Three-dimensional finite element analysis of the biomechanical behavior of implant retained prostheses with different materials in the posterior maxilla

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To my One & Only beloved mother Rawia,
for your boundless love, exceptional support, blessed payers and the warmth that has always guided and uplifted me.

To my Honored father Prof.Khaled Aboelfadl,
whose wisdom, integrity, and dedication have been a constant source of inspiration and a role model for my professional journey.

To my dearest darling Wife
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To my Sweetheart Children & Lovely sisters
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This work is a reflection of your strength, love, and inspiration

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List of Abbreviations

ANOVA	ANalysis Of VAriance
CBCT	Cone-beam computed tomography
CDB	Central Database
CoCr	Cobalt Chrome
DICOM	Digital Imaging and Communications in Medicine
DNA	Desoxyribonukleinsäure
FEA	Finite element analysis
MD	Model Distal Cantilever
MF	Model Fixed Fixed
MM	Model Mesial Cantilever
PAEK	PolyArylEtherKetone
PEEK	PolyEtherEtherKetone
PEKK	PolyEtherKetoneKetone
PMMA	Polymethylmethacrylate
STL	Standard Tessellation language
Zr	Monolithic zirconia

1. English summary

1.1 Introduction

The configuration of prosthetic superstructures on dental implants governs how loads are transmitted through the bone-implant interface, thereby modulating stress patterns influencing functional bone resorption. Implant placement in edentulous areas stimulates bone and helps prevent the progressive resorption observed post-extraction in cases without implant rehabilitation. Wright et al. (2002) confirmed that implant-supported mandibular overdentures minimized ridge resorption in patients with advanced mandibular atrophy. Increased mechanical strain on bone promotes osteoblastic activity; however, implant number, distribution, and prosthetic design critically influence force distribution and resultant bone remodeling. Maló et al. (2015) highlighted that occlusal forces concentrate at the implant's coronal region near the alveolar crest threatening implant longevity.

Avoiding prosthetic cantilevers provides mechanical benefits, but ideal implant distribution demands adequate bone volume, often lacking in clinical situations. Alternatives include bone augmentation, sinus lifting, or prosthetic compromises. Though augmentation improves prosthetic outcomes, it extends treatment duration, increases patient morbidity, and elevates costs. In such cases, cantilevered prostheses offer a simpler solution, as exemplified by the All-on-Four concept. Patients favor this approach due to shorter treatment time and reduced complications, though concerns remain regarding long-term performance. Romeo et al. (2009) and Gallucci et al. (2009) addressed these concerns. In Gallucci's five-year study on distal cantilevers in the edentulous mandible (15 mm average length, 4–6 anterior implants), implant survival reached 100 %, prosthetic survival 95.5 %, and failures were linked to excessively long cantilevers (>17 mm).

In a systematic review by Aglietta et al. (2009) survival and complication rates of implant-supported prostheses with cantilever extensions were examined. Findings varied: some studies reported higher complications, while others showed comparable success to non-cantilevered prostheses. Aglietta et al. (2009) noted that failure rates of implant-supported cantilevered prostheses are comparable to tooth-supported fixed prostheses, supporting their clinical viability.

In 2023, García-Sala Bonmatí et al. examined the biomechanical behaviour of four types of implant-supported prostheses, both screw- and cement-retained. Under in-vitro compressive and cyclic loading, cantilevered prostheses restored partial edentulism effectively, with screw-retained types exhibiting superior mechanical properties.

The evolution of implant-supported prostheses has brought a shift from cast metal and porcelain-fused-to-metal frameworks to digitally fabricated alternatives using advanced materials. Material selection affects load transmission, esthetics, and long-term functionality. Ceramics have grown in popularity due to superior esthetics compared to opaque metals. Mechanically, screw loosening and abutment fatigue fractures are notable challenges in screw-retained designs (López-Píriz et al., 2019).

A key factor in stress response is the modulus of elasticity. Zirconia, with high rigidity, and ceramics like lithium disilicate or hybrid ceramics, with lower moduli, influence stress differently. Datte et al. (2018) found that materials with high elastic moduli reduce stress on abutments, whereas low modulus materials reduce stress in the prosthesis itself. Additionally, zirconia abutments led to more stress concentration in the prosthesis than titanium abutments.

