high porosity promotes bone formation, while pore volumes greater than 50% can result in loss of biomaterial mechanical properties, which means that the balance between porosity and mechanical properties should be established [127].

3. Zirconia Ceramics

3.1 Structure of ZrO_2 Ceramics

Zirconia is an oxide that has corrosion resistance, high hardness and high tensile strength. It is not present in nature as a pure oxide. The minerals zirconate (ZrO_2-SiO_2, $ZrSiO_4$) and baddeleyite (ZrO_2) are the primary sources of zirconia. The zirconia content of baddeleyite ranges from 96.5 to 98.5 Wt% [128]. This mineral is also source in obtaining zirconium metal and its compounds.

Zirconium is the transition element that reacts with oxygen to produce zirconium dioxide (ZrO_2) at 400 ^oC, [129]. Due to the excellent electrical, thermal, optical and mechanical properties, zirconia has received special attention in a wide variety of fields [130-133]. It has a high melting point, high elastic modulus, low friction coefficient, high hardness and stability against aggressive chemicals, etc. [129-132]. Some of these characteristics influenced the interest of the ZrO_2 as a dental material.

For the first time, in 1969, zirconium oxide was used in a medical application for orthopedics. It was suggested as a new material for hip head replacement instead of titanium or alumina prostheses [134]. Such structural ceramics, based on ceramics such alumina or zirconia, have been improved and became increasingly popular in dentistry, with the purpose of replacing the metallic dental prostheses. Because of its biological, mechanical, and optical properties, zirconia became a promising material among dental ceramics, especially its use in CAD/CAM technology for producing various types of prosthetic devices.

Zirconia structures used for dental purposes are manufactured using CAD-CAM processes in two possible ways. One method mills the completely sintered block of zirconia without any distortion (shrinkage) to the final structure. The drawbacks are the large wear of the grinding tools and the generating of flaws created during machining, which could reduce the mechanical properties of the samples [135,136]. The second method is based on machining a green body-pre-sintered block, which ensures mechanical properties and final dimension of the specimen after sintering, where the resulting shrinkage can be compensated at the designing level [137,138]. CAD-CAM methods have three main steps: acquisition of digital data, designing, and computer processing and manufacturing of the zirconia structure with enough accuracy and dyeing to improve esthetics to be used in dentistry [139-146]. It is commonly used in dental applications for manufacturing endodontic posts, implant abutments, bridges, crowns as well as to make esthetic orthodontic brackets [147].

3.2 Phases transformation of zirconia

The spatial organization of the atoms in zirconia is characterized by three polymorphic crystallographic structures. Its three phases are characterized by specific geometry, atom arrangement, and dimensional parameters in crystal structure: monoclinic, tetragonal, and cubic. At room temperature, pure zirconia has a monoclinic structure that is stable up to 1170 °C. Tetragonal zirconia is formed between this temperature and 2370 °C, while cubic zirconia is formed at temperatures above 2370 °C (Figure 12 a,b,c). Depending on process parameters, and cooling process, the tetragonal phase transforms to monoclinic at about 970 °C with a big volume alteration (3-5%). This volume change is enough to pass the fracture and elastic limits, resulting in cracks and flaws in ceramics [148].

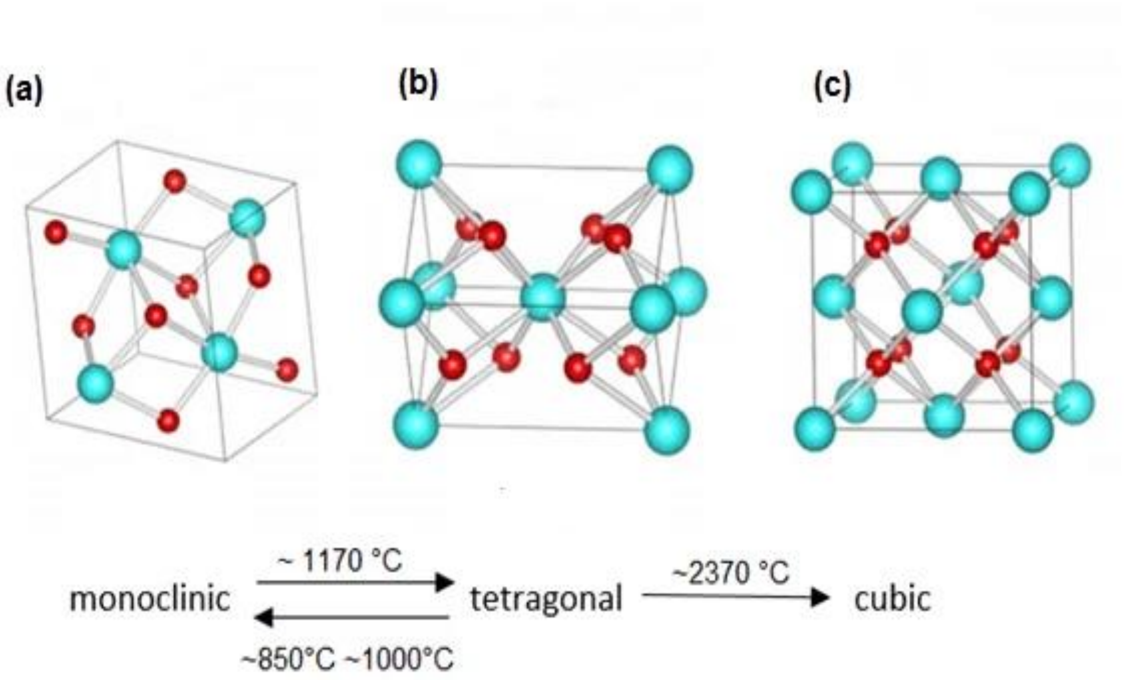

Figure 12. Crystal structure of (a) monoclinic, (b) tetragonal, (c) and cubic zirconia. [148].

The control of phase transformation of the tetragonal to monoclinic phase is used to enhance the mechanical properties of zirconia. The adverse transmission, the monoclinic to tetragonal transformation occurs at approximately 1170 °C, while the tetragonal to monoclinic transformation occurs during cooling between 850 and 1000 °C, depending on the strain energy. Consequently, the production of pure zirconia components is not possible due to automatic failure. The addition of stabilizing oxides is critical because it allows that tetragonal form could be maintained at room temperature [148].

Different oxides may be added to zirconia to stabilize it, such as calcium oxide (CaO), yttrium oxide (Y_2O_3), or magnesium oxide (MgO), causing the tetragonal form to exist at room temperature after sintering. The addition of different quantities of stabilizers allows the creation of partially or completely stabilized zirconia, which, when combined with process modifications, can result in ceramics with outstanding properties including high hardness, high flexural strength, and fracture toughness, strong conductivity ions and excellent chemical resistance [128]. A completely stabilized zirconia is obtained by adding sufficient quantities of stabilizing oxides, such as 16 mol% magnesia (MgO), 8 mol% yttria (Y_2O_3), or 16 mol% of limestone (CaO).

The transformation of tetragonal zirconia into monoclinic is a phenomenon affected by temperature, particle size, steam, the concentration of stabilizing oxides, and also by micro-and macrostructure of the material. Since the transformation to the monoclinic phase is not achievable under 0.2 micrometers, the critical particle size for partially stable zirconia to be preserved in the tetragonal state at room temperature is 0.2 to 1 micrometer (for compositions ranging from 2% to 3 mol% yttria) [149].

3.2.1 Monoclinic zirconia

In monoclinic phase of zirconia, known as baddeleyite, the oxygen ions occupying tetrahedral interstices have a coordination number of seven for Zr^{4+} ions, with an average space of 2.07Å between the zirconia ion and three of the seven oxygen ions. Since the average distance between the zirconium ion and four oxygen ions is 2.21A, in the structure, one of the angles (134.3°) differs significantly from the tetrahedral value (109.5°). Therefore, the structure of the oxygen ion is not planar and a curve occurs in the plane of the four oxygens, and the plane of three oxygens is erratic [148].

3.2.2 Tetragonal zirconia

The tetragonal phase of zirconia takes the shape of a straight prism with rectangular sides. Ions Zr^{4+} have a coordination number of eight, where the form once again appears distorted due to the reality that four oxygen ions are at a space of 2.065A in the shape of a tetrahedron plan, and four others are at a space of 2.455A in a tetrahedron that is elongated and rotated 90° [150].

3.2.3 Cubic zirconia

Cubic zirconia is described by a plain cubic lattice of eight oxygen ions encircled by cubic arranging of cations recognized as fluorite, i.e. the oxygens are found in the tetrahedral interstices of a cubic lattice (CFC) of cations [150].

3.3 Transformation Toughening of Zirconia

Transformation-toughened ceramics constitute the main family of flaw tolerant and tough ceramics. These enhanced properties are usually observed at room temperature. Zirconia is one of the most commonly used ceramics whose property has been based on utilized on the phenomena of transformation toughening. Geller and Yavorsky (1945) investigated the effect of transformation of certain zirconia grains on the thermal expansion of zirconia ceramic, and it was discovered that partially stabilized zirconia had advantages over completely stabilized zirconia [151].

The tetragonal phase can be metastable and if the metastable tetragonal phase is present in appropriate amounts, then the applied stress, magnified by the stress concentration at a crack edge, may allow and initiate the transformation of metastable tetragonal phase to monoclinic, resulting in linked volume expansion. This phase transformation and volume changes will then compress the crack, slowing its development and improving fracture toughness (Figure 13). This technique is recognized as transformation toughening, and it greatly extends the reliability and working life of the products made by stabilized zirconia [152,153].

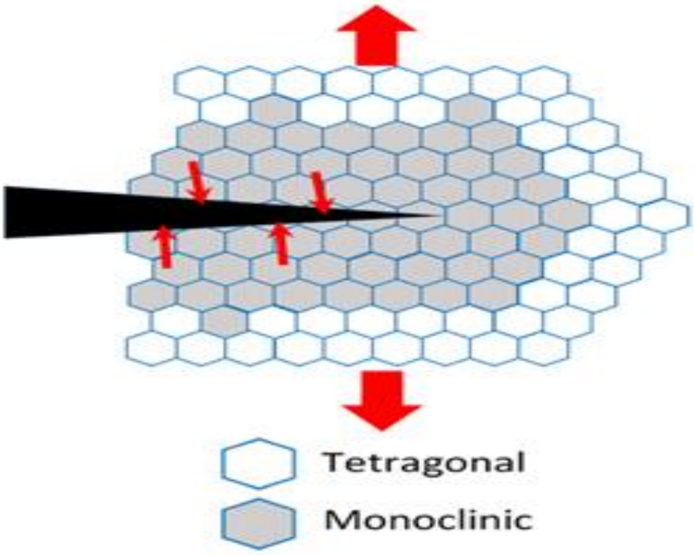

Figure 13. Transformation toughening mechanism in zirconia. [154]

Three toughening mechanisms could be involved in zirconia and in dual phase oxides containing zirconia, such as: stress induced transformation toughening, the evolution of compressive surface layers as a result of transformation caused by surface stress and toughening by micro cracking.

3.4 Dispersion-toughened ceramics

In dispersion-toughened ceramics, zirconia particles are dispersed in matrix of some other materials. ZrO_2-toughened mullite or ZrO_2-toughened alumina are two examples of dispersion-toughened materials that have been named ZTM and ZTA, respectively [154]. The tetragonal phase's stability at room temperature should be utilized by dopants, controlled particle morphology, particle size, and location. In ZTA, for example, particles larger than the critical size will convert into monoclinic phase upon cooling to room temperature [155]. As an example, the commercial dental materials with dispersion-toughened ceramic is In-Ceram Zirconia (Vita Zahnfabrik) which is composite of 30 % glass and 70 % polycrystalline ceramic consisting of Al_2O_3: ZrO_2 in a vol.% ratio of 70:30 [156].

There is ample scientific evidence on toughening of calcium phosphates ceramic. For example, biphasic calcium phosphate (BCP), comprising 70 wt% of beta tricalcium phosphate and 30 wt% of hydroxyapatites, was mixed with different amounts of 3 mol% yttria-stabilized zirconia (YSZ) and sintered at 1200 °C to produce toughened bone substitutes. The obtained fracture toughness value was approximately two times higher than that of the original BCP. This was explained by the grain bridging of YSZ particles during crack growth resistance, formation of microcracks on the tip of the larger cracks, absorbing crack extension energy due to the volume expansion during YSZ tetragonal-monoclinic transformation and crack deflection by the presence of YSZ particles [157].

ZrO_2-hydroxyapatite composites obtained by spark plasma sintering (SPS) have inter and intra particle porosities. The porosity level in the compacts (<3–42%) varied with sintering pressure (4.5–17.3 MPa), and apparently contributed to the increase in indentation fracture toughness. It was found that powders and SPS compacts are composed of HAp, tricalcium phosphate (TCP), zirconia (t- and c-ZrO_2) and $CaZrO_3$. It was found that the overall improvement to the fracture toughness can be attributed to a combination of several toughening mechanisms. First, the ZrO_2 nano-particles, which are distributed both in the matrix and in the shell of the hollow structures, would have contributed to an increase in the overall fracture strength of the composite. Some amounts of crack deflection and shielding would also have been in operation due to the presence of these harder and tougher (ZrO_2) particles increasing the overall toughness of the compacts [9].

In order to improve the mechanical and cytocompatibility properties of hydroxyapatite for medical applications, numerous investigators have proposed combining HAp with high strength materials, specifically zirconia. It was found that sintering at lower temperatures resulted in smaller nanometer grain sizes of the composites possessed with increased surface roughness and a more stable HAp phase. It was suggested to optimize osteoblast adhesion on HAp and partially stabilized zirconia composites for orthopedic applications, by use of low sintering temperatures and low amounts of zirconia [158].

3.5 The types of zirconia used in dentistry

There are three types of zirconia already used in dentistry. Besides the fact that are chemically similar, they have different physical properties such as density, porosity, purity and mechanical properties, which may be important for clinical application. One of these materials is completely sintered zirconia obtained using hot isostatic pressing, also known as HIP zirconia. The sintering method uses pressures at elevated temperatures in order to maximize the density of the ceramic materials. Partially sintered zirconia (PSZ) is another type of ceramics, and non-sintered or "green state" zirconia is the third type [159]. Blocks of these types of materials are manufactured by using a spray-dried zirconia powder that is then isostatically pressed and incompletely sintered. Such “softer” ceramics are easy to machine in desired form comparable to HIP zirconia. After forming, the zirconia is sintered fully in an oven at temperatures ranging from l350 °C to 1500 °C to achieve its final density, form, physical and mechanical properties [160].

Zirconia based fixed partial dentures (FPD’s) have a broader range of applications than other ceramics because they can be utilized on molars, they allow the development of structures resistant to chewing stresses on posterior teeth [161]. Zirconia restorations can be indicated for FPD’s supported by teeth or by implants, although some manufacturers suggest them for full arch restorations, five unit FPD’s are reported to be the maximum possible [162]. Restoration made of zirconia must have chamfer and rounded edges finish lines with at least 1.5 mm occlusal and incisal width, and 1 mm axial width with 4 to 6^o taper of zirconia restorations are recommended [163].

3.5.1 Zirconia for implants and abutments

The relationship between zirconium oxide core and veneer ceramic is not well understood. One of the worst aspects of these restorations is the core-veneer interface, which can lead to ceramic chipping or cracking [164]. Various factors may affect veneer cracking as variations in thermal expansion coefficients between firing shrinkage of ceramic, core and ceramic, poor wetting by veneering core, defects on veneering. Special ceramics for zirconia are now being produced in order to reduce this unfavourable feature, but more assessment of zirconia core veneer bond must be performed [165]. The use of tougher veneer ceramics with strong zirconia bond strength can minimize the risk of chipping and delamination while in use. The liner material must only be utilized with some layering veneers but not in combination with pressable veneers as it will result in the weakening of the microtensile bond strength [165]. CAD/CAM zirconia dental frameworks can be produced according to two various techniques: hard machining of fully sintered blanks or soft machining of pre sintered blanks [166-168]. Frameworks can also be prepared by slipcasting technique as with Inceram zirconia [169,170].

Zirconia implants are a relatively new concept [171]. Because of its high fracture resistance comparative to alumina and other dental ceramics, zirconia has been utilized in dental implant abutments [172]. Zirconia has a high affinity for bone tissue, and bone/

implant interface, comparable to that seen around titanium dental implants [173-176]. Zirconia abutments give recent possibilities for implant restorations and provide enough stabilization to sustain implant-retained reconstructions especially in the incisor and premolar regions [175]. In areas where gingival tissue height is extremely low, zirconia abutments are recommended [175].

The mechanical properties of zirconia can deteriorate with age. Wetness exposure and mechanical stresses are basic to quicken this process [177]. Although ageing decreases mechanical features of zirconia, resistance values reduce to clinically agreeable values [178]. Further assessments are necessary because the long-term behaviour of zirconia has yet to be investigated. Furthermore, the relationship between ZrO_2 ageing and long-term loading must be assessed [156].

4. Dental inserts

Various calcium phosphates can be utilized, in dental practice as coatings and thin films on the surface of metal implants, in the form of bioactive cements, for pulp capping as well as fillers in dental composites and adhesives [179-183]. More recently, it has been investigated as a dental insert to repair large cavities [13,14,15].

One of the most researched calcium phosphates for use in the dental field is hydroxyapatite (HAp), which is the prime inorganic constituent of teeth and bones and is often followed by more bioactive calcium phosphates or reinforced with some stronger nanosized particles such as alumina or stabilized zirconia [9,184].

The aim of the Lezaja et al.'s work was to determine the shear bond strength (SBS) between synthesized controlled porous hydroxyapatite (HAP) inserts and restorative materials, as well as the dimensional changes of insert-containing restorations during the curing process. The null hypotheses were that (1) there is no difference in SBS to HAP inserts between restorative products, and (2) there is no difference in shrinkage strains and displacements between groups with and without HAp inserts. Spherically agglomerated nanosized HAp powder was hydrothermally synthesised. The synthesised HAp powder was isostatically pressed at 400 MPa at 25°C for 30 seconds, yielding uniform cylindrical samples 8 mm in diameter and 2 mm thick. A total of 0.18 g of powder was used to make each specimen. Finally, the inserts were sintered at 1200°C for 2 hours at a rate of 20°C/min. HAp inserts have been shown to bind well to dental composites and to minimise polymerization shrinkage in insert-containing restorations in tests. Significant variations in SBS, as well as disparities in volumetric shrinkage and displacements between restorations with and without HAp inserts, were established, therefore, rejecting the null hypotheses. Final thoughts the ‘total-etch' solution is preferred for adhesive bonding resin-based composites to synthetic, controlled porous HAp inserts. Also for an adhesive device comprising functional monomers capable of chemical bonding with HAp, micromechanical interlocking is a significant adhesion mechanism. In comparison to a flowable composite or a resin-modified glass-ionomer, a universal composite is a safer choice for bonding HAp inserts to dentin. HAp inserts decreased polymerization shrinkage in insert-containing restorations and may have acted as a key stress reducer. HAp inserts could be used as a dentin substitute material when mixed with composites or glass ionomers. Prefabricated HAp inserts, if proven to be viable for therapeutic use, may reduce clinical working time in large cavities by restoring the majority of the dentin [14].

HAp as a logical dentin replacement, is for many reasons a favourable material for the processing of dental inserts as restorative mega „filler“ for a main and central part of dentin (Figure 14). Aside from the similar to human dentin, the benefits of HAp based inserts compared to other ceramic materials include the possibility of chemical interaction with functional monomer groups of commercial adhesives and bonding with resin-based commercial composites or glass-ionomers, which can contribute to suitable bond strength values in general between composite materials and insert.

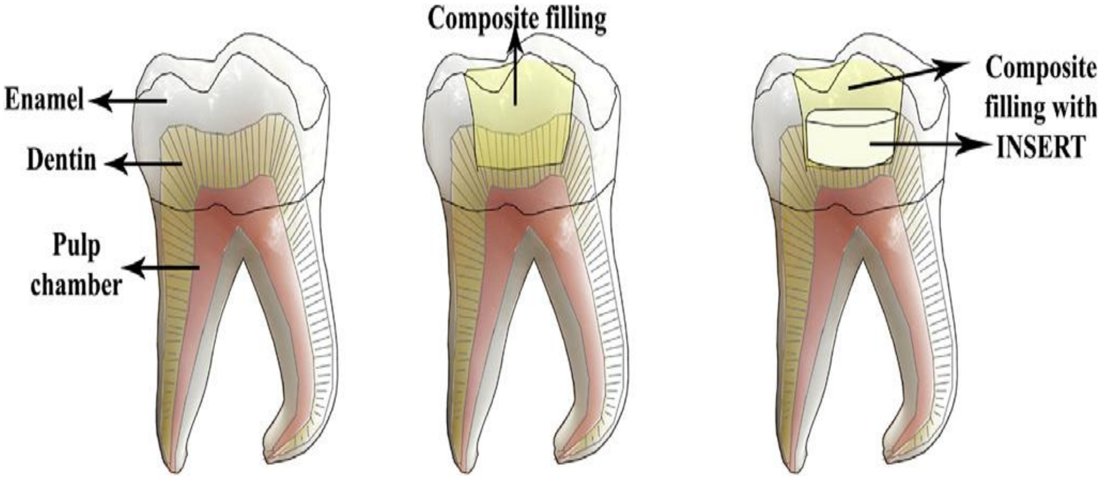

Figure 14. Schematic illustration of dental inserts used in restorative dentistry. [184]

Mechanical properties of bioceramic inserts, phase composition, and microstructure, depend on the properties of starting HAp powder (Ca/P ratio, size, and shape of primary particles, pore size distribution, level of their agglomeration, etc.), conditions and type of pressing through forming of green inserts and used sintering technique and sintering parameters (number of steps, heating rate, reached temperature, and time of final step, etc.) [185-187].

According to previously reported findings, two various clinical methods, „self-etch“ and „total-etch“ may be utilized in order to allow the application of adhesives to sintered HAp-based inserts, whereby the shear bond strength (SBS) values of 12.2 ± 2.1 MPa for the „total-etch“ approach surpassed those for the „self-etch“ approach (8.2 ± 1.6 MPa) [14]. Low values of fracture toughness restrict the utilization of HAp bioceramic implants in some cases, particularly in regions where fracture toughness must be comparable to surrounding natural hard tissue whose damaged part requires to be replaced [188]. Within the case of human dentin, fracture toughness was found to be in the range of 1.13 – 2.02 MPam$^{1/2}$ [189], and generally comparable mechanical properties of insert materials, and fracture toughness in that range, may be a reasonable prerequisite for mechanics of restored teeth.

4.1 Current state in the field of dental inserts

The purpose of Donly et al.'s study was to evaluate changes of internal tooth stress created by placement and polymerization of a composite resin with and without addition of dental inserts made of glass. Six different samples and techniques were used for tooth regeneration with a posterior composite resin after making a mesio-occluso-distal (MOD) preparation in each of the 12 permanent molars. I-polymerization as a single unit; II-polymerization as a single unit with glass inserts; III polymerization in gingival-occlusal increments; IV-polymerization in gingivo-occlusal increments with glass inserts; V-polymerization in bucco-lingual increments; VI- polymerization in gingival increments with glass inserts, then bucco-lingual increments; VII- polymerization in gingival. Scheffj's test shows that composite resin placement and polymerization in bucco-lingual increments (V) resulted in significantly decreased cuspal deflection compared to polymerization as one complete unit, with or without glass inserts (I and II), and gingival-occlusal increments (III). Placement and polymerization in a gingival increment with glass inserts, then bucco-lingual increments (VI), also created significantly less internal deflection than polymerization as one complete unit, with or without glass inserts (I and II), and gingivo-occlusal increments (III). The results have shown that the applied method that created the greatest amount of strain was the placement and polymerization of the complete composite resin due to complete unit polymerization which has the largest volume of composite when polymerized. In such a case, composite resin occupied the entire preparation and pulled the buccal and lingual cusps internally through polymerization-shrinkage contraction forces. Dental inserts are grown for both reasons, to minimize polymerization contraction because the amount of dental composite used is reduced, and to if possible strengthen complete restoration. Bucco-lingual incremental placement and polymerization create the least polymerization shrinkage and stress [190].

Marjanovic et al. (2018) aimed to compare the optical properties (colour and translucency) of resin-based composites and aesthetically unfavourable dentin restoratives in a "sandwich" reconstruction. The EverX Posterior (GC), Biodentine (Septodont), experimental hydroxyapatite (HAp), and conventional composites (Gradia Direct Posterior, GC; Filtek Z250 and Filtek Z500, 3M ESPE) were used to make cylindrical ‘dentin' specimens (8 mm in diameter and 2 mm wide, N = 5/group). For covering dentin restoratives with undesirable aesthetics, a 2 mm thick coating of universal microhybrid or nanohybrid composite is advised, resulting in a final ‘sandwich' restoration that is aesthetically equivalent to a traditional, mono-composite control restoration. Layer thickness had a big impact on translucency parameter (TP), while shadow and layer thickness of the capping composite had a big impact on Color (ΔE). HAp and Biodentine had a lower TP and a higher ΔE (difference from "ideal white") than composites. EverX composite groups had higher TP than equivalent test groups of the same hue and thickness. The TP of composites combined with Biodentine or HAp was less than 2, which was significantly lower than the control groups. ΔE disparities between groups were highest in HAp composite groups. The EverX Gradia and EverX FiltekZ250 variations had the closest ΔE to the control sets. For a final ‘sandwich' restoration that is aesthetically equivalent to a traditional, mono-composite control restoration, a 2 mm thick sheet of composite covering dentin restoratives with undesirable aesthetics is suggested. The current findings revealed variations in the optical properties of final composite restorations compared to various dentin restoratives, as well as the colour, thickness, and composite form of the ‘enamel' composite coating. As a result, all null hypotheses were rejected. 1 mm thick layers may be appropriate for the same results depending on the composite and dentin restorative form. However, for aesthetically difficult dentin restoratives like Biodentine, EverX, or HAp-like materials, capping layers thinner than 1 mm, particularly of light shades, are not recommended. Clinicians should be mindful that the composite thickness has a strong inverse association with the restoration's translucency. Slight differences in composite thickness, rather than shadow or material form, may influence the final outcome in areas that need a highly transparent appearance [15].

Görücü (2003) conducted research in class II cavities to examine the fracture resistance of two distinct posterior restorations. 24 intact human mandibular molars (for testing) and 24 intact human teeth (for achieving contact) were utilised in this investigation. The test teeth were separated into two groups and then put on the same holder in a typical anatomic connection with undamaged human teeth. Each group was therefore made up of 12 pairs of teeth. In each holder, Class II MO cavities were produced on testing teeth. The other tooth was utilised to make contact with the other. The cavities in group 1 were filled with direct composite resin and flowable composite from the manufacturer. SONICSYS inlays (preformed ceramic inserts) were used to repair the cavities in group 2 according to the manufacturer's recommendations. In an Instron testing machine, the marginal ridges of the restorations were loaded at an angle of 13.58 to the long axis of the tooth until failure occurred. Results. The fracture resistance of class II SONICSYS inlay restorations (group 2) was found to be considerably higher than that of class II direct composite resin restorations with flowable composite $(P = 0.000)$. The enhanced fracture resistance of the ceramic insert restoration may be due to the SONICSYS approx. tips, which were designed for the special demands of adhesive dentistry. Using this design, the instrument's dimensions are transferred to the proximal defect in a single process. The oscillating tip was placed into the prepared cavity with light pressure and water cooling until the cervical transition was attained [191]..

Because of the enhanced strength of the reduction in the volume of polymerisable direct resin material, class II ceramic insert restorations exhibited less polymerisation shrinkage than direct composite resin restorations in this investigation. As a result, the stronger bond of class II ceramic insert restorations is most likely to blame for the improved fracture resistance (compared with the direct composite resin restorations). According to the findings of this study, when executing class II fillings, gaining contact with the next tooth using SONICSYS roughly restorative system may be advised while conducting class II fillings. However, clinical research is required to confirm these results. Under simulated occlusal loads, class II circumstances treated with SONICSYS approx showed considerably stronger fracture resistance than direct composite resin restorations, according to the findings of this investigation [191].

Hahn et al. (1998) conducted a research to assess the marginal microleakage of a novel glass-ceramic inlay system when used in conjunction with two distinct composite luting materials and one polyacid-modified composite. After thermocycling, dye penetration along the cavity walls was used to evaluate microleakage in this study. In addition, before and after thermocycling, the marginal quality of the ceramic inlays used in this work was examined using SEM. When comparing Cerana® inlays to Empress® inlays in research by Hahn et al., dye penetration in class II cavities filled with Cerana® inlays in conjunction with composite was not substantially different. There were no variations in gap creation at the occlusal borders, according to SEM analyses [13].

Cerana®/Variolink ultra® had a larger proportion of perfect margins than Empress®/Variolink ultra®. However, when Cerana® inlays were combined with a polyacid modified composite in class II cavities, only 52 percent of the occlusal borders were not penetrated by the dye. In the SEM, 17 percent of the occlusal enamel margins exhibited flawless adaptation and 56 percent of the occlusal enamel margins had gaps following TC. The enamel in this group was not etched with phosphoric acid, as per the manufacturer's instructions. The Dyract® group did not vary from the other materials in terms of gap creation at the occlusal ceramic edges. It achieved a comparable level of marginal adaptation as Empress® inlays. In SEM, the control group had the fewest approximal enamel margin gaps, whereas the Dyract® group had the largest. Whereas the combination of Cerana® with the high viscosity composite caused the least gap creation at the approximal ceramic edges, the Empress® inlay system caused the most leakage.

After heat cycling, a large proportion of flawless margins can only be achieved if the restorative material adheres well to the tooth surface. According to the findings of Hahn et al., the acid-etch process is capable of ensuring a tight occlusal margin. Even the well-known Empress® inlays did not exhibit full adaptation at the gingival localisation, at the cemento-enamel junction. While the results of Cerana® and Empress® inlays in conjunction with a very viscous composite support their clinical usage, prefabricated ceramic inlays in conjunction with a polyacid-modified composite cannot be advised [13].

Modern insert systems have been accessible on the dentistry market since the late 1980s, according to Federlin's research (2000). In general, two types of systems may be distinguished: those that use preparatory tools in conjunction with standardised inserts and those that do not. One of the purported benefits of insert systems is that insert/composite restorations have superior marginal adaptation than simple composite restorations: the incorporation of inserts minimises polymerization shrinkage stress and lowers the total coefficient of thermal expansion. In vitro tests show that tailoring the insert size to the most perfect fit results in marginal adaption that is equivalent to ceramic inlays. Inserts also make it easier to make a proximal touch. In terms of wear, there are no notable differences between composite and implant restorations. During operating procedures, the link between the implant and the composite is vulnerable to contamination. In vitro findings of enhanced marginal adaption and greater wear resistance are confirmed in short-term clinical studies. Long-term controlled clinical trials are underway, but no results have yet been released. Based on the current in vitro and in vivo data, it can be concluded that the insert technology has promising results, but more research is needed to predict the clinical success of this alternative restoration procedure, such as the stability of the insert/composite bond, fracture resistance of the overall restoration, and wear behaviour.

In terms of science, the insert technique has no direct relationship with composite restorations on the one hand, or indirect ceramic inlays on the other. Some writers use clinical experiences with CAD-CAM technology to compare insert technology to traditional restoration procedures and to scientifically evaluate the inserts. For insert technology, the requirements given above can be used. Short-term clinical trials in vivo support the in vitro findings of improved marginal adaption and wear resistance. Long-term controlled clinical trials are now underway, although data is not yet accessible. There is a scarcity of long-term clinical experience. In vitro and in vivo studies show encouraging results, but more research is needed to predict the clinical effectiveness of this alternative restoration process, such as the durability of the insert/composite connection, the total restoration's fracture resistance, and wear behaviour [192].

Heintze et al. (2005) aimed to compare the marginal adaptation of adhesively luted ceramic inserts in standardised cylindrical cavities of bovine dentin and enamel with the marginal adaptation of adhesively luted ceramic inlays in extracted molars after mechanical loading, and to calculate the minimum sample size required to differentiate between material groups. The use of high flow composite resins (so-called resin cements) in modern cementation is a time-consuming and technique-dependent method. High internal tensions can arise during resin cement polymerization, producing rupture between the restoration and cavity walls, as well as marginal leaking, especially when margins are located in dentin. The presence of peripheral enamel is crucial for proper bonding of inlay/onlay preparations.

Clinical investigations suggest that using the percentage of continuous margin as the only acceptable and predictive sign of clinical effectiveness is too strict to be used as a metric for evaluating restorative materials, and clinical trials back this up. The presence of minor gaps and inconsistencies is a typical clinical finding that cannot be avoided. Obviously, the presence of such gaps has no effect on the survival rate of inlays. Because of the high variability of test results, it seems logical to avoid using the laborious, time-consuming, and expensive inlay model to evaluate luting cements until threshold values and acceptance levels have been systematically established in prospective clinical trials, including replicas for SEM evaluation. Because of its simplicity, standardisation, and speed, the insert-dentin model with an acceptable sample size may be a useful approach for screening luting agents for their capacity to correct for marginal inconsistencies. The clinical significance, however, is still unknown. Longitudinal clinical trials are therefore essential for evaluating the performance of luting agents, particularly when new product concepts such as self-etching primers, self-adhesive cements, or cements containing new compounds are to be used in conjunction with indirect restorations, particularly those with high aesthetic function. When revisions of current products with long-term clinical records are introduced to market, typical laboratory tests such as solubility, expansion, flexural strength, adherence to dental surfaces, colour stability, and so on are adequate. [193]

5. Experimental Part

5.1. Synthesis and Processing of Materials

5.1.1. Synthesis of powders and inserts preparation

In this study, stoichiometric nanosized hydroxyapatite powders have been synthesized using two methods: 1). Precipitation method. 2). Hydrothermal method.

1) Stoichiometric nanosized hydroxyapatite powder HAp_1 has been synthesized using the precipitation method [187,188,194], starting from calcium oxide (obtained by calcination of $CaCO_3$ at 1,000°C in air atmosphere) and 85% phosphoric acid solution. Calcium oxide in small portions was added and stirred in distilled water and phosphoric acid was added drop-wise in calcium hydroxide suspension, at stoichiometric Ca/P molar ratio according to the equation:

$$10\ Ca(OH)_2 + 6\ H_3PO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 18\ H_2O$$

The synthesis was performed at 94°C in open system and during the synthesis pH value, the rate of reactant addition and time of reaction were kept under control. The final suspension of HAp was spray-dried at 120°C.

2) HAp_2 was synthesized by hydrothermal method [185, 195,196], using $Ca(NO_3)_2.4H_2O$ (11.80 g), $Na_2H_2EDTA.2H_2O$ (11.18 g), $NaH_2PO_4.2H_2O$ (4.68g), and $(NH_2)_2CO$ (12.0 g) as precursors, at stoichiometric Ca/P molar ratio. The precursors were dissolved in 1.5 L deionized water, and the synthesis was performed in closed system in an autoclave by heating a precursor solution at 160°C under the pressure of 8 bars. The precipitate was filtered, washed with deionized water and dried at 105°C.

The plasma technology was used to synthesize nano-sized yttrium-stabilized zirconia powder (YSZ), starting from zirconium (IV) carbonate (abcr GmbH &Co. - Germany) and Y_2O_3 (Treibacher Industry AG - Austria). The nanosized powders of refractory compounds and their composites are prepared by evaporation of coarse commercially available powders of chemical elements and their compounds and subsequent condensation of products into a radio frequency inductively coupled nitrogen plasma. The experimental apparatus (Figure 15) consists of a radio-frequency (5,28 MHz) oscillator with a maximum power of 100 kW, a quartz discharge tube with an induction coil, raw powder and gas supply systems, water-cooled stainless-steel reactor and heat exchanger, and cloth filter for collecting powder. The flow rate of the plasma-forming gas (nitrogen) is 7,2-8,0 m^3/h, the feed rate of raw powders is 0,6-1,8 kg/h.

The calculated fractions of raw powders of chemical elements, as well as some oxides, are premixed and introduced into plasma tail through 4 or 8 tubes by carrier gas. Conditions of injection and particle size are determined by theoretical calculations and preliminary experiments. The complete evaporation of raw powders can be reached by varying the particle size and their injection rate, feeding rate, plasma velocity and temperature [197]. The formation of products, their particle size, chemical and phase composition are controlled by introduction of cold nitrogen, ammonia and hydrocarbon into the reaction chamber [198].

Composite powder was obtained by mixing 80 wt% stoichiometric Hap$_1$ and 20 wt% YSZ with an ultrasound procedure homogenized for 30 minutes (powder HAp/YSZ).

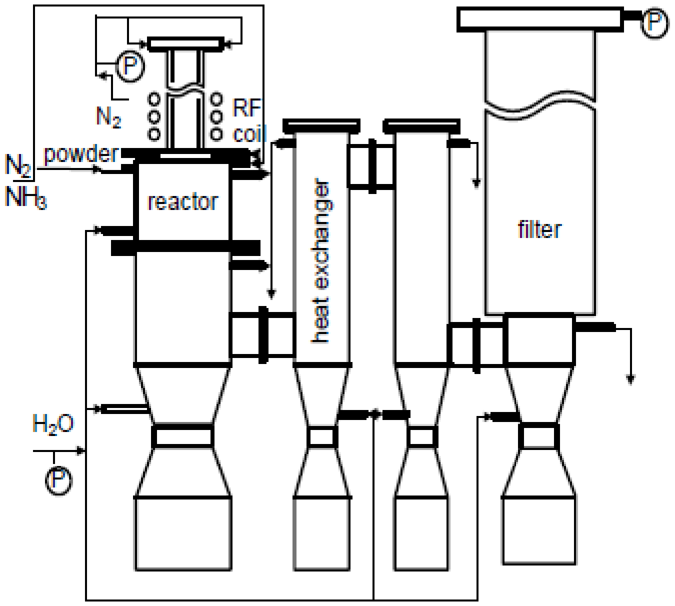

Figure 15. Schematic view of the plasma apparatus for plasma processed nanosized-powders of refractory compounds for obtaining fine-grained advanced ceramics.

The composite powder was isostatically pressed into green bodies in the shape of a cylinder (*d* = 6 mm, *h* = 2 mm) at 100 MPa or 400 MPa (Figure 16). The comparative dilatometric study of green bodies was performed on the system Setaram SETSYS Evolution TMA, in the range of room temperature to 1350 °C, with a heating rate of 20 °C/min in the air atmosphere. With the same heating rate as in the case of dilatometric analysis, the compacts of HAp/YSZ powder were sintered at 1200 °C, 1250 °C and 1300 °C for 2 h.

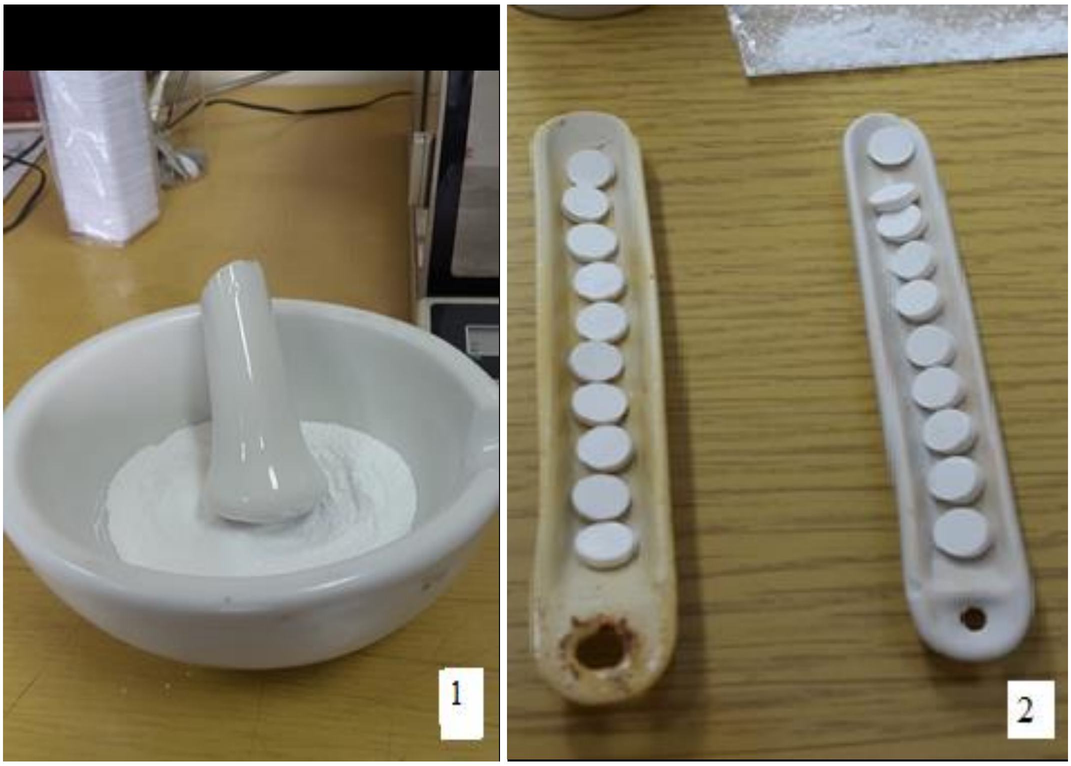

Figure 16. Photographs of 1) The composite powder. 2) Insert green samples.

In the second part of the study, three separate dental inserts were processed using HAp_1, HAp_2 and HAp/YSZ powders.

The first type of insert was prepared by a two-step sintering of powder HAp_1. The HAp_1 powder obtained was pressed isostatically at 400 MPa and sintered in two steps at a heating rate of 20 ºC/min. Green samples were first heated to 1075 ºC and then cooled down to 980 ºC after 15 min and then kept at the second step temperature during the next 24 h (inserts TSSHAp).

The second type of insert was processed by traditional single-step sintering of hydrothermally synthesized Hap_2 powder. The obtained powder HAp_2 was pressed isostatically at the same pressure as the first group of inserts and sintered for 2 h at 1200 ºC with a heating rate of 20 ºC/min (inserts HAp/TCp).

The third type of insert was prepared from the composite powder HAp/YSZ, which was consolidated into green compacts by isostatic pressing at the same pressure as in the case of the first and second group of inserts, and further heated with the same heating rate and sintered conventionally at 1300 ºC for 2 h (inserts HAp/YSZ).

5.2. Characterization of Materials

The morphology of starting powders and microstructure of fractured surface of sintered dental inserts (insert surfaces etched with 37% phosphoric acid for 15 s (Scotchbond Universal Etchant, 3M ESPE) and fractured surfaces after etching) were visualized by TESCAN MIRA 3 XMU field emission scanning electron microscope (FESEM), operated at 20 keV. All the samples before analysis were covered with a thin gold layer, in order to provide conductivity. The element analyses of all HAp and YSZ powder samples were carried out by an energy dispersive spectroscopy (EDS), Oxford Inca 3.2, coupled with the scanning electron microscope (EDS) Jeol JSM 5800, operated at 20 keV.