Monolithic zirconia has garnered interest for combining the strength of conventional zirconia with better translucency, improving esthetics without sacrificing durability (Candido et al., 2018). Another promising material is PolyEtherKetoneKetone (PEKK), a high-strength, thermally stable polymer from the PAEK family. Its double ketone structure imparts rigidity, while its semi-crystalline nature balances shock absorption. Its lightweight, natural coloration makes it attractive for implant frameworks (Moharil et al., 2023).

With the multitude of available prosthetic materials, clinicians face the challenge of selecting one that offers both adequate strength and shock absorption - particularly critical in the posterior maxilla where low-density bone is prone to resorption. Minimizing bone strain and implant stress is vital for long-term success (Bordin et al., 2021).

To assess material performance, various study types - clinical, in vitro, animal, and FEA - have been utilized. Finite Element Analysis (FEA) provides cost-effective simulations of stress and deformation, especially beneficial when evaluating new materials pre-clinically (Geng et al., 2001). Cantilever prostheses inherently generate uneven load patterns, yet they can be a practical option when implant sites are limited. By angling implants, choosing wider-diameter fixtures, and incorporating more rigid framework, you can redistribute occlusal forces more evenly and reduce stress concentrations on supporting implants (Lee et al., 2022).

Despite many FEA studies evaluating prosthetic material effects, results remain conflicting. Some studies (Ersöz and Mumcu, 2022; Rani et al., 2017) report substantial material influence. Conversely, Kaleli et al. (2018) reported no significant biomechanical difference among lithium disilicate, translucent zirconia, hybrid ceramic, PEEK, and zirconia restorations, emphasizing implant geometry and occlusal forces as more influential.

FEA's main limitation lies in its assumption of homogenous bone tissue, which ignores patient-specific anatomical variation (Güzelce, 2023). Nevertheless, it remains a reliable predictor of in-vitro mechanical behavior and clinical performance (Xie et al., 2025).

In this study FEA was used to evaluate the biomechanical behavior of different cantilevered implant-supported bridge designs and materials. Two null hypotheses were defined: (1) Bridge design has no impact on biomechanical behavior of implant-supported prosthesis, and (2) Bridge material does not affect Implant prosthetic biomechanics.

1.2 Material and Methods

Maxillary Implant FEA Assemblies

Three maxillary FEA assemblies were created representing three groups - MF, MM and MD - each hosting two tioLogic implants (4.2 × 7 mm; Dentaurum, Pforzheim, Germany) but differing in prosthetic span:

- MF (fixed–fixed): First premolar and first molar implant positions.
- MM (mesial cantilever): Second premolar and first molar implant positions.
- MD (distal cantilever): First and second premolar implant positions.

CBCT-Based Maxillary Generation

A patient-specific maxillary model was generated using cone-beam computed tomography (CBCT) imaging obtained with the Planmeca ProMax 3D Mid system (Planmeca Inc., Helsinki, Finland) from an anonymized patient. The scan was conducted with parameters set to 90 kV, 12 mA, and a voxel size of 75 µm. The captured DICOM data were seamlessly integrated into the Mimics Innovation Suite (Mimics 14.0 / 3-Matic 7.01, Materialise, Leuven, Belgium), where they underwent advanced 3D image processing and were meticulously transformed into detailed surface models ready for analysis. During preprocessing, noise was reduced by removing microscopic surface irregularities and holes (Fig. 1).

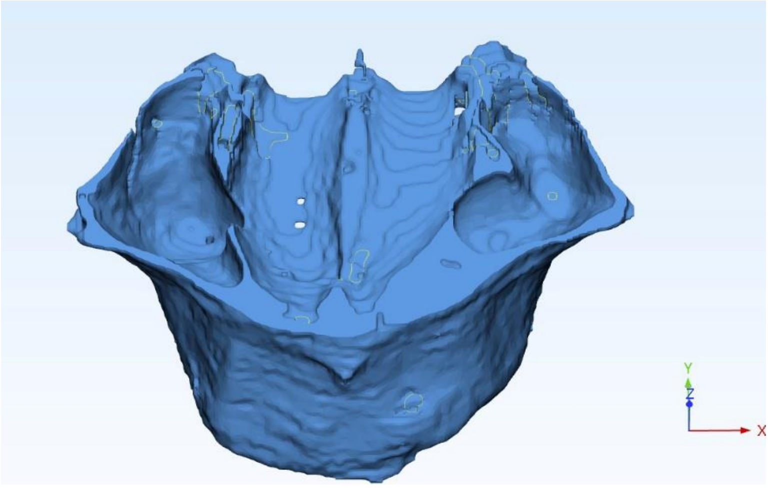

Fig. 1: Patient-specific finite element model of maxilla reconstructed from anonymized CBCT data. (Modified from Aboelfadl et al., 2024)

To achieve accurate anatomical representation, cortical and trabecular bone compartments were delineated in Mimics through hybrid approach combining threshold-based segmentation with region-growing algorithms. Boolean operations were applied to separate structures, which were then color-coded for visualization purposes (Fig. 2).