The particle size distribution of YSZ and HAp/YSZ powders was determined from water dispersions using a laser particle size analyzer, Mastersizer 2000 Malvern Instruments Ltd., UK. The phase composition of the powders and sintered inserts was determined by X-ray diffraction analysis (XRD) using Ital Structure APD 2000 and Rigaku Smartlab diffractometers, using CuKα radiation. The diffraction intensity was measured in the 2θ range of 20–60° with a scanning step width of 0.02°.

The measurements of hardness were done on the polished surface of inserts using a Buehler Indentament 1100 series, Vickers Indentation Hardness Tester. The fracture toughness assessment by the Vickers indentation method was done by generating cracks at the corners of the indenter and the calculation of the toughness value using the following equation [199] $K_{Ic} = 0.0824\, P \cdot c^{-3/2}$, where P is the indentation load and c is the induced crack length.

5.3. Shear bond strength test

The shear bond strength (SBS) test was performed for the HAp/YSZ sintered at different temperatures, TSSHAp and HAp/TCp inserts. Dental materials used for SBS measurements are shown in Table 4.

Table 4. Details on the tested materials

Material	**Manufacturer**	**Type**	**Composition***
Filtek™ Z250 Universal Restorative	3M ESPE, St. Paul, MN, USA	Conventional composite, micro-hybrid 3M ESPE, St. Paul, MN, USA Microhybrid universal composite	BisEMA6, UDMA, BisGMA, TEGDMA, silane-treated ceramic (75–85 wt%), benzotriazol, EDMAB
Single Bond Universal (SBU)		Adhesive, Total Etch or Self Etch Protocol 3M ESPE, St. Paul, MN, USA. Universal adhesive System	BisGMA, HEMADMDMA, ethanol, water, silica filler (5–15 wt%), 2- propenoic acid, 2- methyl-, reaction products with 1,10 decanediol and phosphorous oxide (P2O5), copolymer of acrylic itaconic acid, camphorquinone, EDMAB, toluene
GC Fuji VIII (Fuji VIII)	GC Corporation, Tokyo, Japan	Auto-cured resin- modified Glass- Ionomer cement	HEMA, UDMA, tartaric acid, 2-Hydroxy- 1,3 dimethacryl oxypropane, glass fillers
Maxcem Elite (Maxcem)	Kerr Corporation, Orange, CA, USA	Self-adhesive, resin luting cement	Methacrylate ester monomers, mineral fillers, Ytterbium fluoride, activators, stabilizers, colorants

* Manufacturers' material safety data sheets. Abbreviations: HEMA –2-hydroxyethyl methacrylate; Bis-EMA - ethoxylated bisphenol A glycol dimethacrylate; UDMA - urethane dimethacrylate; Bis-GMA - bisphenol A diglycidyl ether dimethacrylate; TEGDMA- triethylene glycol dimethacrylate; EDMAB - ethyl-4-dimethylamino benzoate, BisEMA6 - Bisphenol A polyethylene glycol diether dimethacrylate, UDMA - Diurethane dimethacrylate, DMDMA - Decamethylene dimethacrylate.

Different groups of samples were prepared, depending on the type of: insert surface treatment, adhesive application and restorative material application. Details of the preparation procedure in each group are given in Table 5. Five samples per each group/type (N = 5) were prepared.

1) Z250_SBU_TE is etched insert for 15 s, applied Single Bond Universal, light cured for 20 s, applied 2mm thick layer of dental composite Filtek Z250 and light cured for 40 s.

2) Z250_SBU_SE is no acid etching of the inserts, just Water rinsing and Mild air-drying, applied Single Bond Universal, light cured for 20 s, applied 2mm thick layer of dental composite Filtek Z250 and light cured for 40 s.

3) Fuji VIII is no surface treatment of inserts was performed, just Water rinsing and Mild air-drying, there is not an adhesive application, Fuji VIII was prepared by mixing instructions, applied directly to the untreated surface left to set for 10 min.

4) Maxcem is no surface treatment of inserts was performed, just Water rinsing and Mild air-drying, there is not an adhesive application, Maxcemsingle layer, pressed though the mixing tip from the original cartridge, light-cured for 20 s using the same LEdition unit.

5) Maxcem+acid, inserts were etched for 15 s, rinsed with water and mildly air-dried, there is not an adhesive application, Maxcem single layer, pressed through the mixing tip from the original cartridge, light-cured for 20 s using the same LEdition unit.

For inserts HAp/YSZ, first two types of test groups (1 and 2) were prepared for SBS test, while all five groups were prepared with inserts TSSHAp, HAp/TCp and HAp/YSZ sintered at 1300 ºC.

Each sample was prepared by placing an insert into a custom-made mold (Figure 17), 6 mm in diameter and 2 mm deep bottom part for insert placement and 3 mm in diameter and 2 mm deep upper part for restorative material application. Inserts were placed in the bottom part of the mold. The diameter of the inserts fitted the mold. The adhesive was rubbed into the insert surface, air-dried and light-cured using an LED light-curing unit (LEDition, Ivoclar Vivadent, Schaan, Liechtenstein) at an intensity of 800 mW/cm^2. Composite material was applied on top of the insert in one 2-mm increment by filling the entire upper part of the mold and light-cured using the same light source. All samples were kept dry at 37 °C for 24 h before SBS testing.

Table 5. Preparation procedure in each group

<table>
<tr><th>Group >
Procedure ∨</th><th>Z250_SBU_TE</th><th>Z250_SBU_SE</th><th>Fuji VIII</th><th>Maxcem</th><th>Maxcem + acid etching</th></tr>
<tr><td>Insert surface treatment</td><td>Acid etching with 37% phosphoric acid, 15 s
Water rinsing
Mild air-drying</td><td colspan="3">Water rinsing
Mild air-drying</td><td>Acid etching with 37% phosphoric acid, 15 s
Water rinsing
Mild air-drying</td></tr>
<tr><td>Adhesive application</td><td colspan="2">Rubbing SBU adhesive for 20 s with a disposable applicator onto the insert surface
Mild air-drying
Light-curing for 20 s at 1 mm distance</td><td colspan="3">No adhesive application</td></tr>
<tr><td>Restorative material application (standardized mold Ø 3 and 2 mm thick placed on the top of insert)</td><td colspan="2">Z250single layer, applied and adapted with a spatula, light-cured for 40 s at 1 mm distance</td><td>Fuji VIII mixed per instructions, single layer adapted with a spatula, left to set for 10 min</td><td colspan="2">Maxcem single layer, pressed though the mixing tip from the original cartridge, light-cured for 20 s</td></tr>
</table>

Figure 17. Photographs of 1) Inserts etched with phosphoric acid 37% and copiously rinsed with water and mildly air-dried 2) and 3) Negative model of insert; 4) LED light-curing; 5) Composite material was applied on top of the insert.

The SBS was measured using a knife-edge shearing blade in a universal test machine (Force Gauge PCE-FM200, Southampton, United Kingdom), as shown in Figure 18. Force was applied to the composite/restorative material build-up parallel to the composite-adhesive-insert interface 1 mm from the bonded surface at 1 mm/min speed until fracture. SBS (τ) in MPa was calculated using the maximum force reached (F in Newton) and bonded surface area (A in mm^2) according to the equation: $\tau=F/A$.

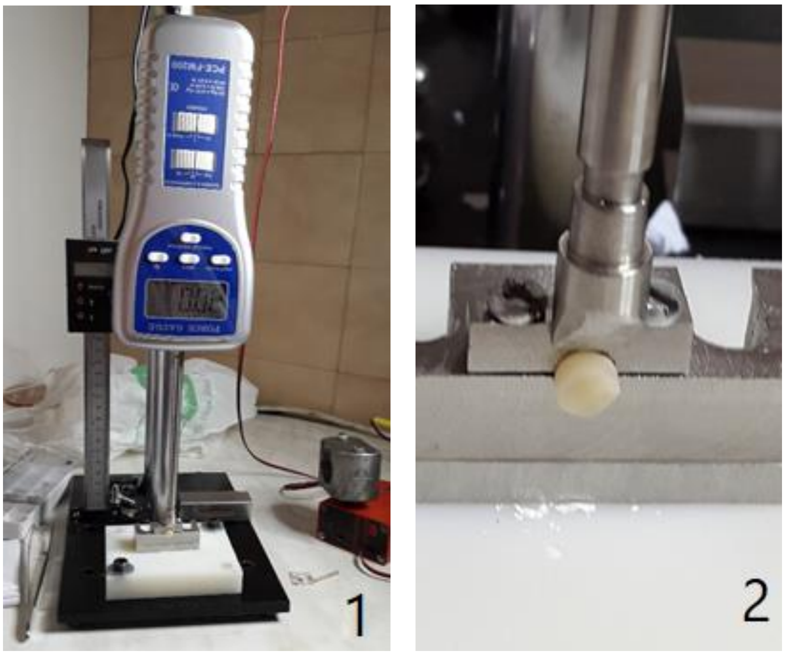

Figure 18. Photographs of 1) Universal test machine (Force Gauge PCE-FM200, Southampton, United Kingdom) to measure SBS; 2) Knife-edge shearing blade.

Statistical analysis was performed in Minitab Express (Minitab Inc., State College, PA, USA). SBS data were analyzed using a two-way analysis of variance (ANOVA) for factors ’material’ and ’application protocol’ as well as their interaction and the General Linear Model (GLM) for factors “Insert type” and “Material/Treatment” and their interaction at 0.05 level of significance.

6. Results

6.1. Characterization of HAp_1, HAp_2 and YSZ powders

Table 6 displays the elemental analysis of starting powders. In the case of HAp_1 powder, the stoichiometric molar ratio Ca/P of 1.67 has been confirmed. EDS spectra of yttrium-stabilized zirconia powder showed that YSZ contains approximately 4.75 at% of yttrium as a stabilizer. Figure 19 shows SEM micrographs of both powders. HAp_1 powder was composed mainly of elongated particles 50–100 nm in size (Figure 19a), while two different types of particles were visible on the SEM image of YSZ powder (Fig. 19b and 19c). Nano-particles had a relatively spherical shape, less than 50 nm in size, whereas spherical micron-sized particles had a diameter of about 1 μm.

Table 6. The quantitative results of EDS analysis

	HAp	
Ca, at%	P, at%	O, at%
18.66	11.16	70.18
	YSZ	
Zr, at%	Y, at%	O, at%
18.56	4.75	76.69

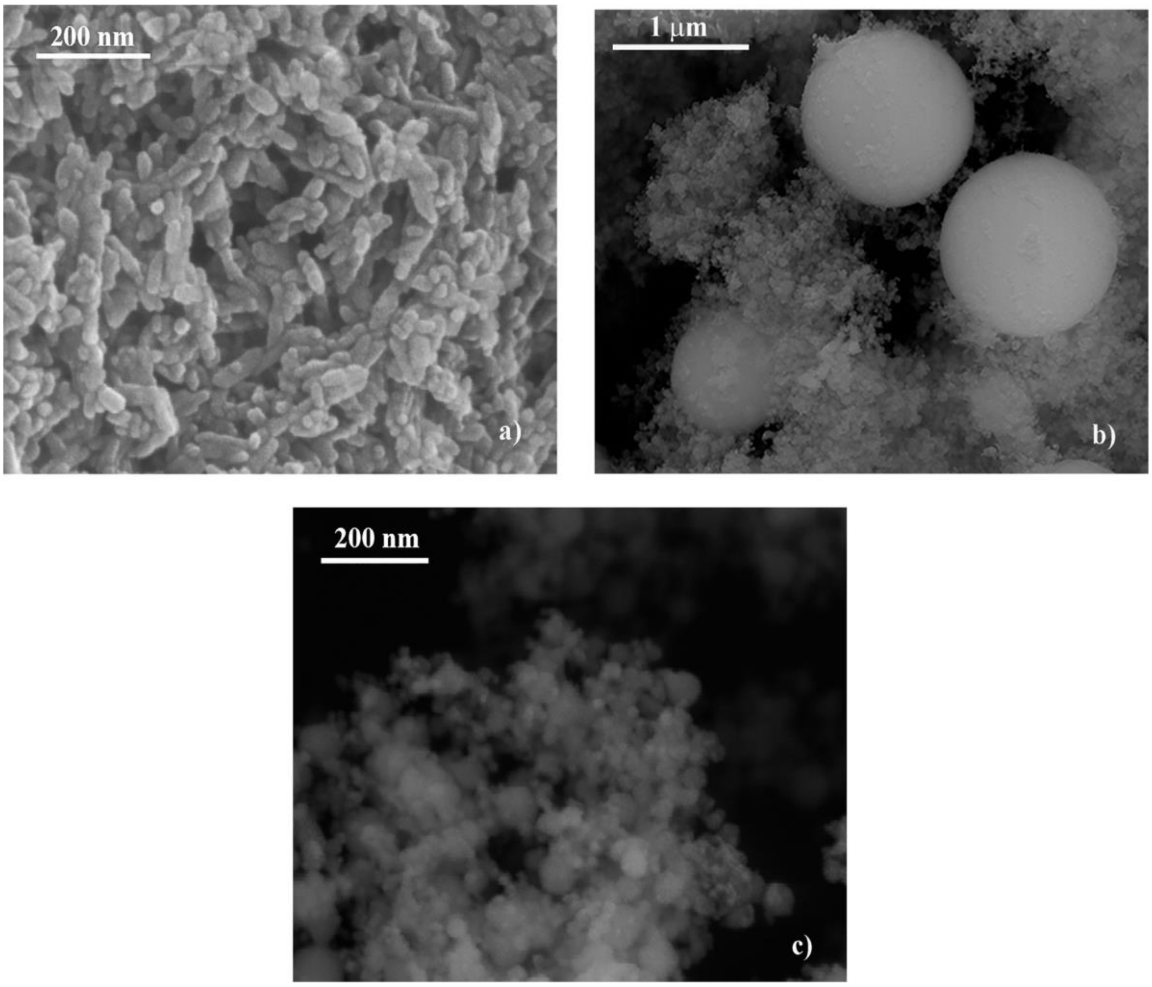

Figure 19. SEM micrographs of: a) HAp1 powder, b and c) YSZ powder.

Figure 20a shows SEM micrograph of HAp_1 powder, which was used to process TSSHAp inserts. The powder consists of soft agglomerated rod-like particles. Previously, monophasic hydroxyapatite powder composition and stoichiometric Ca/P molar ratio of 1.67 are confirmed [184,187,203]. HAp_2 powder, which was used for the processing of second type of inserts contains spherically agglomerated rod-like particles (Figure 20b). EDX analysis showed that the molar ratio Ca/P was 1.45, indicating a calcium deficiency in HAp_2 powder. Analysis of XRD showed only peaks corresponding to the crystalline phase of hydroxyapatite [200].

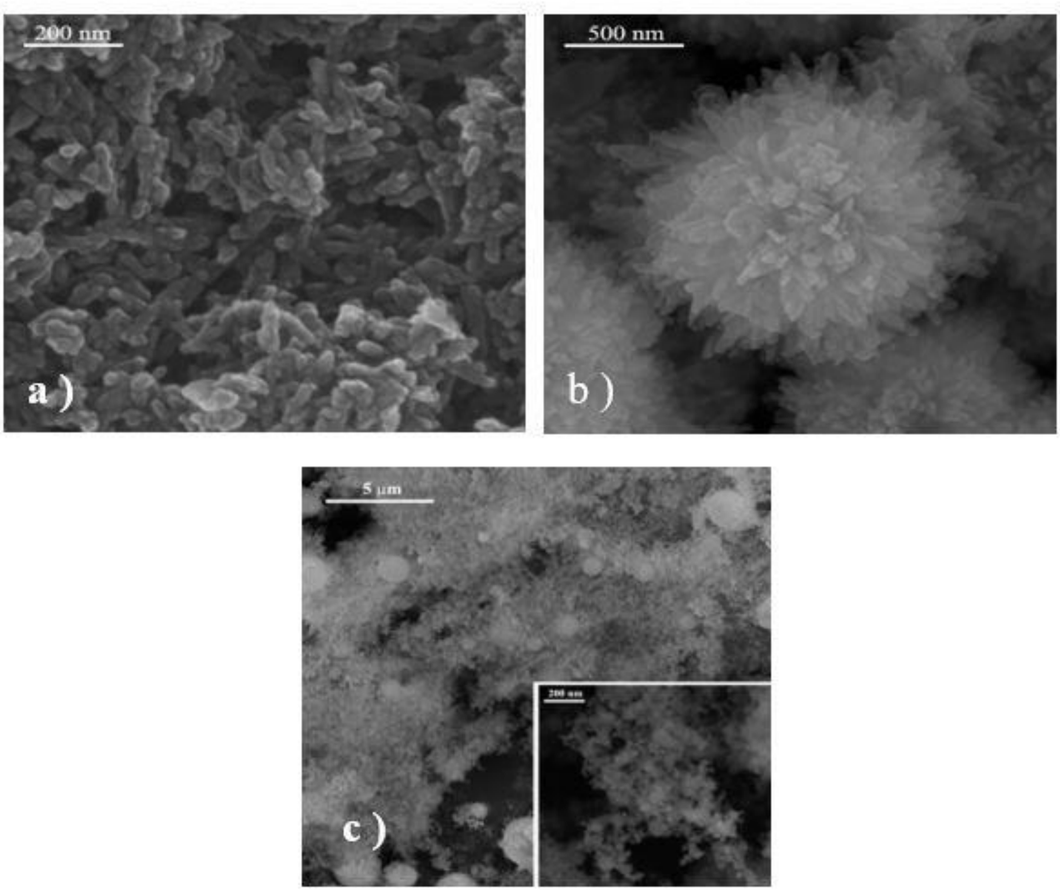

Figure 20. FE-SEM micrographs of powders: a) HAp1, b) HAp2, c) YSZ.

Particle size distribution of HAp_1 powder, determined in previous investigations [186,188] showed that agglomerated particles ranged between 200 nm to 5 µm. Particle size distributions of YSZ and HAp/YSZ after ultrasound treatment are shown in Figure 21. YSZ powder was composed of agglomerated particles in the range of 150 nm to a few microns, according to particle size distribution of YSZ powder per number (Figure 21a). The largest number of particles was a few hundred nanometers in size. Most of the YSZ powder volume consisted of micron-sized particles (Figure 21b), whose number is relatively low (Figure 21a). The composite powder consisted of agglomerates between 300 nm and a few microns in the range (Figure 20a).

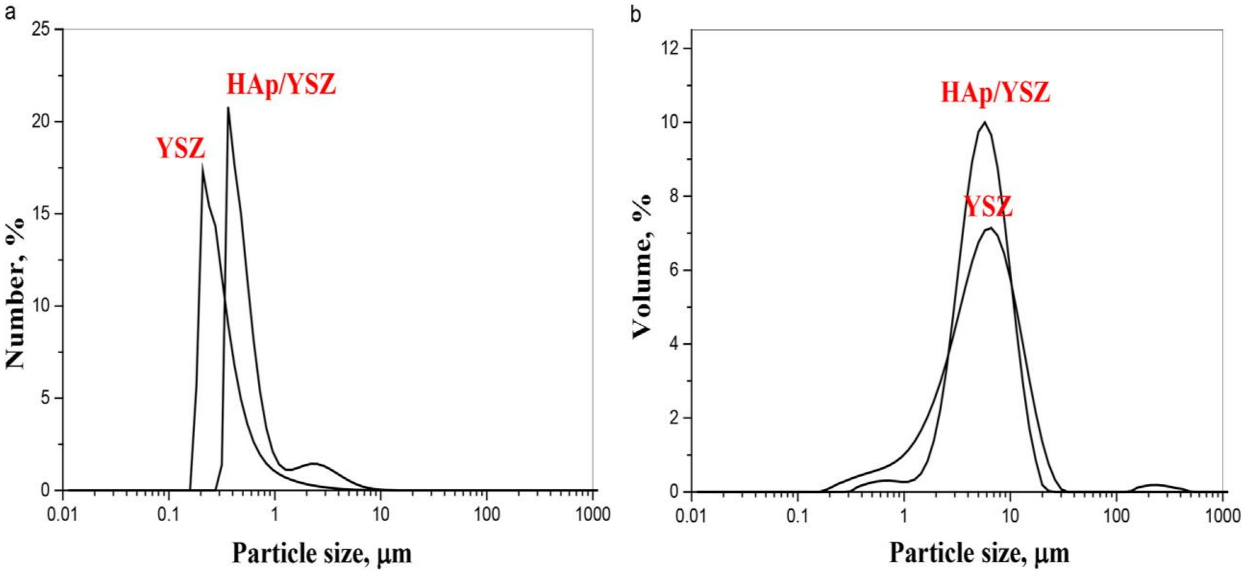

Figure 21. a) Number and b) volume particle size distribution of yttrium-stabilized ZrO2 and composite powders.

XRD pattern of HAp_1 powder displayed peaks only corresponding to the hydroxyapatite phase (Figure 22) and perfectly matched the standard pattern of hydroxyapatite (Card No. JCPDS 9-432). XRD analysis of stabilized zirconia powder confirmed the presence of t-ZrO_2 as dominant phase (Card No. JCPDS-80–0965) and also the typical reflections of m-ZrO_2 (Card No. JCPDS:37-1484) as a phase presents to a much lower content [201,202].

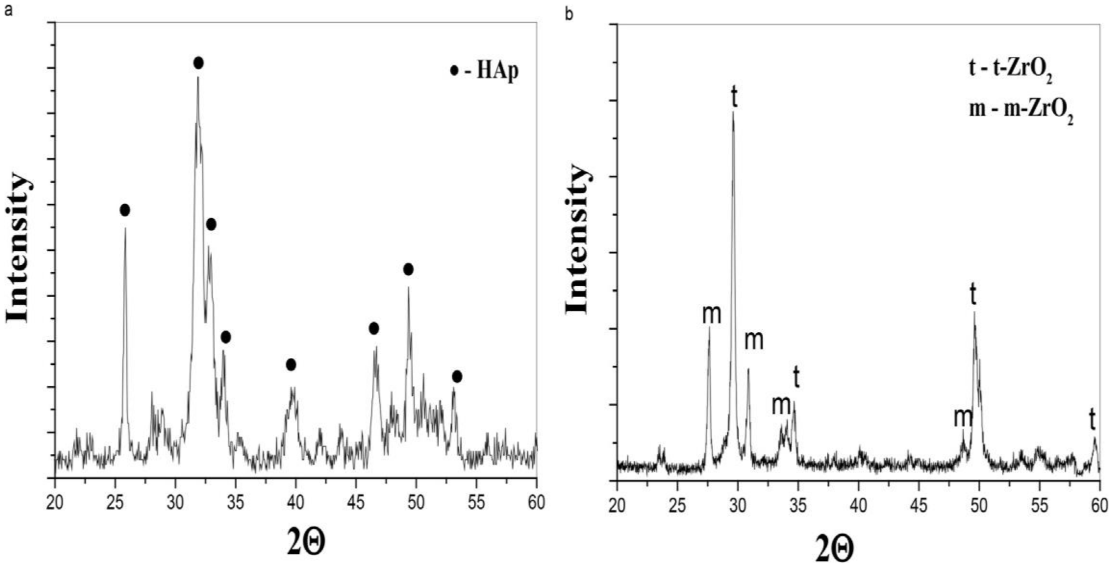

Figure 22. XRD patterns of: a) HAp$_1$ and b) YSZ powders.

HAp/YSZ powder dilatometric analysis was performed at a heating rate of 20 °C/min up to the temperature of 1350 °C. Under the same conditions, HAp$_1$ powder was analysed as a control sample to test the effect of YSZ addition (Figure 23). The addition of YSZ powder affected lower shrinkage by approximately 4% compared to pure HAp. In the range of 1200 °C to 1300 °C, the dilatometric curve for HAp/YSZ showed very low shrinking. Based on the dilatometric curves, sintering temperature of green insert samples was determined to be 1200 °C, 1250 °C and 1300 °C for 2h.

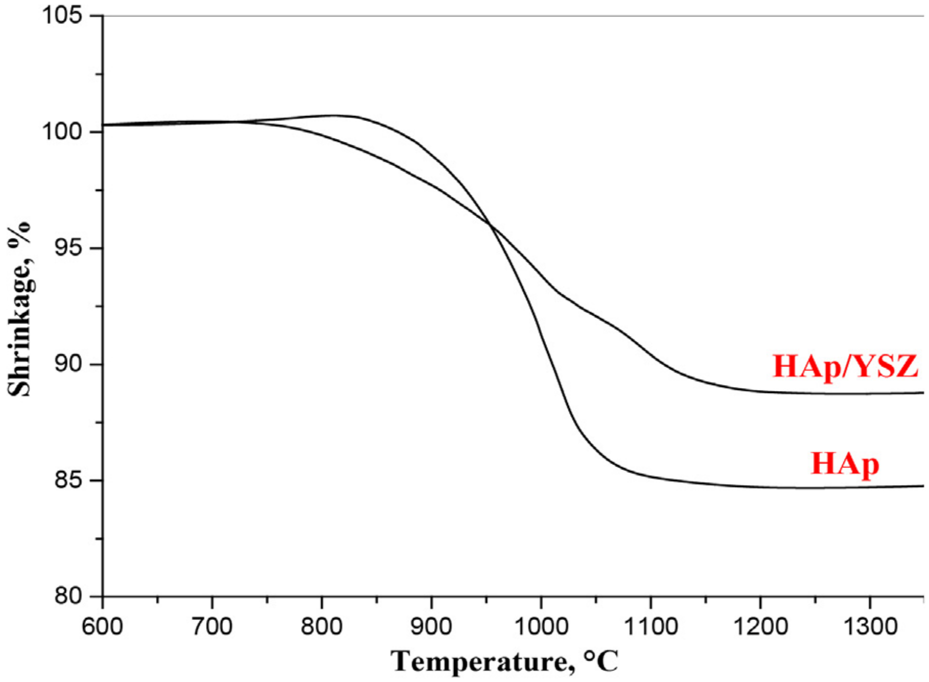

Figure 23. Dilatometric curves of HAp/YSZ of HAp_1 as a control.

6.2. Characterization of the HAp/YSZ sintered samples

XRD patterns of composite inserts sintered at 1200 °C, 1250 °C and 1300 °C for 2 h (Figure 24) showed peaks that correspond to HAp. No other phases of calcium phosphate were observed. All peaks of zirconia were perfectly matched with the peaks of t-ZrO_2 (Card No. JCPDS-80-0965), in the case of inserts sintered at 1250 °C and 1300 °C, whereas in the case of inserts sintered at 1200 °C, low amounts of m-ZrO_2 were detected.

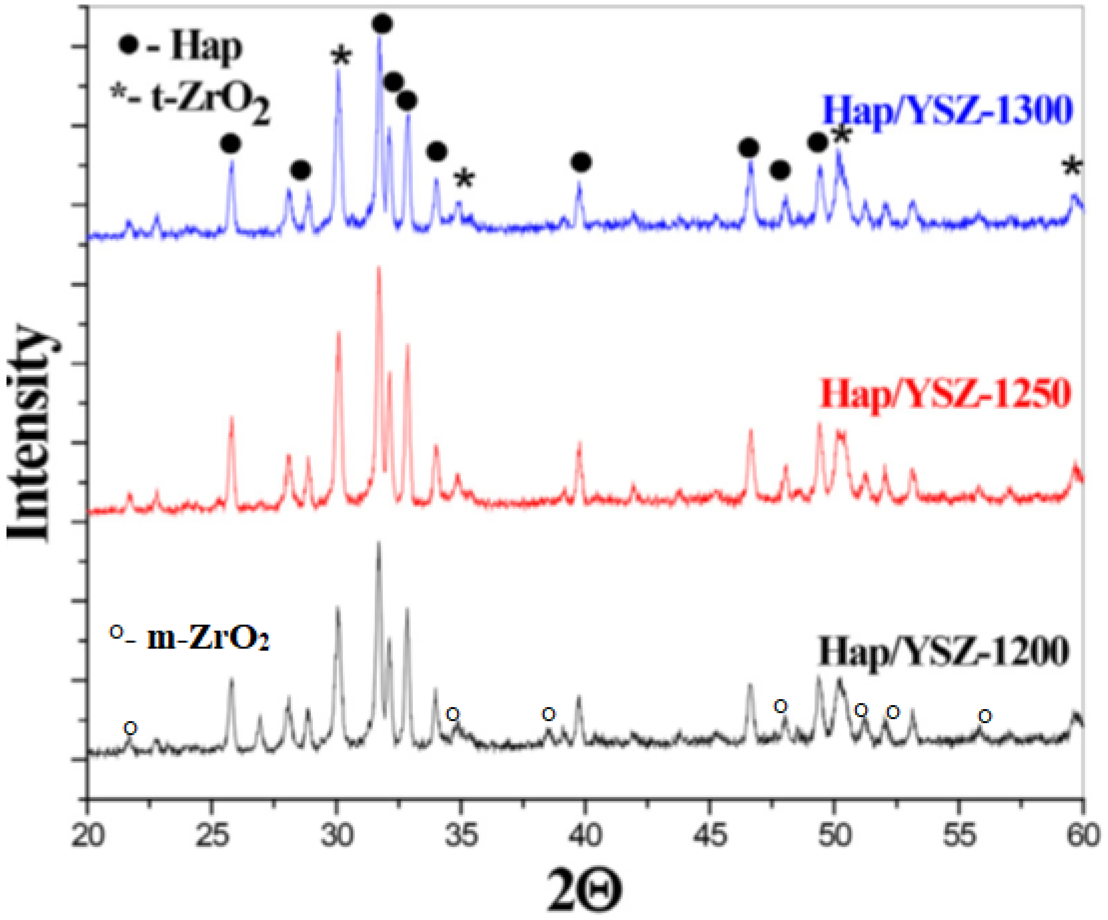

Figure 24. XRD patterns of sintered HAp/YSZ insert materials.

Figure 25a-c shows fractured surfaces of inserts pressed at 100 MPa and further sintered at the temperatures mentioned above. Porous microstructures were observed in all cases, but there was also a visible decrease in the number of pores with irregular shape and overall porosity, with an increase in sintering temperature. In the case of the insert sintered at 1300 °C as a final isothermal step (Figure 25c), the most densified and most uniform microstructure was observed, as well as the uniform distribution of nanosized yttrium-stabilized ZrO_2 particles.

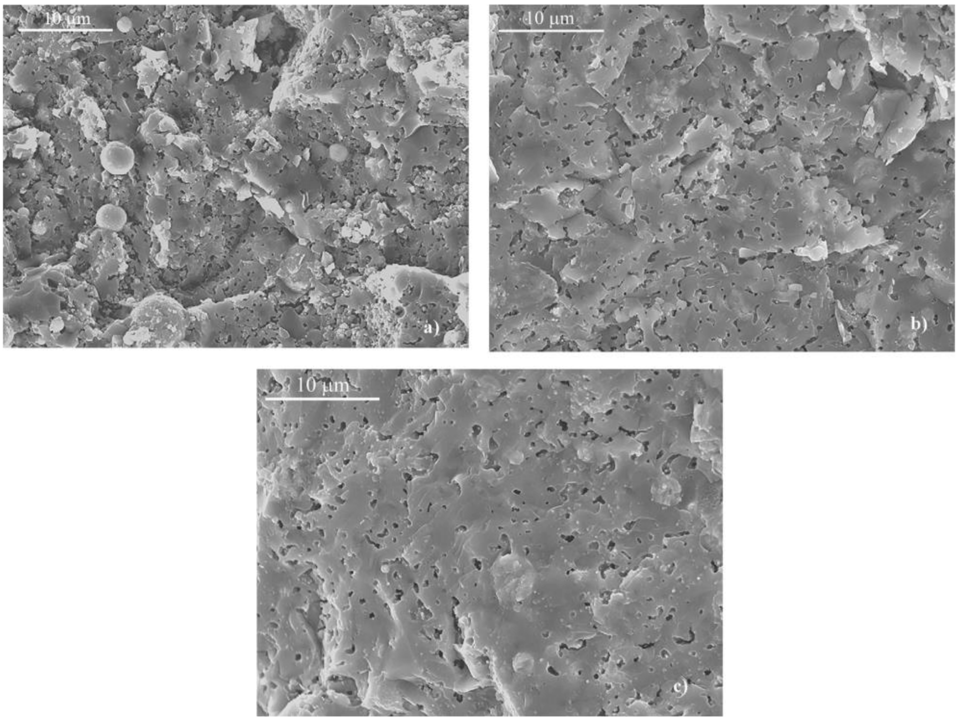

Figure 25. SEM micrographs of inserts pressed at 100 MPa and sintered at: a) 1200 °C, b) 1250 °C and c) 1300 °C for 2 h.

The relatively porous microstructures of the composite HAp/YSZ inserts affected the relatively low hardness values shown in Table 7. In the case of an insert sintered at 1300 °C for 2 h, the maximum hardness of 2.72 ± 0.06 GPa and accompanying fracture toughness of 1.61 ± 0.04 MPam$^{1/2}$ were measured. This value of fracture toughness is relatively high for HAp based bioceramics.

Table 7. Mechanical properties of sintered inserts pressed at 100 MPa

Insert	Hardness (HV), GPa	Fracture toughness (K_{Ic}), MPam$^{1/2}$
HAp/YSZ-1200	2.18 ± 0.10	1.44 ± 0.05
HAp/YSZ-1250	2.60 ± 0.02	1.47 ± 0.02
HAp/YSZ-1300	2.72 ± 0.06	1.61 ± 0.04

During the formation of green insert specimens, the application of 400 MPa isostatic pressure provided significantly higher densification levels under the same sintering conditions (Figure 26a–c). On the fractured surfaces of inserts a significantly smaller number of pores is visible as well as a uniform distribution of YSZ particles of nano and micron size. Upon temperatures increasing from 1200 °C to 1300 °C, microstructures became denser, and the hardness of HAp/YSZ slightly increased from 3.90 ± 0.20 GPa to 3.95 ± 0.12 GPa (Table 8), which were the certainly higher values compared to inserts pressed at 100 MPa.

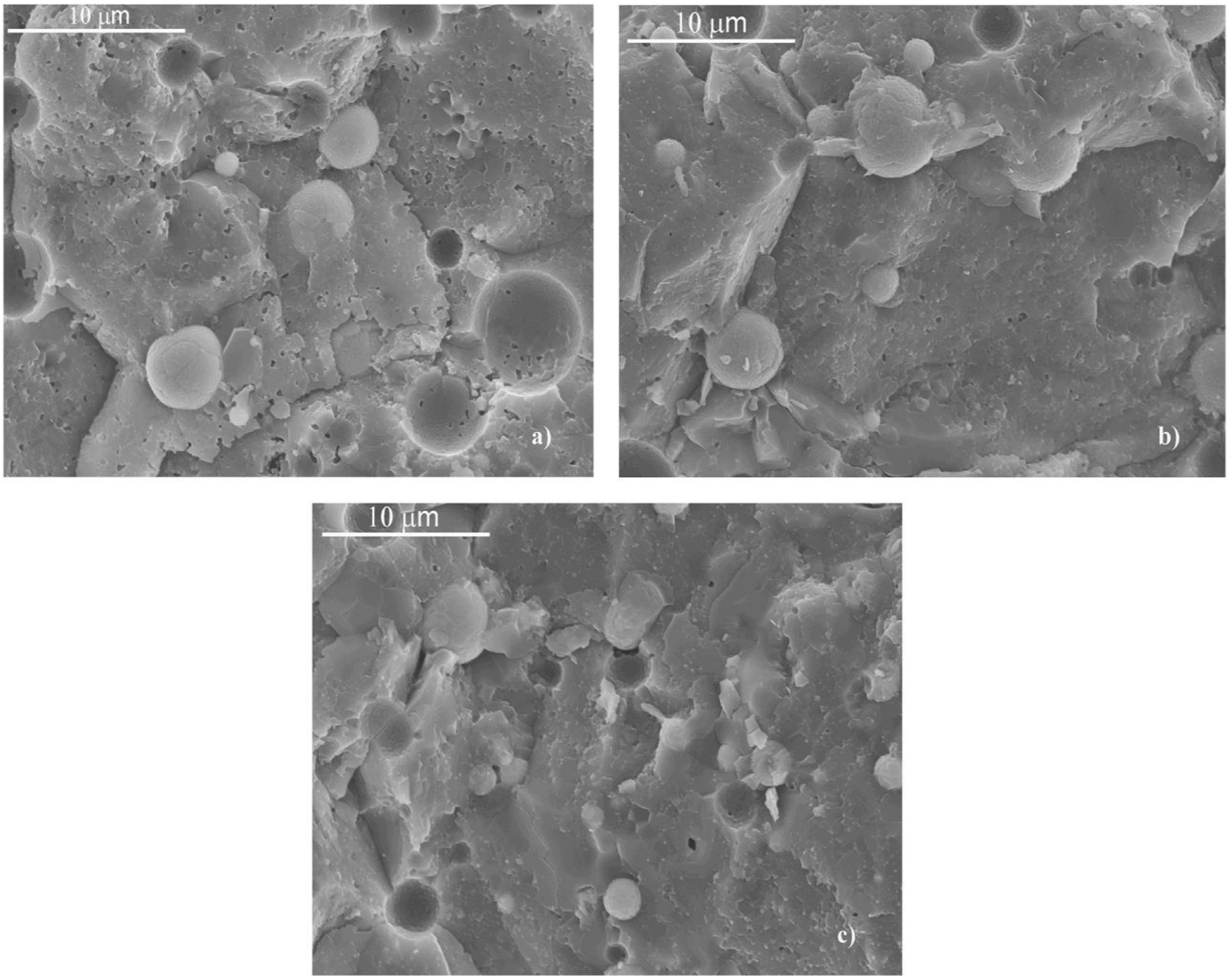

Figure 26. SEM micrographs of inserts isostatically pressed at 400 MPa and sintered at: a) 1200 °C, b) 1250 °C and c) 1300 °C for 2 h.

Table 8. Mechanical properties of sintered inserts isostatically pressed at 400 MPa

Insert	Hardness (HV), GPa	Fracture toughness (K_{Ic}), MPam$^{1/2}$
HAp/YSZ-1200	3.90 ± 0.20	1.88 ± 0.03
HAp/YSZ-1250	3.92 ± 0.08	1.82 ± 0.04
HAp/YSZ-1300	3.95 ± 0.12	1.85 ± 0.02

In the case of inserts isostatically pressed at 400 MPa, a significantly lower increase in hardness was noticed with an increase in the sintering temperature compared to inserts pressed at 100 MPa. Table 8 shows the very high and similar fracture toughness values of sintered inserts. The fracture toughness ranged from 1.82±0.04 MPam$^{1/2}$ to 1.88±0.03 MPam$^{1/2}$, which were certainly higher than 100 MPa pressed inserts and generally relatively high values for dentin replacement materials based on HAp.

6.3 Shear bond strengths of the composite inserts

For analyzing the SBS of composite inserts with Single Bond Universal adhesive and universal composite Z250, two separate protocols, „ total-etch “and „ self-etch” were used. Figure 27 shows HAp/YSZ insert etched surface sintered at 1250 °C after etching with phosphoric acid concentrate 37 % for 15 s. The relatively rough surface is visible after etching and YSZ particles are also mostly deagglomerated and distributed relatively equally in the HAp matrix.

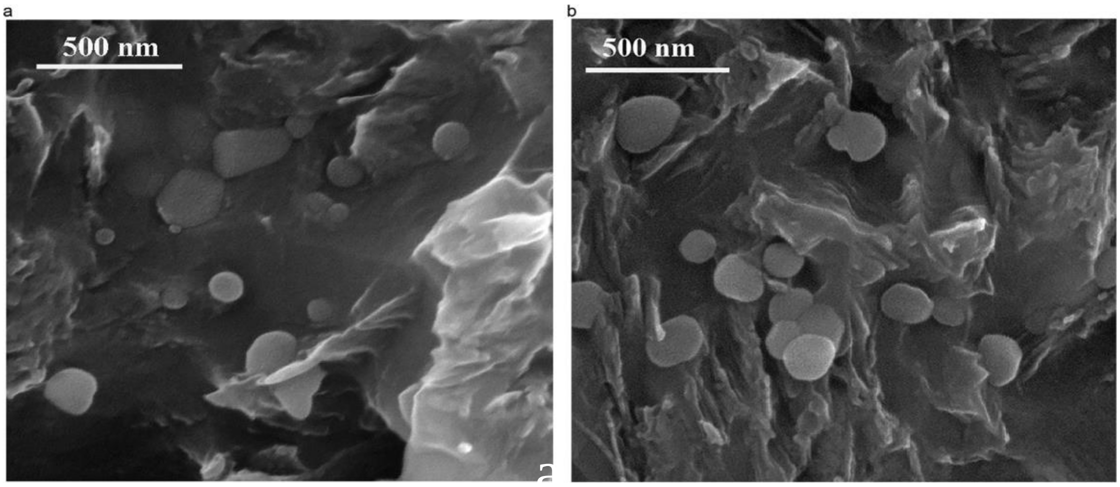

Figure 27. SEM micrographs of two randomly selected places on the etched surface of insert sintered at 1250 °C and used in the „total-etch" protocol of adhesive application.

The results of the "total-etch" and "self-etch" groups of SBS measurements are shown in Figure 28. No statistically significant differences between sintered inserts at different temperatures (*p*=0.1808) and application protocols (*p*=0.4077) were reported by ANOVA. There was also no important interaction between these variables (*p*=0.8170). This indicates that both "total-etch" and "self-etch" adhesive application protocols resulted in comparable SBS values for each insert group. In addition, all inserts performed similarly in terms of SBS within each application protocol.

The values of SBS of restorative materials to HAp/YSZ inserts were in the range between 10.50 ± 4.94 MPa (SBU_SE) and 7.03 ± 0.97 MPa (SBU_TE). In the case of both protocols, due to the increase in the mean SBS values of restorative materials to HAp/YSZ inserts with a sintering temperature increase from 1200–1300 °C, inserts were also sintered at 1325 °C and under the same conditions, SBS was measured. After measuring SBS of four groups of inserts, slightly higher mean SBS were measured with inserts sintered at 1300 °C (Figure 28). In applying the "total-etch" procedure, mean SBS values increased with temperature increase to 1300 °C and then decreased as the sintering temperature increased to 25 °C. For the „self-etch" approach, the mean SBS value also dropped with the increase in the sintering temperature to 1325 °C.

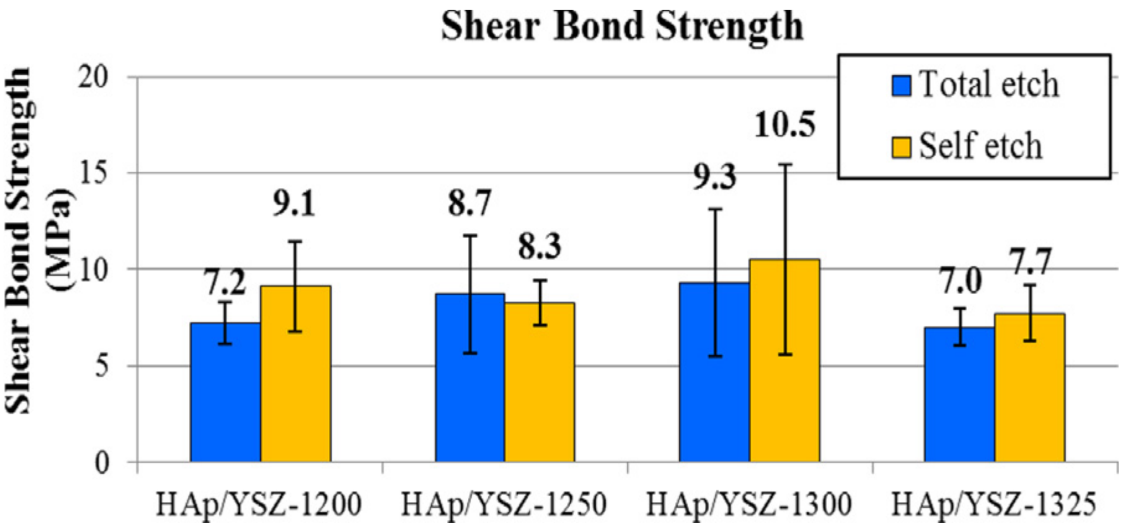

Figure 28. SBS of HAp/YSZ inserts sintered at different temperatures bonded to dental composite using adhesives applied by „total-etch“ or „self-etch“ protocol.

6.4. Characterization of TSSHAp, HAp/TCp and HAp/YSZ inserts

XRD patterns of the inserts TSSHAp and HAp/TCp are given in Figure 29. Only peaks corresponding to hydroxyapatite were visible in the XRD pattern of TSSHAp inserts, according to the standard JCPDS 9-432 card (Figure 29a). Hydroxyapatite is the main crystalline phase of the inserts HAp/TCp, but there are also some quantities of β-TCp and α-TCp (Cards No. JCPDS 09 -0169 and JCPDS 09-0348), Figure 29b. As it was shown (Figure 23), HAp/YSZ inserts sintered at 1300 ºC contains HAp as the only calcium phosphate phase as in the case of TSSHAp inserts, and stabilized tetragonal zirconia.

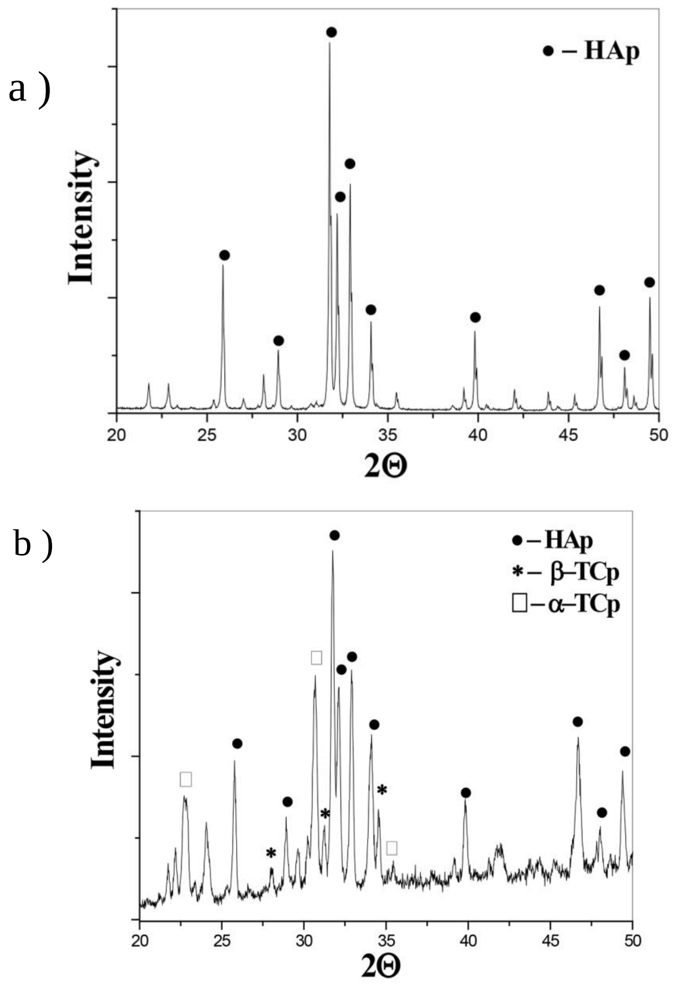

Figure 29. XRD patterns of inserts: a) TSSHAp, b) HAp/TCp.

SEM micrograph in Figure 30a shows the acid etched surface and fractured surface of the TSSHAp insert (lateral side of the etched surface). SEM micrograph (Figure 30a) confirmed full density of TSSHAp inserts, whereas the fractured surface acid-etched side (right edge of the sample shown in the micrograph in Figure 30a) and the acid-etched surface, shown in Figure 30b, resulted in relatively low effect of etching with standard 37% phosphoric acid. Figure 30b, acid etched surface of TSSHAp insert, shows relatively flat and non-porous surface, where the boundaries of grain have been etched while HAp grains are stable.

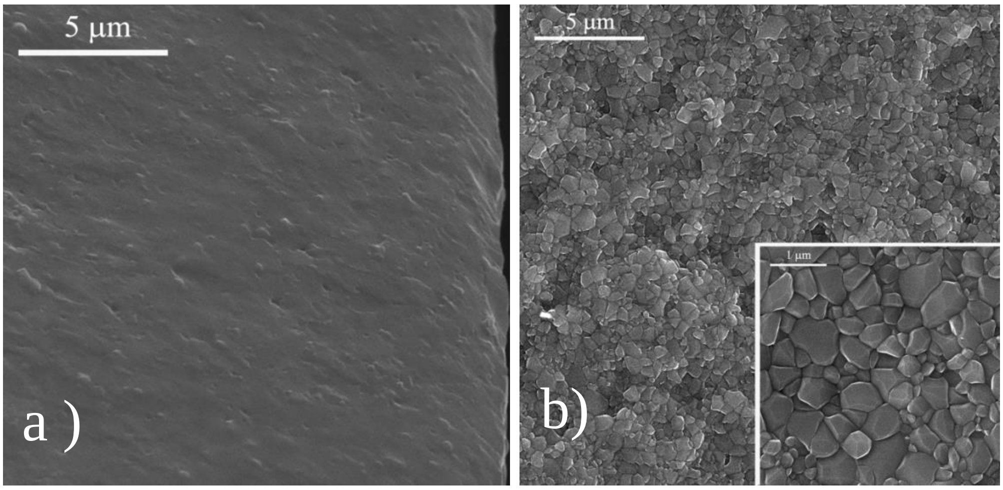

Figure 30. TSSHAp inserts: a) Fractured surface and b) acid etched surface.

Fractured surface of HAp/TCp insert showed porous microstructure (Figure 31a), similar to previously published results related to dental inserts obtained under similar conditions of processing [14], whereas calcium chloride ($CaCl_2$) was the source of calcium, instead of calcium nitrate ($Ca(NO_3)_2$). Figure 31b showed that the etched HAp/TCp insert surface was significantly more porous than TSSHAp. Pores sizes were up to 2 μm on the etched surface, while the right edge of the sample was shown in Figure 31a showed an etching depth of up to approximately 2,5 μm.

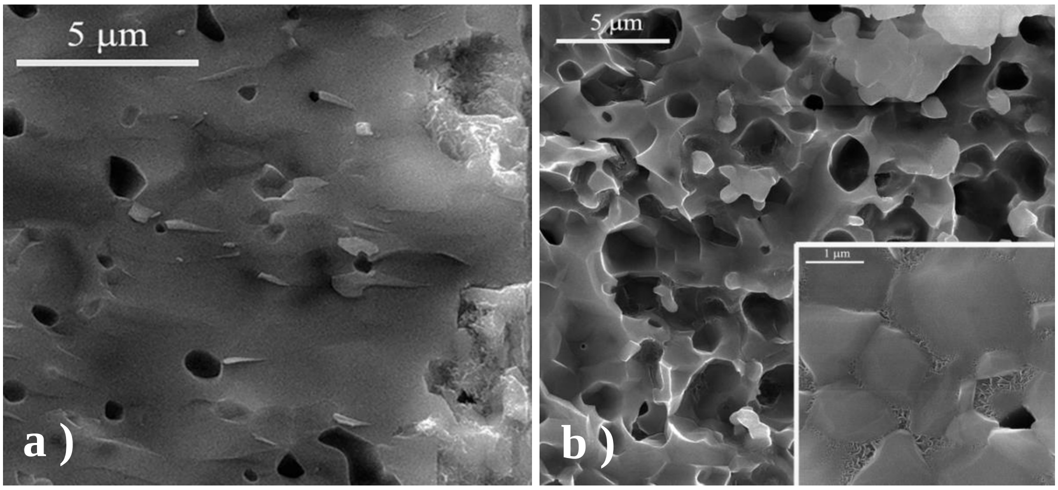

Figure 31. HAp/TCp inserts: a) Fractured surface and b) acid etched surface.

Figure 32a shows that the HAp/YSZ insert etching depth was up to around 2 µm. Figure 32b confirms an important etching effect, especially on the HAp matrix. There was also noticed uniform distribution of zirconia particles after etching.

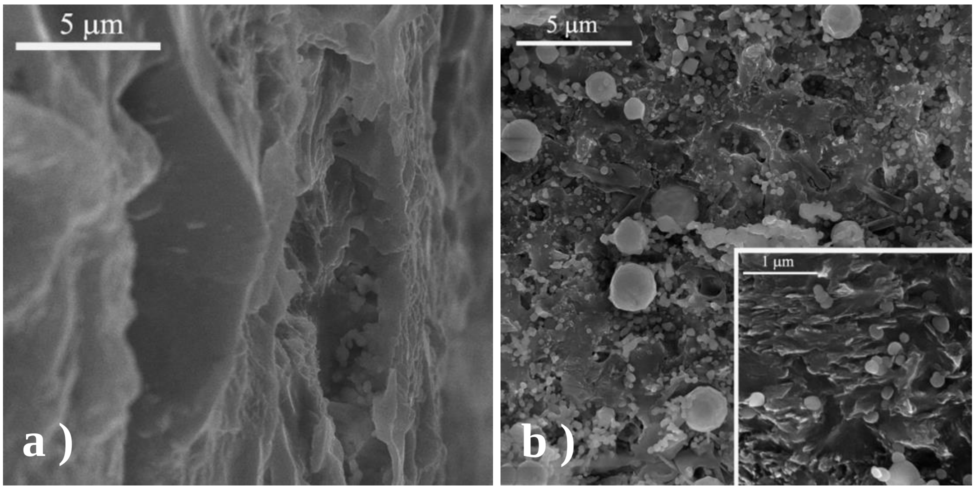

Figure 32. HAp/YSZ inserts: a) Fractured surface and b) acid etched surface.

Hardness and fracture toughness of the inserts are given in Table 9. Hardness differences between the three types of inserts were statistically significant ($p < 0.05$), with TSSHAp having the largest and HAp/TCp having the lowest hardness values. On the other hand, fracture toughness of HAp/YSZ was significantly higher ($p < 0.05$) than those of HAp/TCp and TSSHAp. The last two types of inserts presented no significant variation in fracture toughness ($p > 0.05$).

Table 9. Hardness and fracture toughness of used inserts

Insert	Hardness (HV), GPa	Fracture toughness (K_{Ic}), MPam$^{1/2}$
TSS HAp	5.22±0.10	1.02±0.015
HAp/TCp	3.71±0.12	1.19±0.35
HAp/YSZ	3.95±0.12	1.85±0.02

6.5. Shear bond stress

Figure 33 and Table 10 summarize the SBS values of the tested groups and statistical significance between the tested factors. Two-way interaction of the factors “insert” and “restoration” was not significant ($p = 0.244$), while both “insert” and “restoration” main effects were significant ($p < 0.005$ and $p < 0.001$, respectively). Concerning factor “insert,” Tukey's pairwise comparison of marginal means showed significantly higher SBS for TSSHAp than HAp/YSZ ($p < 0.05$). SBS of HAp/TCp was not significantly various from TSSHAp and HAp/YSZ ($p > 0.05$). Concerning factor “restoration,” Z250_SBU in both TE and SE adhesive application modes showed significantly higher SBS compared to Maxcem and Fuji VIII groups ($p < 0.05$). Higher SBS compared to Maxcem and Fuji VIII groups ($p < 0.05$). Phosphoric acid etching slightly improved SBS of Maxcem compared to Maxcem without etching, albeit the difference did not reach statistical significance ($p > 0.05$). Fuji VIII showed comparable SBS to Maxcem without acid etching ($p > 0.05$) and was significantly lower than Maxcem with acid etching ($p < 0.05$).

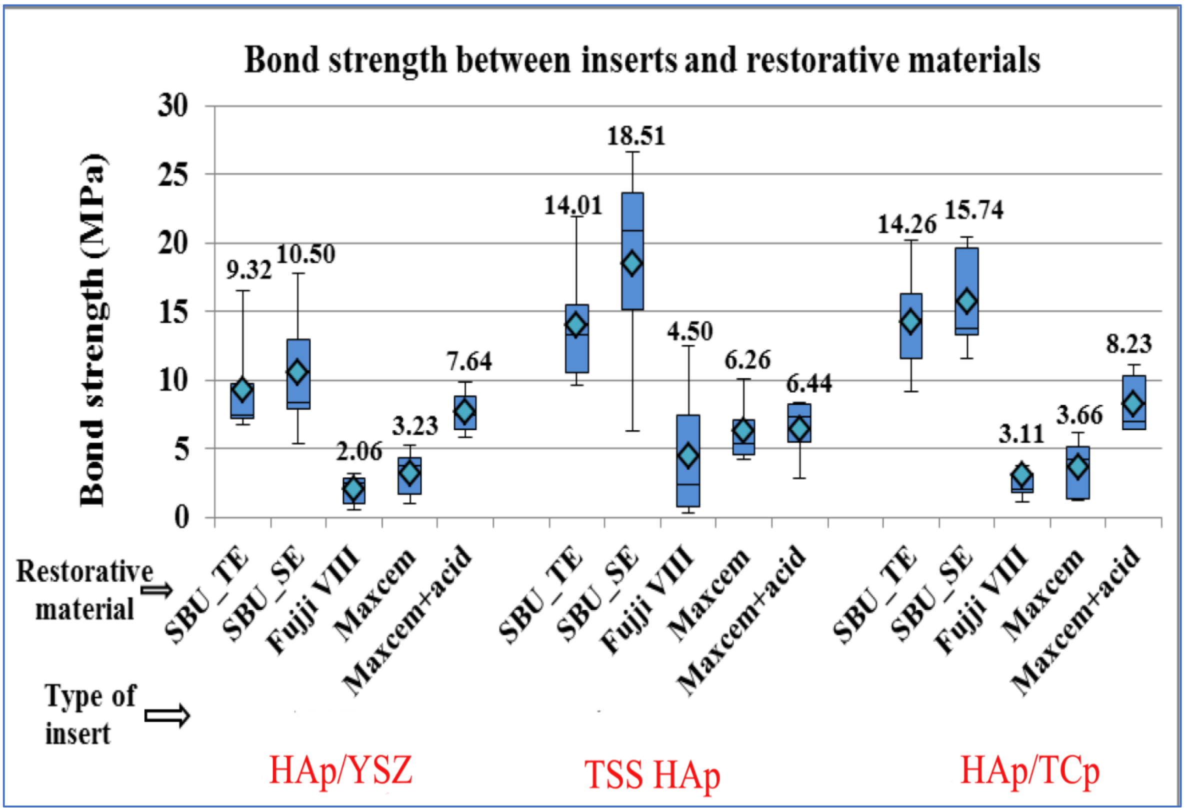

Figure 33. Box-and-whisker plots of SBS values between the tested groups.

Table 10. Summary of the GLM statistics. Mean and standard deviation (SD) values relate to the tested factors e.g. one insert type comprising SBS values for all restorative materials and vice versa one material/treatment group comprising SBS values for all inserts. Groups sharing the same letter were not significantly different (*p* > 0.05).

Source	DF	Seq SS	Adj SS	F	p
Insert	**2**	**203.57**	**161.99**	**5.77**	**0.005**
Restoration	**4**	**1,741.78**	**1,735.5**	**30.89**	**0.000**
Insert*restoration	**8**	**149.44**	**149.44**	**1.33**	**0.244**
Grouping information using Tukey Method and 95.0% confidence					
Insert	**Mean**	**Grouping**			
TSSHAp	**9.9**	**A**			
HAp/TCp	**8.9**	**AB**			
HAp/YSZ	**6.5**	**B**			
Restoration	**Mean**	**Grouping**			
Z250_SBU_SE	**14.9**	**A**			
Z250_SBU_TE	**12.5**	**A**			
Maxcem + etching	**7.4**	**B**			
Maxcem	**4.4**	**BC**			
Fuji VIII	**3**	**C**			

7. Discussion

The stoichiometric nature of the HAp powder, confirmed by the EDS analysis and by the absence of the phase transformation after sintering, was a great prerequisite for determining the effect of tetragonal zirconia on the fracture toughness, hardness and SBS of bioceramic inserts. It was shown previously that the absence of HAp phase transformation to other phases of calcium phosphate at high temperatures had a positive effect on the sintering process and consequently on the fracture toughness of sintered HAp based materials [188, 203, 204].

Further, the YSZ powder synthesized by plasma method consists of spherical nanoparticles uniformly distributed in the HAp matrix and a certain smaller number of spherical microparticles, has complete phase transformation of m-ZrO_2 to t-ZrO_2, at temperatures above 1250 °C. In order to improve fracture toughness of synthesized inserts, the idea was to use YSZ powder consisting of nanoparticles and microspheres and in that way to apply two different but synergetic mechanisms for improving fracture toughness.

The composite HAp/YSZ powder had similar particle size distribution as soft agglomerated HAp powder after homogenization and ultrasound treatment (agglomerated particles ranged from 200 nm to 5 μm [186,188]). Minimum agglomerate size values of HAp/YSZ powder approximately 300 mn, slightly larger than pure HAp, indicated the connection of YSZ particles to soft agglomerated HAp. This was a prerequisite for obtaining uniform and relatively dense green compacts. Dilatometric analysis of both HAp compacts (Figure 22), with and without 20 wt% of YSZ particles, shows differences in shrinkage during sintering at temperatures higher than 1000 °C, due to the presence of YSZ particles in the HAp matrix. The shrinkage of both samples becomes insignificantly small with heating after 1200 °C. Because of this, and the fact that at the temperatures in the range of 1200–1300 °C occurred full phase transformation of m-ZrO_2 to t-ZrO_2, it was decided to investigate the effect of the temperature of isothermal part of the sintering curves on the microstructure and the mechanical properties of the inserts at 1200 °C, 1250 °C and 1300 °C [184].

Within the sample pressed at 100 MPa, the porous microstructures (Figure 25), and relatively low hardness (Table 7) of sintered samples showed that the densification process was not completed. However, in the case of the insert sintered at 1300 °C, a relatively high value of fracture toughness 1.61 ± 0.04 MPam$^{1/2}$ indicated a positive effect of uniformly distributed t-ZrO_2 nanoparticles in the HAp matrix. Following the formation of green bodies under the 400 MPa isostatic pressure, significantly intensive densification was achieved, which is verified by microstructures shown in Figure 26, and by a higher hardness of about 4 GPa (Table 8).

The fracture toughness values higher than 1.80 MPam$^{1/2}$ showed the significant positive influence of integration YSZ on strengthening and reinforcing the matrix of HAp. The above-mentioned two possible mechanisms for increasing fracture toughness by incorporating YSZ synthesized by the plasma method could provide an explanation for the relatively high fracture toughness of the processed dentin substitutes. The first was based on the addition of mechanically superior deagglomerated and uniformly distributed stabilized nanoparticles of zirconium that would enable resistance to crack propagation through the material, by shortening the cracks and making the material tougher. The second is the effect due to the presence of hard microspheres of YSZ, which affects the crack shortening by hiding around the spherical micro-particles, whereby the crack loses energy and becomes shorter. Kumar et al. had earlier explained this toughening mechanism and the effect of spherical ZrO_2 particles on crack deflection [9]. Such mechanism of the influence of spherical micro-agglomerated HAp particles was later confirmed by Veljovic et al [185]. The effect of the integrated YSZ particles in the HAp matrix is evident by comparing hardness and fracture toughness of such inserts with those of a similar HAp without YSZ sintered at identical processing conditions (HV = 2.39 ± 0.24 GPa, K_{Ic} = 0.28 ± 0.080 MPam$^{1/2}$) [187].

The hardness values of the obtained HAp/YSZ inserts were in the range of previously published values for HAp-based bioceramic materials with incorporated various stabilized types of ZrO_2 [157,205- 207]. Considering that human dentin fracture hardness is within the range of 1.13–2.02 MPam$^{1/2}$, it can be concluded that the inserts obtained in this work have values closer to the upper limit. HAp/YSZ fracture toughness values from 1.82 ± 0.04 MPam$^{1/2}$ to 1.88 ± 0.03 MPam$^{1/2}$ are relatively high compared with the values previously published for dense bioceramic materials based on HAp [187, 188, 208, 209]. Relatively small variations between the inserts sintered at three different temperatures in the values of hardness and fracture toughness showed a significantly greater influence of the YSZ addition compared to the sintering temperature.

By comparing the values of fracture toughness and hardness of the inserts obtained in this study with these values of the HAp-based dental inserts previously published (HV = 3.05 ± 0.05 GPa, K_{Ic} = 1.30 ± 0.01 MPam$^{1/2}$ [14]), we can conclude that HAp/YSZ inserts are considerably harder and tougher. It could be concluded that in the case of all final stage temperatures, the tooth mechanics would be significantly improved after restoration with HAp/YSZ inserts. SBS values measured with commercial restorative materials during different clinical procedures did not show any important differences from the point of the application. For both protocols, the highest mean values of SBS were measured (9.32 ± 3.79 MPa in the case of „total-etch“, 10.50 ± 4.94 MPa in the case of „self-etch“ approach) for the insert sintered at 1300 °C. Results obtained for biphasic HAp/TCp inserts previously published [14] showed that in the case of the "total-etch" protocol, higher SBS values were obtained, while phosphoric acid etching did not have such a beneficial effect on adhesion in the case of HAp/YSZ inserts. This result can be explained by the fact that acid etching of YSZ ceramic, even with hydrofluoric acid, has a limited effect on bond strength [210]. In comparison to the previous findings for HAp/TCp inserts [14], the addition of 20% YSZ powder to HAp inserts may be responsible for the inefficiency of acid etching pre-treatment in this study. It can be concluded that resin-based composites could be adequately bonded to HAp/YSZ inserts sintered at 1300 °C. In addition, the values of fracture toughness and hardness of the inserts show the possibility of using them as substitutes for dentin.

Though the mean SBS values in the "self-etch" groups were slightly higher, there was no statistically significant difference between the protocols "total-etch" and "self-etch". The probable reason for this finding is the relative inefficiency of phosphoric acid in their clinically acceptable concentrations of 32–37 %. This would suggest equal opportunities for dentists without having to change their clinical procedures to apply their chosen adhesive application method.

The research has resulted in HAp and YSZ-based dentin substitutes, which can potentially be used as dental inserts in dental restorative medicine. The mechanical properties of insert fillers achieved in this study, as well as the contact mechanics between inserts and commercial adhesive and composite, obtained by application of two different clinical protocols, can be a good starting point for satisfactory tooth mechanics after the incorporation of the dentin substitutes.

The aim of this study was also to analyze comparatively the microstructure, phase composition, fracture toughness and hardness of different types of dental inserts based on HAp and also SBS between the inserts and different restorative materials. The influence of different clinical protocols on the SBS between the inserts and commercial dental adhesive and composites was also investigated [211].

In order to fulfil the aims of this work, for the preparation of dental inserts as dentin substitutes, two separate HAp powders and yttrium-stabilized zirconia powder were used. Soft agglomerated stoichiometric HAp nano-particles (Figure 20a) have been verified as adequate starting material for the application of two-step sintering, as the method which implies densification at certainly lower temperatures than traditional processes [187]. The highest density of 3.11 g/cm^3 near the theoretical for hydroxyapatite (3.16 g/cm^3) was reached during the optimization of two-step sintering conditions by applying 1075 °C in the first step and then at 980 °C as the temperature of the final step. Hydroxyapatite was not converted into β-TCp and α-TCp due to the relatively low temperature of the final sintering phase and the stoichiometric Ca/P ratio of the powder.

As a consequence, monophasic dense inserts (Figure 29a and 30a) were obtained (TSSHAp). On the other hand, spherically agglomerated rod-like particles (Figure 20b) were suitable for the preparation of controlled porous inserts (Figure 31) by traditional sintering at relatively high temperatures (2 h at 1200) °C. The high temperature and Ca/P ratio lower than stoichiometric have caused the partial conversion of HAp to more soluble phases, β-TCp and α-TCp (Figure 29b). Therefore, porous multiphase inserts HAp/TCp with density 2.79 g/cm^3 were obtained. The third used type of samples in this comparative study was the composite inserts based on 80 wt.% of soft agglomerated stoichiometric HAp nano-particles (Figure 20a), and 20 wt.% of nanosized yttrium-stabilized zirconia

(Figure 20c), sintered at 1300 ºC for 2 h [184,211]. As it was mentioned earlier in this work, during the previous investigation of processing conditions to optimize the mechanical properties and microstructure of inserts based on hydroxyapatite and zirconia, various pressures were applied during the formation of green bodies and different insert sintering temperatures. HAp/YSZ inserts isostatically pressed at 400 MPa and further sintered at 1300 ºC were utilized in the study due to measured fracture toughness close to the maximum values, maximum hardness, density and mean SBS values between inserts and resin based composites and commercial adhesive [184]. Although the sintering temperature was high, the HAp matrix densification was lower than in the case of TSSHAp, where, due to the stoichiometric Ca/P ratio of the powder, monophasic HAp matrix (Figure 29c), was obtained.

According to the density nearby to the theoretical value for HAp, the maximum hardness value (Table 9) was obtained in the case of TSSHAp inserts. Fracture toughness of these inserts was at the level close to literature values for human dentine [189]. Due to the lower densification of the HAp matrix in the presence of tough zirconia particles, a significantly lower hardness value was measured in the case of composite HAp/YSZ inserts. On the other hand, adding 20 wt.% of YSZ resulted in a significant improvement in the fracture toughness, which was a relatively high value for bioceramics based at HAp [184]. Controlled porous HAp/TCp inserts had hardness value similar to the hardness of HAp/YSZ, as well as similar to previously published results [212]. Fracture toughness of HAp/TCp inserts was in the range of values for human dentine (Table 9).

The effect of etching with standard 37% phosphoric acid, which was frequently utilized for dentin treatment during tooth restorations, is closely related to the microstructure and insert density. Owing to the highest density and no presence of β-TCp and α-TCp as the more dissolvable phases than hydroxyapatite, etching had the slightest impact on the surface of TSSHAp inserts (Figure 30). In the case of HAp/YSZ inserts, a more important etching effect was noted (Figure 32), although these inserts were extracted from the same HAp powder as TSSHAp and were not observed calcium phosphate phases after sintering in both cases. The most noteworthy impact of etching was observed within the case of HAp/TCp inserts, as a consequence of simultaneous effects of porous microstructure and the presence of more soluble β-TCp and α- TCp phases.

SBS was tested in this study as one of the usual methods for assessing the adhesion of dental materials. Shear was selected over tensile bond strength testing because of its easy performance, avoiding pre-test failures and as a general screening method indicating the adhesion quality between different restorative materials and HAp-based inserts. Despite HAp-based dental inserts are expected to be utilized as dentin substitutes enclosed in a restoration, shear loads may happen in multi-surfaced restorations including proximal tooth surfaces, necessitating such testing *in vitro*. It should be noted that SBS of a universal SBU adhesive to all three types of insert was comparable to SBS values of many different adhesives bonded to human dentin[213,211]. Maxcem cement was shown to be on the low end of the SBS spectrum in this investigation, similar to a prior study by Sarr et al. [214], in which microtensile bonding to dentin of a series of luting cements was examined. In spite of the fact that various bonding methods and substrates were utilized, Maxcem showed bond strength values less than 5 MPa in both experiments. When bonded to dentin, the current SBS findings for glass-ionomer Fuji VIII (*c*. 3.0 MPa) were slightly lower than those published in the literature for a comparable material (Fuji II), which ranged from 4.8 to 7.3 MPa [215,211]. Similarities in SBS to HAp-based inserts with formerly reported results on dentin for a variety of restorative materials indicate that HAp-based inserts have acceptable surface characteristics for clinical bonding.

In spite of the fact that Maxcem is self-adhesive resin cement, before application of cement, phosphoric acid etching of dental inserts was examined as a potential way to improve bond strength. The insert microstructure varies from that of dentin as there are no collagen fibrils exist in inserts. Exposure of collagen fibrils in dentin during phosphoric acid etching is followed by adhesive monomers penetrating into the collagen fibrillar network [216]. Acid-etching of dentin is not recommended for luting cement because the increased viscosity of cements prevents them from penetrating the collagen network, leaving collagen fibrils uncovered but not encapsulated. With HAp-based inserts, there is no such problem. Acid pretreatment of HAp-based inserts also with phosphoric acid, which is weaker than e.g. hydrofluoric acid indicated for indirect restoration, indicates bonding improvements for Maxcem luting cement, probably due to increased surface roughness and open pores.

Lower SBS ofto HAP/TSZ inserts compared to another two types of insert may be related to the presence of zirconia which is recognized to be an exceedingly difficult bonding substrate. Stronger acidic pretreatments or other types of pretreatment, such as selective infiltration etching or air-abrasion [217], may be more suited for enhanced binding to inserts containing YSZ and deserve further investigation.

Even after pre-treatment with phosphoric acid, the denser and more compact surface of TSSHAp inserts suggests that additional bonding mechanisms may be at play particularly in the SBU_SE groups. Chemical bonding and surface free energy of these inserts should be more thoroughly investigated as possible contributors factors to improved bonding in the SBU_SE groups. Chemical bonding between 10-MDP monomer utilized in HAp and SBU was formerly confirmed [218]. Dentin etching with phosphoric acid has been found to increase contact angles of universal adhesives, including SBU, thus creating the surface less susceptible for adhesive distribution compared to the SE procedure in which does not include acid etching [219]. Because HAp is the prime component of hard dental tissues, this might also be the case with synthetic HAp inserts, resulting in a slightly higher SBS when using the SE adhesive application technique rather than the TE adhesive application protocol.

8. Conclusion

In this work, starting from stoichiometric hydroxyapatite (HAp) powder synthesized by modified precipitation method and yttrium-stabilized zirconia (YSZ) powder synthesized by plasma method, HAp/YSZ bioceramic inserts were successfully processed. The addition of YSZ particles influenced the simultaneous increase of HAp's hardness and fracture toughness, although the dilatometric analysis indicated a decrease in shrinkage of HAp matrix in the presence of YSZ particles. Fracture toughness of HAp/YSZ inserts above 1.80 MPam$^{1/2}$ indicated the significant positive effect of incorporating stabilized tetragonal ZrO_2 particles on HAp matrix reinforcement. The fracture toughness values of the sintered inserts in this study are nearby to the human dentine's upper limit. Addition of YSZ has greater effect on hardness and fracture toughness of the inserts compared to the temperature of the final sintering step.

SBS values between HAp/YSZ inserts and commercial adhesive and composite showed that the etching with phosphoric acid has no influence on the bond strength. Resin-based composites might be satisfactorily bonded to HAp/YSZ inserts using the "self-etch" adhesive application protocol, as a clinically simpler method compared to "total-etch", yet with a similar result. The inserts ' values of fracture toughness and hardness indicated the possibility of their utility as dentin substitutes.

HAp/YSZ insert obtained by isostatic pressing and sintering at 1300 ºC for 2 h was compared with monophasic two-step sintered dense HAp inserts (TSSHAp) and biphasic single-step sintered controlled porous inserts based on HAp and TCp (HAp/TCp). Before the application of 'total-etch' protocol, a more articulated impact of etching with 37% phosphoric acid was appeared within the case of HAp/TCp compared to TSSHAp inserts, as a result of the nearness of more soluble α- and β-TCp phases and controlled porous microstructure. Fracture toughness of three types of inserts ranged between 1.02 - 1.85 MPam$^{1/2}$ (greatest value within the case of HAp/YSZ), while hardness values were within the range of 3.71 to 5.22 GPa (greatest value in the case of TSSHAp). Phosphoric acid etching before application of SBU had no effect on subsequent SBS, but acid pre-treatment improved SBS between inserts and Maxcem compared to direct application of cement. No statistical significance was identified between TSSHAp and HAp/TCp inserts adhesively bonded following the TE or SE protocols, TSSHAp and HAp/TCp inserts showed comparable and relatively high SBS values, certainly higher than HAp/YSZ inserts. In the case of TSSHAp inserts, slightly higher mean SBS values were measured and the maximum mean SBS value of 18.51 MPa was determined between TSSHAp inserts and Filtek Z250_SBU following the 'self-etch' protocol. The mechanical properties of used inserts and SBS values demonstrated the potential for their use as dentin substitute material and enable restore of teeth using calcium phosphate-based dental inserts in combination with composites and adhesives following current application protocols.

9. References

[1] Mythili. P., Janis. L., Kristine, Dania L. Alain. L., Liga. B.: Fabrication, Properties and Applications of Dense Hydroxyapatite: A Review. Journal of Functional Biomaterials. 2015, 6, 1099-1140.

[2] Ducheyne. P., Healy. K., Hutmacher. D. E., Grainger. D. W., Kirkpatrick, C. J.: Comprehensive Biomaterials. Six-Volume Set. Elsevier, Amsterdam, Netherlands. 2011.

[3] Ratner. B. D., Hoffman. A. S., Schoen. F. J., Lemons. J. E.: Biomaterials science: an introduction to materials in medicine. MRS Bulletin. 2006, 31(01), 58-60.

[4] Chem. J., Dalton. T., Vallet-Regí. M.: Ceramics for medical applications. Journal of the Chemical Society, Dalton Transactions. 2001, 2, 97-108.

[5] Heimke. G.: Graphical Abstract. Angewandte Chemie International Edition in English. 1989, 28(4), 397-534.

[6] Dorozhkin. S. V., Epple, M.: Biological and medical significance of calcium phosphates. Angewandte Chemie International Edition, 2002, 41, 3130-3146.

[7] Le Geros. R. Z.: Calcium phosphate-based osteoinductive materials. Chemical Reviews. 2008, 108, 4742-4753.

[8] Le Guéhennec, L., Soueidan, A., Layrolle, P., Amouriq, Y.: Surface treatments of titanium dental implants for rapid osseointegration. Dental Materials, 2007, 23, 844-854.

[9] Kumar. R., Prakash. K. H., Cheang. P., Khor, K. A.: Microstructure and mechanical properties of spark plasma sintered zirconiahydroxyapatite nano-composite powders. Acta Materialia, 2005, 53, 2327-2335.

[10] Roozbahani. M., Alehosseini. M., Kharaziha. M., Emadi. R.: Nano-calcium phosphate bone cement based on Si-stabilized α-tricalcium phosphate with improved mechanical properties, Materials Science and Engineering C. 2017, 81, 532-541.

[11] da Rosa. W. L. O., Cocco. A. R., Silva. T. M. D., Mesquita. L.C., Galarca. A. D., Silva. A. F. D., Piva, E.: Current trends and future perspectives of dental pulp capping materials: a systematic review, Journal of Biomedical Materials Research Part B. 2018, 106(3), 1358-1368.

[12] George. L. A., Richards. N. D.: Polymerization shrinkage in a composite restoration involving a glass-ceramic insert. Journal of Dental Research. 1993, 72, 351.

[13] Hahn. P., Schaller. H. G., Müllner. U., Hellwig. E.: Marginal leakage in class II-restorations after use of ceramic inserts luted with different materials. Journal of Oral Rehabilitation. 1998, 25, 567-574.

[14] Lezaja. M., Veljovic. Dj., Manojlovic. D., Milosevic. M., Mitrovic. N., Janackovic. Dj.,Miletic, V.: Bond strength of restorative materials to hydroxyapatite inserts and dimensional changes of insert containing restorations during polymerization. Dental Materials. 2015, 31, 171-181.

[15] Marjanovic. J., Veljovic. Dj., Stasic. J., Savic-Stankovic. T., Trifkovic. B., Miletic. V.: Optical properties of composite restorations influenced by dissimilar dentin restoratives. Dental Materials. 2018, 34, 737-745.

[16] Zaytsev, D., Ivashov, A. S., Mandra, J. V., Panfilov, P.: On the deformation behavior of human dentin under compression and bending. Materials Science and Engineering C. 2014, 41, 83-90.

[17] Lenzi, T. L., Guglielmi cde, A., Arana-Chavez, V. E., Raggio, D. P. Tubule density and diameter in coronal dentin from primary and permanent human teeth. Microsc Microanal, 2013, 19, 1445-1449.

[18] Trowbridge, H. O.: Dentin today: research reveals new information about the complexity of dentin. Dentistry. 1982, 2, 22-29.

[19] Irini, D.: Sideridou Chapter in: Encyclopedia of Polymer Composites: Properties, Performance and Applications. Editor: Mikhail Lechkov and Sergej Prandzheva. Nova Science Publishers. 2010, 593-619.

[20] Brady. L. A.: Why do we Etch Dentin? Etched and Unetched Dentin. Dental Materials. 2011. https://leeannbrady.com/esthetic-dentistry/why-do-we-etch-dentin.

[21] Sarrett, D. C.: Clinical challenges and the relevance of materials testing for posterior composite restorations. Dental materials, 2005, 21, 9-20.

[22] Van Nieuwenhuysen, J. P., D'hoore, W., Carvalho. J., QVIST. V. Long-term evaluation of extensive restorations in permanent teeth. Journal of dental, 2003, 31, 395-405.

[23] Gagliardi. M.: Bioactive Glasses, Ceramics, Composites, Other Advanced Materials, Report Code: AVM054A, Analyst, 2006. http://www.bccresearch.com/

[24] Boccaccini, A. R.: Assessment of brittleness in glass-ceramics and particulate glass matrix composites by indentation data. Journal of materials science. 1996, 15, 1119-1121.

[25] Burg. K. L., Porter. S., Kellam, J. F.: Biomaterial developments for bone tissue engineering. Biomaterials. 2000, 21 (23), 2347-2359.

[26] Braun, S.:Glass Ionomer Cements for Primary Teeth – Pediatric Dentistry. 2015. https://www.dentalnews.com/2015 /06/16/glass-ionomer-cements-primary-teeth/ .

[27] El-Meliegy. E. and van Noort. R.: Glasses and Glass Ceramics for Medical Applications, Springer Science+Business Media, New York, LLC. 2012.

[28] Cho. M., Lee. Y., Lim. B., Lim. Y.: Changes in optical properties of enamel porcelain after repeated external staining. Journal of Prosthetic Dentistry. 2006, 95 (6), 437-443.

[29] Poitout. D. G. (ed.). Biomechanics and Biomaterials in Orthopedics Springer-Verlag London. 2004.

[30] Fishmann. G., Hench, L., Bioceramics: Materials and Applications. American Ceramic Society, Westerville, OH, USA, 1994.

[31] Heffernan. M., Aquilino. S., Arnold. M., Haselton. D., Stanford. C., Vargas. M.: Relative translucency of six all-ceramic systems. Part I: Core materials. Journal of Prosthetic Dentistry. 2002a, 88 (1), 4-9.

[32] Heffernan. M., Aquilino. S., Arnold. M., Haselton. D., Stanford. C., Vargas. M.: Relative translucency of six all-ceramic systems. Part II: Core and veneer materials. Journal of Prosthetic Dentistry. 2002b, 88 (1), 10-15.

[33] Hench. L. L.: Bioceramics. Journal of the American Ceramic Society. 1998, 81 (7), 1705-1728.

[34] Dubok. V. A.: Bioceramics - Yesterday, Today, Tomorrow. Powder Metallurgy and Metal Ceramics. 2000, 39, 381-394.

[35] Salinas. A. J., Vallet-Regí. M.: Evolution of Ceramics with Medical Applications. Zeitschrift für anorganische und allgemeine Chemie. 2007, 11-12, 1762-1773

[36] Lowenstam. H. A., Weiner. S.: On biomineralization. Oxford University Press: New York, USA. 1989.

[37] Weiner. S., Addadi. L.: Design strategies in mineralized biological materials. Journal of Materials Chemistry. 1997, 7, 689-702.

[38] Weiner. S., Wagner. H. D.: The material bone: structure-mechanical function relations. Annual review of materials science. 1998, 28, 271-298.

[39] Boskey. A.: Bone mineral crystal size. Osteoporosis International. 2003, 14, 16-21.

[40] Alivisatos, A. P.: Biomineralization: Enhanced: Naturally Aligned Nanocrystals. Science. 2000, 289(5480), 736-737.

[41] Cai. Y., Tang, R.: Calcium phosphate nanoparticles in biomineralization and biomaterials. Journal of Materials Chemistry. 2008, 18, 3775-3787.

[42] Ginebra. M. P., Driessens, F. C. M., Planell, J. A.: Effect of the particle size on the micro and nanostructural features of a calcium phosphate cement: a kinetic analysis. Biomaterials. 2004, 25, 3453-3462.

[43] Dorozhkin, S.: Nanodimensional and Nanocrystalline Apatites and Other Calcium Orthophosphates in Biomedical Engineering, Biology and Medicine. Materials, 2009, 2(4), 1975-2045.

[44] Karch, J., Birringer, R., Gleiter, H.: Ceramics ductile at low temperature. Nature, 1987, 330(6148), 556-558.

[45] Webster, T. J.: Nanophase ceramics: The future orthopedic and dental implant material. Advances in Chemical Engineering. 2001, 27, 125-166.

[46] Tasker. L. H., Sparey-Taylor. G. J., Nokes. L. D.: Applications of nanotechnology in orthopaedics. Clinical Orthopaedics and Related Research. 2007, 456, 243-249.

[47] Afshar. A., Ghorbani. M., Ehsani. N., Saeri. MR., Sorrell. CC.: Some important factors in the wet precipitation process of hydroxyapatite. Material and Design. 2003, 24, 197-202.

[48] Arcos, D., Vallet-Regí. M.: Sol–gel silica-based biomaterials and bone tissue regeneration. Acta Biomaterialia. 2010, 6, 2874-2888.

[49] Kim. IS., Kumta. PN.: Sol-gel synthesis and characterization of nanostructured hydroxyapatite powder. Materials Science and Engineering, Part B. 2004, 111, 232–236.

[50] Fukui K, Kaneuji A., Sugimori T., Ichiseki T., Kitamura K., Matsumoto. T.: Wear comparison between a highly cross-linked polyethylene and conventional polyethylene against a zirconia femoral head: minimum 5-year follow-up. Journal of arthroplasty. 2011, 26, 45-49.

[51] White. A. A., Kinloch. I. A., Windle. A. H., Best. S. M.: Optimization of the sintering atmosphere for high-density hydroxyapatite-carbon nanotube composites. Journal of the Royal Society Interface. 2010, 7, 529-539.

[52] Nath, S., Biswas. K., Basu. B.: Phase stability and microstructure development in hydroxyapatite-mullite system. Scripta Materialia. 2008, 58, 1054-1057.

[53] Kazuya. D., Takayasu. K., Yusuke. M., Hiroshi. O., Koji M., et al.: Osseointegration aspects of placed implant in bone reconstruction with newly developed block-type interconnected porous calcium hydroxyapatit. Journal of Applied Oral Science. 2016, 24(4), 325-331.

[54] Sopyan. I., Mel. M., Ramesh. S., Khalid. K. A.: Porous hydroxyapatite for artificial bone applications. Science and Technology of Advanced Materials. 2007, 8, 116-123.

[55] Cui. F. Z., Li. Y., Ge. J.: Self-assembly of mineralized collagen composites. Materials Science and Engineering. 2007, 57, 1-27.

[56] Yan. X., Yu. C., Zhou. X., Tang. J., Zhao. D.: Highly ordered mesoporous bioactive glasses with superior in vitro bone-forming bioactivities. Angewandte Chemie International Edition. 2004, 43, 5980-5984.

[57] Dorozhkin S. V.: Bioceramics based on calcium orthophosphates (Review). Glass and Ceramics. Biomaterials for Medicine. 2007, 64, 442-447.

[58] Anushini. I. M., Jie Mohan. J. E., Oana. B., Aldo. R. B.: Dipping and electrospraying for the preparation of hydroxyapatite foams for bone tissue engineering. Biomedical Materials. 2008, 3(2), 025009

[59] Wang. L., Nancollas. G. H., Henneman. Z. J., Klein. E., Weiner. S.: Nanosized particles in bone and dissolution insensitivity of bone mineral. Biointerphases. 2006, 1, 106-111.

[60] Gao. H., Ji. B., Jager. I. L., Arz. E., Fratzl. P.: Materials become insensitive to flaws at nanoscale: lessons from nature. Proceedings of the National Academy of Sciences. 2003, 100(10), 5597-5600.

[61] Gupta. H. S., Seto. J., Wagermaier. W., Zaslansky. P., Boesecke. P., Fratzl. P.: Cooperative deformation of mineral and collagen in bone at the nanoscale. Proceedings of the National Academy of Sciences. 2006, 103, 17741-17746.

[62] Porter. A. E., Nalla. R. K., Minor. A., Jinschek. J. R., Kisielowski. C., Radmilovic. V., Kinney. J. H., Tomsia. A.P., Ritchie. R.O.: A transmission electron microscopy study of mineralization in age-induced transparent dentin. Biomaterials. 2005, 26, 7650-7660.

[63] Dorozhkin, S. V.: Calcium orthophosphates. Journal of Materials Science. 2007, 42, 1061-1095.

[64] Kirkham. J., Brookes. S. J., Shore. R. C., Wood. S. R., Smith. D. A., Zhang. J., Chen. H., Robinson. C.: Physico-chemical properties of crystal surfaces in matrix-mineral interactions during mammalian biomineralisation. Current Opinion in Colloid and Interface Science. 2002, 7, 124-132.

[65] Daculsi. G., Mentanteau. J., Kerebel. L.M., Mitre. D.: Length and shape of enamel crystals. Calcified Tissue International. 1984, 36, 550-555.

[66] Robinson, C., Connell, S., Kirkham, J., Shorea, R., Smith, A.: Dental enamel – a biological ceramic: regular substructures in enamel hydroxyapatite crystals revealed by atomic force microscopy. Journal of Materials Chemistry. 2004, 14, 2242-2248.

[67] Dorozhkin. S. V.: Calcium orthophosphates in nature, biology and medicine. Materials. 2009, 2, 399-498.

[68] Chen. H., Tang. Z., Liu, J., Sun. K., Chang. S. R., Peters. M. C., Mansfield. J. F., Czajka- Jakubowska. A., Clarkson. B.H.: Acellular synthesis of a human enamel-like microstructure. Advanced Materials. 2006, 18, 1846-1851.

[69] Sivakumar. M., Oliveira. V., Vilar. R.: Sealing of human dentinal tubules by KrF 248 nm laser radiation. Journal of Laser Applications. 2006, 18(4), 330-333.

[70] Valeri. S., Gshalaev and Aleksandra. C., Demirchan. C: Hydroxyapatite: synthesis, properties, and applications. 2012.

[71] Carlo. M., Antonio. S., Giovanna. I., Giovanna. O.: Maxillary Sinus Augmentation Using an Engineered Porous Hydroxyapatite: A Clinical, Histological, and Transmission Electron Microscopy Study in Man. Journal of Oral Implantology. 2006, 32(3), 122-131.

[72] Hench. L. L, Thompson. I.: Twenty-first century challenges for biomaterials. Journal of Royal Society Interface. 2010, 7(4), S379-S391.

[73] Weiner. S., Wagner. HD.: The material bone: Structure-Mechanical Function Relations. Annual Review of Materials Science. 1998, 28, 271-298.

[74] Ripamonti. U., Crooks. J, Khoali. L, Roden. L.: The induction of bone formation by coralderived calcium carbonate/hydroxyapatite constructs. Biomaterials. 2009, 30, 1428-1439.

[75] Ben-Nissan. B., Milev. A., Vago. R.: Morphology of sol–gel derived nano-coated coralline hydroxyapatite. Biomaterials. 2004, 25, 4971-4975.

[76] Lambert. F., Lecloux. G., Leonard. A., Sourice. S., Layrolle. P., Rompen. E.: Bone Regeneration Using Porous Titanium Particles versus Bovine Hydroxyapatite: A Sinus Lift Study in Rabbits. Clinical Implant Dentistry and Related Research. 2011, 15(3), 412-426.

[77] Hayami. T., Hontsu. S., Higuchi. Y., Nishikawa. H., Kusunoki. M.: Osteoconduction of a stoichiometric and bovine hydroxyapatite bilayer-coated implant. Clinical Oral Implants Research. 2010, 22(7), 774-776.

[78] Boutinguiza. M., Pou. J., Comesaña. R., Lusquiños. F., de Carlos. A., León B.: Biological hydroxyapatite obtained from fish bones. Materials Science and Engineering: C. 2012, 32, 478-486.

[79] Muzzarelli. R. A. A.: Chitins and chitosans for the repair of wounded skin, nerve, cartilage and bone. Carbohydr Polym. 2009, 76, 167-182.

[80] Fraga. A. F., Filho. E. de A., Rigo. E. C. da S., Boschi, A. O.: Synthesis of chitosan/hydroxyapatite membranes coated with hydroxycarbonate apatite for guided tissue regeneration purposes. Applied Surface Science. 2011, 257(9), 3888–3892.

[81] Zhang. Y., Liu. Y., Ji. X., Banks. C. E., Zhang. W.: Conversion of egg-shell to hydroxyapatite for highly sensitive detection of endocrine disruptor bisphenol. Journal of Materials Chemistry. 2011, 21, 14428-14431.

[82] Goller. G., Oktar. F. N., Agathopoulos. S., Tulyaganov. D. U., Ferreira. J. M. F., Kayali. E. S., Peker. I.: Effect of sintering temperature on mechanical and microstructural properties of bovine hydroxyapatite (BHA). Journal of Sol-Gel Science and Technology. 2006, 37, 111-115.

[83] Vallet-Regí. M., Peña. J., Izquierdo-Barba. I.: Synthesis of β-tricalcium phosphate in layered or powdered forms for biomedical applications. Solid State Ionics. 2004, 172, 445-449.

[84] Weller, M., Overton, T., Rourke, J., and Armstrong, F.: Links to Inorganic Chemistry 7th Edition. University of Liverpool. England and Wales License. 2018. https://www.chemtube3d.com/sshydroxyapatite/

[85] Stanciu. GA., Sandulescu. I., Savu. B., Stanciu. SG., Paraskevopoulos. KM., Chatzistavrou. X., Kontonasaki. E., Koidis. P.: Investigation of the Hydroxyapatite Growth on Bioactive Glass Surface. Journal of Biomedical and Pharmaceutical Engineering. 2007, 1, 34-39.

[86] Hench. L. L., Wilson. J.: Bioactive Glasses. An Introduction to Bioceramics. Singapore: World Scientific Publishing. 1993, 1, 41-62.

[87] Le Geros. R. Z.: Properties of osteoconductive biomaterials: calcium phosphates. Clinical Orthopaedic and Related Research. 2002, 395, 81-98.

[88] Ramesha. S., Awb. K. L., Tolouеic. R., Amiriyanc. M., Tanb. Hamdia. C. Y., M., Purbolaksonoa. J., Hassana. M., Tengd. W. D.: Sintering properties of hydroxyapatite powders prepared using different methods. Ceramics International. 2013, 1, 39, 111-119.

[89] Santos. M. H, de Oliveira. M., de Freitas Souza. P., Mansur. H. S., Vasconcelos. W. L.: Synthesis control and characterization of hydroxyapatite prepared by wet precipitation process. Journal of Materials Research. 2004, 7(4), 625-630.

[90] Manuel. C. M., Ferraz. M. P., Monteiro F. J.: Nanoapatite and microporous structures of hydroxyapatite. Journal of applied biomaterials & biomechanics. 2003, 2(2), 74-80.

[91] Manuel. C. M., Ferraz. M. P., Monteiro. F. J.: Synthesis of hydroxyapatite and tri calcium phosphate nanoparticles. Preliminary Studies. Key Engineering Materials. 2003, 240-242, 555-558.

[92] Manafi. S. A., Joughehdoust. S.: Synthesis of hydroxyapatite nanostructure by hydrothermal condition for biomedical application. Iranian Journal of Pharmaceutical Sciences. 2009, 5(2), 89-94.

[93] Chai. C. S., Ben-Nissan. B.: Bioactive nanocrystalline sol-gel hydroxyapatite coatings. Journal of Materials Science: Materials in Medicine. 1999, 10, 465-469.

[94] Shikhanzadeh. M.: Direct formation of nanophase hydroxyapatite on cathodically polarized electrodes. Journal of Materials Science: Materials in Medicine. 1998, 9, 67-72.

[95] Kimura. I.: Synthesis of hydroxyapatite by interfacial reaction in a multiple emulsion. Research Letters in Materials Science. 2007, 1-4.

[96] Tas. A. C.: Synthesis of biomimetic Cahydroxyapatite powders at 37 degrees C in synthetic body fluids. Biomaterials. 2000, 21, 1429-1438.

[97] Thamaraiselvi. T. V., Prabakaran. K., Rajeswari. S.: Synthsis of hydroxyapatite that mimic bone mineralogy. Trends in Biomaterials and Artificial Organs. 2006, 19(2), 81-83.

[98] Rao. R. R., Roopa. H. N., Kannan. T. S.: Solid state synthesis and thermal stability of HAP and HAP-β-TCP composite ceramic powders. Journal of Materials Science: Materials in Medicine. 1997, 8, 511-518.

[99] Gshalaev. I., Valeri. S., Demirchan. II., Aleksandra. C.: Hydroxyapatite: synthesis, properties, and applications. Nova Science Publishers. 2012, 549, 72-dc23, 017836.

[100] Adzila. S., Sopyan. I., Hamdi. M., Ramesh. S.: Mechanochemical Synthesis of Nanosized Hydroxyapatite Powder and its Conversion to Dense Bodies. Materials Science Forum. 2011, 694, 118-122.

[101] Coreño. A. J., Coreño. A. O., Cruz. R. JJ., Rodríguez. C. C.: Mechanochemical synthesis of nanocrystalline carbonate-substituted hydroxyapatite. Optical Materials. 2005, 27, 1281- 1285.

[102] Nasser. Y.M.: Characterization, thermal stability and sintering of hydroxyapatite powders prepared by different routes. Materials Chemistry and Physics. 2005, 94, 333-341.

[103] Saeri. M. R., Afshar. A., Ghorbani. M., Ehsani. N., Sorrell. CC.: The wet precipitation process of hydroxyapatite. Materials Letters. 2003, 57, 4064-4069.

[104] Afshar. A., Ghorbani. M., Ehsani. N., Saeri MR, Sorrell CC.: Some important factors in the wet precipitation process of hydroxyapatite. Materials and Design. 2003, 24, 197-202.

[105] Arcos. D., Vallet-Regí. M.: Sol-gel silica based biomaterials and bone tissue regeneration. Acta Biomater, Acta Biomaterialia. 2012, 6(8), 2874-2888.

[106] Chen. J., Wang. Y., Chen. X., Ren. L., Lai. C., He. W., Zhang. Q.: A simple sol-gel techniquefor synthesis of nanostructured hydroxyapatite, tricalcium phosphate and biphasic powders. Materials Letters. 2011, 65, 1923-1926.

[107] Bajgai. M. P., Parajuli. D. C., Park. S. J., Chu K. H., Kang. H. S., Kim. H. Y.: In vitro bioactivity of sol-gel-derived hydroxyapatite particulate nanofiber modified titanium. Journal of Materials Science: Materials in Medicine. 2010, 21, 685-694.

[108] Goto. T., Kim. I. Y., Kikuta. K., Ohtsuki C.: Hydrothermal synthesis of composites of wellcrystallized hydroxyapatite and poly(vinyl alcohol) hydrogel. Materials Science and Engineering: C. 2012, 32, 397-403.

[109] Liu. H. S., Chin T. S., Lai L. S., Chiu S. Y., Chung. K. H., Chang. C. S., Lui. M. T.: Hydroxyapatite synthesized by a simplified hydrothermal method. Ceramics International. 1997, 23, 19-25.

[110] Hattori. T., Lwadate. Y.: Hydrothermal Preparation of Calcium Hydroxyapatite Powders. Journal of the American Ceramic Society 1990, 73, 1803-1805.

[111] Murakami. S., Kato. K., Enari. Y., Kamitakahara. M., Watanabe. N., Ioku. K.: Hydrothermal synthesis of porous hydroxyapatite ceramics composed of rod-shaped particles and evaluation of their fracture behavior Ceramics International. 2012, 38, 1649-1654.

[112] Wei. G., Ma. P.X.: Structure and properties of nano-hydroxyapatite/polymer composite scaffolds for bone tissue engineering. Biomaterials. 2004, 25, 4749-4757.

[113] Kuroda. K., Nakamot. S., Miyashita. Y., Ichino. R., Okido. M.: Osteoinductivity of HAp films with different surface morphologies coated by the thermal substrate method in aqueous solutions. Materials Transactions. 2006, 47, 1391-1394.

[114] Halouani. R., Bernache-Assolant. D., Champion. E., Ababou A.: Microstructure and related mechanical properties of hot pressed hydroxyapatite ceramicsJournal of Materials Science: Materials in Medicine. 1994, 5, 563-568.

[115] Itatani. K., Tsuchiya. K., Sakka. Y., Davies. I.J., Koda. S.: Superplastic deformation of hydroxyapatite ceramics with B2O3 or Na2O addition fabricated by pulse current pressure sinteringJournal of the European Ceramic Society. 2011, 31, 2641-2648.

[116] Verma. D., Katti. K., Katti. D.: Bioactivity in in situ hydroxyapatite-polycaprolactone composites. Journal of Biomedical Materials Research Part A. 2006, 78, 772–780.

[117] Wang. M.: Developing bioactive composite materials for tissue replacement. Biomaterials. 2003, 24, 2133-2151.

[118] Viswanath. B., Ravishankar. N.: Interfacial reactions in hydroxyapatite/alumina nanocomposites. Scripta Materialia. 2006, 55, 863-866.

[119] Hasegawa. M., Sudo. A.: In vivo wear performance of highly cross-linked polyethylene vs. yttria stabilized zirconia and alumina stabilized zirconia at a mean seven-year follow-up. BMC Musculoskeletal Disorders. 2013, 14(1), 154-160.

[120] Jones. A. C., Arns. C. H., Sheppard. A. P., Hutmacher. D. W., Milthorpe. B.K., Knackstedt. M.A.: Assessment of bone ingrowth into porous biomaterials using MICRO-CT. Biomaterials. 2007, 28, 2491-2504.

[121] Ayers. R. A., Simske. S. J., Nunes. C. R., Wolford. L. M.; Long-term bone ingrowth and residual microhardness of porous block hydroxyapatite implants in humans. Journal of Oral and Maxillofacial Surgery. 1998, 56, 1297-1302.

[122] Charriere. E., emaitre, J., Zysse. P.: Hydroxyapatite cement scaffolds with controlledmacroporosity: Fabrication protocol and mechanical properties. Biomaterials. 2003, 24, 809-817.

[123] Jang. D. W., Franco. R. A., Sarkar. S. K., and Lee. B. T.: Fabrication of Porous Hydroxyapatite Scaffolds as Artificial Bone Preform and its Biocompatibility Evaluation. ASAIO Journal. 2014, 60(2), 216-223.

[124] Rainer, A,. Giannitelli,S .M., Abbruzzese, F,. Traversa, E., Licoccia. S., Trombetta, M.: Fabrication of bioactive glass–ceramic foams mimicking human bone portions for regenerative medicine. Acta Biomaterialia. 2008, 4,362-369.

[125] Dorozhkin. S. V.: Calcium Orthophosphate-Based Bioceramics. Materials. 2013, 6(9), 3840-3942.

[126] Anushini I. M., Jie. H., Mohan. J. E., Oana. B., Aldo. R. B.: Dipping and electrospraying for the preparation of hydroxyapatite foams for bone tissue engineering. Biomedical Materials. 2008, 3, 493-497

[127] Lu. J. X., Flautre. B., Anselme. K., Hardouin. P., Gallur. A., Descamps. M., Thierry. B.: Role of interconnections in porous bioceramics on bone recolonization in vitro and in vivo. Journal of Materials Science: Materials in Medicine 1999, 10, 111-120.

[128] Piconi. C., Maccauro. G.L.: Zirconia as a ceramic biomaterial. Biomaterials. 1999, 20(1), 1–25.

[129] Díaz-Parralejo. A., Macías-García. A., Sánchez-González. J., Díaz-Díez. M. Á., Cuerda-Correa, E. M.: A novel strategy for the preparation of yttria-stabilized zirconia powders. Journal of Non-Crystalline Solids. 2011, 357(3), 1090-1095.

[130] Zijun. Z., Jiurong. L., Fenglong. W., Jing. K., Xinzhen. W., Fabrication of bulk macroporous zirconia by combining sol–gel with calcination processes. Ceramics International. 2011, 37 (7), 2549-2553.

[131] Wang. J. A., Valenzuela. M. A., Salmones. J., Vázquez. A., Garcia-Ruiz. A., Bokhimi. X.: Comparative study of nanocrystalline zirconia prepared by precipitation and sol–gel methods. Catalysis Today. 2001, 68(1-3), 21-30.

[132] Felora. H., Reza. B. A.: Synthesis and characterization of nanocrystalline zirconia powder by simple sol–gel method with glucose and fructose as organic additives. Powder Technology. 2011, 205(1-3), 193-200.

[133] De la Rosa. J. R., Hernandez. A., Rojas. F., Ledezma. J. J.: Sol–gel synthesis and characterization of novel La, Mn and Fe doped zirconia: Catalytic combustion activity of trichloroethylene. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2008, 315(1-3), 147–155.

[134] Helmer. J. D, Driskell T. D. Research on bioceramics. Symposium on use of ceramics as surgical implants. Clemson University, South Carolina: USA 1969.

[135] Luthard. R. G., Holzhüter. M., Sandkuhl. O., Herold. V., Schnapp. J. D., Kuhlisch. E., Walter. M.: Reliability and properties of ground Y-TZP-zirconia ceramics. Journal of Dental Research. 2002, 81, 487-491.

[136] Corazza. P. H., de Castro. H. L., Feitosa. S. A., Kimpara. E. T., Della Bona, A.: Influence of CAD-CAM diamond bur deterioration on surface roughness and maximum failure load of Y-TZP-based restorations. American Journal of Dentistry. 2015, 28, 95-99.

[137] Cales. B.: Colored zirconia ceramics for dental applications. Bioceramics. 1998, 11, 591-594.

[138] Liu. D., Matinlinna. J. P., Pow. E.H.N.: Insights into porcelain zirconia bonding. Journal of Adhesion Science and Technology. 2012, 26, 1249-1265.

[139] Coli. P., Karlsson. S.: Precision of a CAD/CAM technique for the production of zirconium dioxide copings. International Journal of Prosthodontics. 2004, 17, 577-580.

[140] Abduo. J., Lyons. K., Swain. M.: Fit of zirconia fixed partial denture: A systematic review. Journal of Oral Rehabilitation. 2010, 37, 866-876.

[141] Boitelle. P., Mawussi. B., Tapie. L., Fromentin. O.: A systematic review of CAD/CAM fit restoration evaluations. Journal of Oral Rehabilitation. 2014, 41, 853-874.

[142] Hjerppe. J., Närhi. T., Fröberg. K., Vallittu. P. K., Lassila. L. V.: Effect of shading the zirconia framework on biaxial strength and surface microhardness. Acta Odontologica Scandinavica. 2008, 66, 262-267.

[143] Batson. E. R., Cooper. L. F., Duqum. I., Mendonça. G.: Clinical outcomes of three different crown systems with CAD/CAM technology. Journal of Prosthetic Dentistry. 2014, 112, 770-777.

[144] Sun. T., Zhou. S., Lai. R., Liu. R., Ma. S., Zhou. Z., Longquan. S.: Load-bearing capacity and the recommended thickness of dental monolithic zirconia single crowns. Journal of the Mechanical Behavior of Biomedical Materials. 2014, 35, 93-101.

[145] Rashad. M. M., Baioumy. H. M.: Effect of thermal treatment on the crystal structure and morphology of zircon nanopowders produced three different routes. Journal of Materials Processing Technology. 2008, 195, 1-3,178-185.

[146] Della Bona. A., Pecho. O. E., Alessandretti. R.: Zirconia as a Dental Biomaterial. Materials. 2015, 8(8), 4978-4991.

[147] Keith. O., Kusy. R. P., Whitley J. Q.: Zirconia brackets: an evaluation of morphology and coefficients of friction. American Journal of Orthodontics and Dentofacial Orthopedics. 1994, 106, 605-614.

[148] Hannink, R.H.J., Kelly. P. M., Muddle. B. C.: Transformation toughening in zirconia –containing ceramics. Journal of the American Ceramic Society. 2000, 83(3), 461 - 487.

[149] Kelly. J. R., Denry. I.: Stabilized zirconia as a structural ceramic: An overview. Dental Materials. 2008, 24(3), 289-298.

[150] Vagkopoulou. T., Koutayas. S. O., Koidis. P., Strub. J. R.: Zirconia in Dentistry: Part 1. Discovering the nature of an upcoming bioceramic. European journal of esthetic dentistry, 2009, 4, 2, 130-151.

[151] Wachtman. J. B., Roger Cannon. W., John Matthewson. M.: Mechanical properties of ceramics. 2nd Edition. 2009.

[152] Porter. D.L., Evans. A.G., Heuer. A.H.: Transformation-toughening in partially-stabilized zirconia (PSZ). Acta Metallurgica. 1979, 27(10) 1649-1654.

[153] Evans. A. G., Cannon. R. M.: Overview no. 48: Toughening of brittle solids by martensitic transformations. Acta Metallurgica. 1986, 34(5), 761-800.

[154] Heuer. D. A. H.: Transformation toughening in ZrO2-containing ceramics. Journal of the American Ceramic Society. 1987, 70(10), 689-698.

[155] Heuer. A. H., Claussen. N., Kriven. W. M., R ¨ uhle. M.: Stability of tetragonal ZrO2 particles in ceramic matrices. Journal of the American Ceramic Society. 1982. 65(12). 642-650.

[156] Ramesh. T. R., Gangaiah. M., Harish. P.V., Krishnakumar U., Nandakishore. B.: Zirconia Ceramics as a Dental Biomaterial – An Over View. Trends in Biomaterials and Artificial Organs. 2012, 26(3), 154-160.

[157] Fakhraei. O., Hesarakin. S., Alizadeh. M.: Evaluation of biphasic calcium phosphate/nanosized 3YSZ composites as toughened materials for bone substitution. Ceramics International, 2016, 42, 11201-11208.

[158] Zafer. E., Michiko. S., Thomas. J.: Webster. Increased osteoblast adhesion on nanograined hydroxyapatite and partially stabilized zirconia composites. Journal of Biomedical Materials Research Part A. 2006, 78A, 500-507.

[159] Salomoni. A., Tucci. A., Esposito. L., Stamenkovich. I.: Forming and sintering of multiphase bioceramics. Journal of Materials Science: Materials in Medicine. 1994, 5, 651-653.

[160] White. S. N., Miklus. V. G., McLaren EA.: al atthetic Flexural strergth of a layered zirconia and porcelain dental all-ceramic system. Journal of Prosthetic Dentistry. 2005, 94, 125-131.

[161] Raigrodski. A. J.: Contemporary materials and technologies for all-ceramic fixed partial dentures: a review of the literature. Journal of Prosthetic Dentistry. 2004, 92, 557-562.

[162] Larsson. C., Vult. Von., Steyern. P., Sunzel. B., et al.: All-ceramic two to five-unit implant-supported reconstructions. A randomized, prospective clinical trial. Swedish Dental Journal. 2006, 30, 45-53.

[163] Witowski. S.: (CAD-)/CAM in dental technology. Quintessence of Dental Technology. 2005, 28, 169-184.

[164] Aboushelib. M. N., de Jager. N., Kleverlaan. C. J., Feilzer. A. J.: Effect of loading method on the fracture mechanics of two layered all-ceramic restorative systems. Dental Materials. 2007, 23(8), 952–959.

[165] Aboushelib. M. N., Kleverlaan. C. J., Feilzer. A. J.: Microtensile bond strength of different components of core veneered allceramic restorations. Part II: Zirconia veneering ceramics. Dental Materials. 2006. 22, 857-863.

[166] Cales. B.: Colored zirconia ceramics for dental applications. In: LeGeros RZ, Legeros JP, editors. Bioceramics. New York: World Scientific Publishing Co. Pte. Ltd.; 1998.

[167] Sorensen, J. A.: The Lava system for CAD/CAM production of high strenght precision fixed prosthodontics. Quintessence of Dental Technology. 2003, 26, 57-67.

[168] Lampe K., Luthy. H., Mörmann, W. H.: CAD/ CAM, in Aesthetic Dentistry, Cerec 10 Year Anniversary Symposium (Mörmann W.H.), Chicago, II: Quintessence. 1996, 463-482.

[169] Segal, BS.: Retrospective assessment of 546 all-ceramic anterior and posterior crowns in a general practice. Journal of Prosthetic Dentistry. 2001, 85, 544-550.

[170] Sorensen, J. A., Kang, S. K., Torres, T. J., Knode, H.: In-Ceram fixed partial dentures: three-year clinical trial results. Journal of California Dental Association. 1998, 26, 207-214.

[171] Kohal. R. J., Klaus. G.: A zirconia implant-crown system: a case report. International Journal of Periodontics Restorative Dentistry. 2004, 24, 147-153.

[172] Yildirim. M., Fischer. H., Marx. R., et al.: In vivo fracture resistance of implant-supported all-ceramic restorations. Journal of Prosthetic Dentistry. 2003, 90, 325-331.

[173] Akagawa. Y., Ichikawa. Y., Nikai. H., et al.: Interface histology of unloaded and early loaded partially stabilized zirconia endosseous implant in initial bone healing. Journal of Prosthetic Dentistry. 1993, 69, 599-604.

[174] Ichikawa. Y., Akagawa. Y., Nikai. H., et al.: Tissue compatibility and stability of a new zirconia ceramic in vivo. Journal of Prosthetic Dentistry. 1992, 68, 322-326.

[175] Glauser. R., Sailer. I., Wohlwend. A., et al.: Experimental zirconia abutments for implant-supported single-tooth restorations in esthetically demanding regions: 4-year results of a prospective clinical study. International Journal of Prosthodontics. 2004, 17, 285-290.

[176] Brodbeck. U.: The ZiReal Post. A new ceramic implant abutment. Journal of Esthetic and Restorative Dentistry. 2003, 15, 10-23.

[177] Swab. JJ.: Low temperature degradation of Y-TZP materials. Journal of Materials Science. 1991, 26, 6706-6714.

[178] Att. W., Grigoriadou. M., Strub. J. R.: ZrO2 three-unit fixed partial dentures: comparison of failure load before and after exposure to a mastication simulator. Journal of Oral Rehabilitation. 2007, 34, 282-290.

[179] Ginebra. M., Traykova. P., Planell. J. A.: Calcium phosphate cements as bone drug delivery systems: A review. Journal of Controlled Release. 2006, 113, 102-110.

[180] Kothapalli. C. R., Shaw. M. T., Olson. J. R., Wei. M.: Fabrication of novel calcium phosphate/poly (lactic acid) fiber composites. Journal of Biomedical Materials Research. Part B, Applied Biomaterials. 2008, 84, 89-97.

[181] Lezaja. M., Veljovic. Dj., Jokic. B., Cvijovic-Alagic. I., Zrilic. M., Miletic, V.: Effect of hydroxyapatite spheres, whiskers, and nanoparticles on mechanical properties of a model BisGMA/TEGDMA composite initially and after storage. Journal of Biomedical Materials Research. Part B, Applied Biomaterials. 2013, 101, 1469-1476.

[182] Lezaja. M., Jokic. B., Veljovic. Dj., Miletic, V.: Shear bond strength to dentine of dental adhesives containing hydroxyapatite nano-fillers. Journal of Adhesion Science and Technology. 2016, 30, 2678-2689.

[183] Natale. L. C., Rodrigues. M. C., Alania. Y., Chiari. M. D., Vilela. H. S., Vieira. D. N., Braga, R. R. Development of calcium phosphate/ ethylene glycol dimethacrylate particles for dental applications. Journal of Biomedical Materials Research. Part B, Applied Biomaterials. 2019, 107, 708-715.

[184] Ayoub. G., Veljovic. Dj., Zebic. M., Miletic. V., Palcevskis. E., Petrovic, R., Janackovic, Dj.: Composite nanostructured hydroxyapatite/yttrium stabilized zirconia dental inserts—The processing and application as dentin substitutes. Ceramics International. 2018, 44, 18200-18208.

[185] Veljovic. Dj., Jancic-Hajneman. R., Balac. I., Jokic. B., Putic. S., Petrovic. R, Janackovic, Dj.: The effect of the shape and size of the pores on the mechanical properties of porous HAP-based bioceramics. Ceramics International. 2011, 37, 471-479.

[186] Veljovic. Dj., Kojic. V., Bogdanovic. G., Kojic. Z., Banjac. A., Palcevskis. E. Janackovic. Dj.: The effect of grain size on the biocompatibility, cell–materials interface, and mechanical properties of microwave sintered bioceramics. Journal of Biomedical Materials Research. Part A. 2012, 100, 3059–3070.

[187] Veljovic. Dj., Palcevskis. E., Zalite. I., Petrovic. R., & Janackovic. Dj.: Two-step microwave sintering – A promising technique for the processing of nanostructured bioceramics. Materials Letters. 2013, 93, 251-253.

[188] Veljovic. Dj., Zalite. I., Palcevskis. E., Smiciklas. I., Petrovic. R., Janackovic. Dj.: Microwave sintering of fine grained HAP and HAP/TCP bioceramics. Ceramics International. 2010, 36, 595-603.

[189] Iwamoto. N., Ruse. N. D.: Fracture toughness of human dentin. Journal of Biomedical Materials Research. Part A. 2003, 66, 507-512.

[190] Donly. K. J., Wild. T. W., Bowen. R. L., Jensen. M. E.: An in vitro investigation of the effects of glass inserts on the effective composite resin polymerization shrinkage. Journal of dental research.1989, 68(8), 1234-1237.

[191] Görücü, J.: Fracture resistance of class II preformed ceramic insert and direct composite resin restorations. Journal of Dentistry. 2003, 31, 83-88.

[192] Federlin. M., Thonemann. B., Schmalz. G.: Inserts–megafillers in composite restorations: A literature review. Clinical Oral Investigations. 2000, 4, 1-8.

[193] Heintze, S.D., Cavalleri, A. and Rousson, V.: The marginal quality of luted ceramic inserts in bovine teeth and ceramic inlays in extracted molars after occlusal loading. Journal of Adhesive Dentistry. 2005, 7(3), 213-223.

[194] Veljovic. Dj, Jokic. B., Petrovic. R., Palcevskis. E., Dindune. A., Mihailescu. I.N., Janackovic. Dj.: Processing of dense nanostructured HAP ceramics by sintering and hot pressing. Ceramics International. 2009, 35, 1407-1413.

[195] Veljovic, Dj., Matic, T., Stamenic, T., Kojic, V., Dimitrijevic-Brankovic, S., Lukic, M. J. Janackovic, Dj.: Mg/cu co-substituted hydroxyapatite–biocompatibility, mechanical properties and antimicrobial activity. Ceramics International. 2019, 45, 22029-22039.

[196] Janackovic. Dj., Petrovic-Prelevic. I., Kostic-Gvozdenovic. Lj., Petrovic. R., Jokanovic. V., Uskokovic. D.: Influence of synthesis parameters on the particle sizes of nanostructured calcium hydroxyapatite. Key Engineering Materials. 2001, 203, 192-195

[197] Grabis. J., Zalite. I.: Nanosized Powders of Refractory Compounds for Obtaining of Fine-Grained Ceramic Materials. Materials Science Forum. 2007, 555, 267-272.

[198] Zalite. I., Grabis. J., Palcevskis. E., Herrmann. M.: Plasma processed nanosized-powders of refractory compounds for obtaining fine-grained advanced ceramics. Materials Science and Engineering. 2011, 18, 062024.

[199] Evans. A.G., Charles. E.A.: Fracture toughness determinations by indentation. Journal of the American Ceramic Society. 1976, 59, 371-372.

[200] Radovanovic. Z., Jokic. B., Veljovic. Dj., Dimitrijevic. S., Kojic. V., Petrovic. R., Janackovic Dj.: Antimicrobial activity and biocompatibility of Ag+ and Cu2+ doped biphasic hydroxyapatite/-tricalcium phosphate obtained from hydrothermally synthesized Ag+ and Cu2+ doped hydroxyapatite. Applied Surface Science. 2014, 307, 513-519.

[201] Stojadinovic. S., Vasilic. R.: Formation and photoluminescence of Eu3+ doped zirconia coatings formed by plasma electrolytic oxidation. Journal of Luminescence. 2016, 176, 25-31.

[202] Smits. K., Grigorjeva. L., Millers. D., Sarakovskis. A., Opalinska. A., Fidelus. J.D., Lojkowski. W.: Europium doped zirconia luminescence. Optical Materials. 2010, 32, 827-831.

[203] Tang. C. Y., Uskokovic. P. S., Tsui. C. P., Veljovic. D., Petrovic. R., Janackovic, Dj.: Influence of microstructure and phase composition on the nanoindentation characterization of bioceramic materials based on hydroxyapatite. Ceramics International. 2009, 35, 2171-2178.

[204] Raynaud. S., Champion. E., Bernache-Assollant. D.: Calcium phosphate apatites with variable Ca/P atomic ratio II. Calcination and sintering, Biomaterials. 2002, 23, 1073-1080.

[205] Gergely. G., Sahin. F.C., Goller. G., Yucel. O., Balazsi. C.: Microstructural and mechanical investigation of hydroxyapatite–zirconia nanocomposites prepared by spark plasma sintering. Journal of the European Ceramic Society. 2013, 33, 2313-2319.

[206] Curran. D.J., Fleming. T.J., Towler. M.R., Hampshire. S.: Mechanical properties of hydroxyapatite–zirconia compacts sintered by two different sintering methods. Journal of Materials Science: Materials in Medicine. 2010, 21, 1109-1120.

[207] Evis. Z., Usta. M., Kutbay. I.: Improvement in sinterability and phase stability of hydroxyapatite and partially stabilized zirconia composites. Journal of the European Ceramic Society. 2009, 29, 621-628.

[208] Ramesh. S., Tan. C.Y., Bhaduri. S.B., Teng. W.D., Sopyan. I.: Densification behaviour of nanocrystalline hydroxyapatite bioceramics. Journal of Materials Processing Technology. 2008, 206, 221-230.

[209] Mobasherpour. I., Solati Hashjin. M., Razavi Toosi. S.S., Darvishi Kamachali. R.: Effect of the addition ZrO2–Al2O3 on nanocrystalline hydroxyapatite bending strength and fracture toughness. Ceramics International. 2009, 35, 1569-1574.

[210] Qeblawi. D.M., Munoz. C.A., Brewer. J.D., Monaco. E.A.: The effect of zirconia surface treatment on flexural strength and shear bond strength to a resin cement. Journal of Prosthetic Dentistry. 2010, 103, 210-220.

[211] Ayoub. G., Veljovic. Dj., Zebic. M., Miletic. V., Palcevskis. E., Petrovic. R., Janackovic. Dj.: Dissimilar sintered calcium phosphate dental inserts as dentine substitutes: Shear bond strength to restorative materials. Journal of Biomedical Materials Research. Part A. 2020, 108(6), 2461-2470.

[212] Radovanovic. Z., Veljovic. Dj., Radovanovic. L., Zalite. I., Palcevskis. E., Petrovic. R., Janackovic. Dj.: Ag+, Cu2+ and Zn2+ doped hydroxyapatite/tricalcium phosphate bioceramics: Influence of doping and

sintering technique on mechanical properties. Processing and Application of Ceramics. 2018, 12, 269-277.

[213] Bracher. L., Özcan. M. Adhesion of resin composite to enamel and dentin: A methodological assessment. Journal of Adhesion Science and Technology, 2018, 32, 258–271.

[214] Sarr. M., Mine. A., De Munck. J., Cardoso. M. V., Kane. A. W., Vreven, J., Van Landuyt. K. L. Immediate bonding effectiveness of contemporary composite cements to dentin. Clinical Oral Investigations, 2010, 14, 569–577.

[215] Moshaverinia. A., Ansari. S., Moshaverinia. M., Roohpour. N., Darr. J. A., Rehman. I. Effects of incorporation of hydroxyapatite and fluoroapatite nanobioceramics into conventional glass ionomer cements (GIC). Acta Biomaterialia, 2008, 4, 432–440.

[216] Pashley. D. H., Tay. FR., Breschi. L., Tjäderhane. L., Carvalho. R. M., Carrilho. M., Tezvergil- Mutluay. A.: State of the art etch-and-rinse adhesives. Dental Materials. 2011, 27, 1-16.

[217] Khan. AA., Al Kheraif. AA., Jamaluddin. S., Elsharawy. M., Divakar. DD.: Recent trends in surface treatment methods for bonding composite cement to zirconia: A Reveiw. Journal of Adhesive Dentistry. 2017, 19, 7-19.

[218] Yoshihara. K., Yoshida. Y., Nagaoka. N., Hayakawa. S., Okihara. T., De Munck. J., Maruo. Y., Nishigawa. G., Minagi. S., Osaka. A., Van Meerbeek. B.: Adhesive interfacial interaction affected by different carbon-chain monomers. Dental Materials. 2013, 29, 888-897.

[219] Stasic. J. N., Selaković. N., Puač. N., Miletić. M., Malović. G., Petrović. Z. L., Veljovic. D. N., Miletic. V.: Effects of non-thermal atmospheric plasma treatment on dentin wetting and surface free energy for application of universal adhesives. Clinical Oral Investigations. 2019, 23, 1383-1396.

Biography

Giuma Khalifa Giuma Ayoub was born on 9 May, 1975. In Zawia, Libya. He finished high school in the Kabaw High School in Kabaw in 1993. He graduated in 1998. At the Naser University, Faculty of Medical Technology, Misurata, Libya.

Master year of Graduation: August 2012. Danube-University of Krems, Austria, Faculty of Health and Medicine. Master of Science in Dental Sciences (MSc). Area of Concentration: Interceptive Orthodontic Orthodontic.

Doctoral Studies started in 2014 at the University of Belgrade, Faculty of Technology and Metallurgy, Materials Engineering.

He has worked since 2003. As an assistant at Al Gabal Al Gharbi University, Faculty of Medical Technology of Nalut, Libya.

Прилог 1.

Изјава о ауторству

Потписани-а ___**Giuma Khalifa Giuma Ayoub**___

број уписа ________4046/2014________

Изјављујем

да је докторска дисертација под насловом

„Процесирање, својства и примена денталних инсерата на бази калцијум-фосфата и цирконијум(IV)-оксида (The processing, properties and application of dental inserts based on calcium phosphates and zirconia)“

- резултат сопственог истраживачког рада,
- да предложена дисертација у целини ни у деловима није била предложена за добијање било које дипломе према студијским програмима других високошколских установа,
- да су резултати коректно наведени и
- да нисам кршио/ла ауторска права и користио интелектуалну својину других лица.

Потпис докторанда

У Београду, 04.11.2021.

Прилог 2.

Изјава о истоветности штампане и електронске верзије докторског рада

Име и презиме аутора **Giuma Khalifa Giuma Ayoub**

Број уписа 4046/2014

Студијски програм Инжењерство материјала

Наслов рада **„**Процесирање, својства и примена денталних инсерата на бази калцијум-фосфата и цирконијум(IV)-оксида (The processing, properties and application of dental inserts based on calcium phosphates and zirconia)**“**

Ментор _проф. Др Ђорђе Јанаћковић

изјављујем да је штампана верзија мог докторског рада истоветна електронској верзији коју сам предао/ла за објављивање на порталу **Дигиталног репозиторијума Универзитета у Београду.**

Дозвољавам да се објаве моји лични подаци везани за добијање академског звања доктора наука, као што су име и презиме, година и место рођења и датум одбране рада.

Ови лични подаци могу се објавити на мрежним страницама дигиталне библиотеке, у електронском каталогу и у публикацијама Универзитета у Београду.

Потпис докторанда

У Београду, 04.11.2021.

Прилог 3.

Изјава о коришћењу

Овлашћујем Универзитетску библиотеку „Светозар Марковић“ да у Дигитални репозиторијум Универзитета у Београду унесе моју докторску дисертацију под насловом:

„Процесирање, својства и примена денталних инсерата на бази калцијум-фосфата и цирконијум(IV)-оксида (The processing, properties and application of dental inserts based on calcium phosphates and zirconia **)“**

која је моје ауторско дело.

Дисертацију са свим прилозима предао/ла сам у електронском формату погодном за трајно архивирање.

Моју докторску дисертацију похрањену у Дигитални репозиторијум Универзитета у Београду могу да користе сви који поштују одредбе садржане у одабраном типу лиценце Креативне заједнице (Creative Commons) за коју сам се одлучио/ла.

1. Ауторство
2. Ауторство - некомерцијално
3. Ауторство – некомерцијално – без прераде
4. Ауторство – некомерцијално – делити под истим условима
5. Ауторство – без прераде
6. Ауторство – делити под истим условима

(Молимо да заокружите само једну од шест понуђених лиценци, кратак опис лиценци дат је на полеђини листа).

Потпис докторанда

У Београду, 04.11.2021.