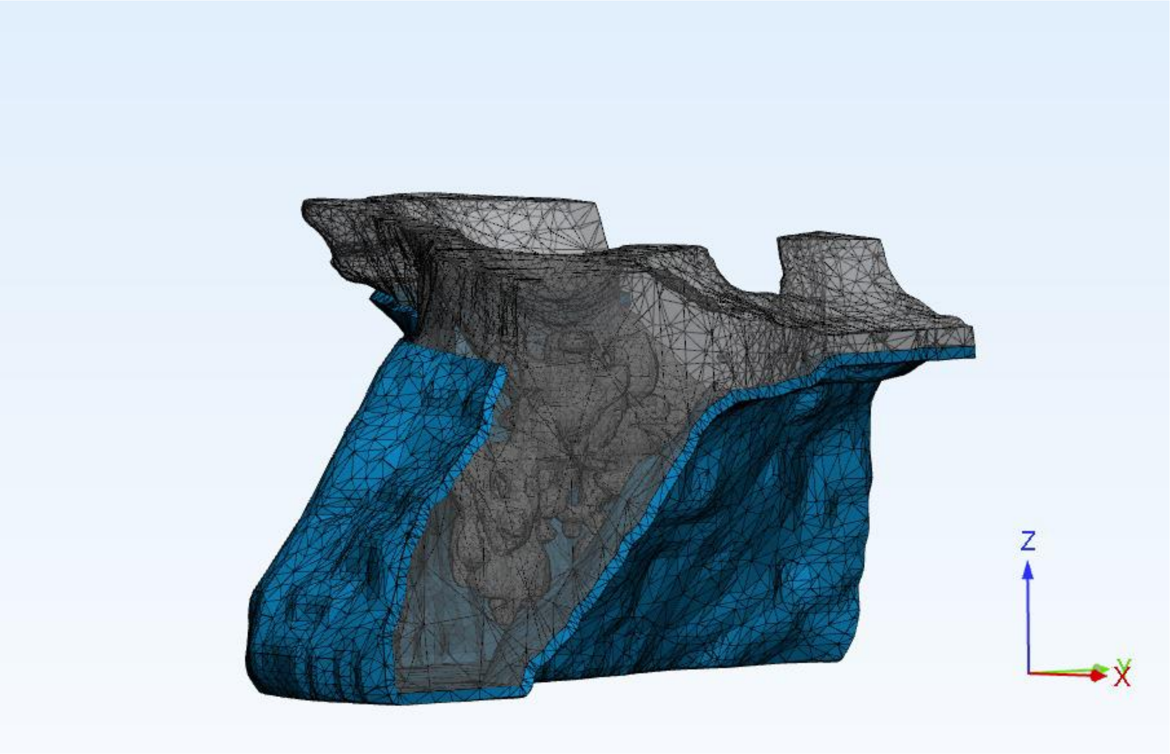

Fig. 2: Boolean-based segmentation masks of cortical and cancellous bone.

The FE model was created by exporting the segmented structures as triangulated surface mesh files standard tessellation language (STL) format into Materialize 3-Matic software. These STL files were used to generate surface meshes. The outer surface of the segmented bone was fitted with an analytical surface to enable the construction of a solid volumetric model representing the maxillary bone.

<u>Implant Prosthetic Assembly</u>

Anatomical and prosthetic geometries were established by importing STL datasets of tioLogic implant fixtures (4.2 × 7 mm) and matching anatomic abutments (tioLogic Anatomic Abutment; Dentaurum, Pforzheim, Germany) into Materialise 3-Matic. Mesh resolution was tuned to minimize computational cost while preserving shape accuracy. Each implant–abutment unit was then duplicated and placed centrally in the maxillary bone mesh, with the implant platform positioned 1 mm supracrestal.

Three implant distribution patterns were used to reflect the three prosthetic configurations: MF (first premolar and first molar), MM (second premolar and first molar), and MD (first and second premolars). Boolean subtraction was applied to create implant insertion sites within the solid bone model. Anatomically accurate solid abutments were then placed according to implant positions (Fig. 3).

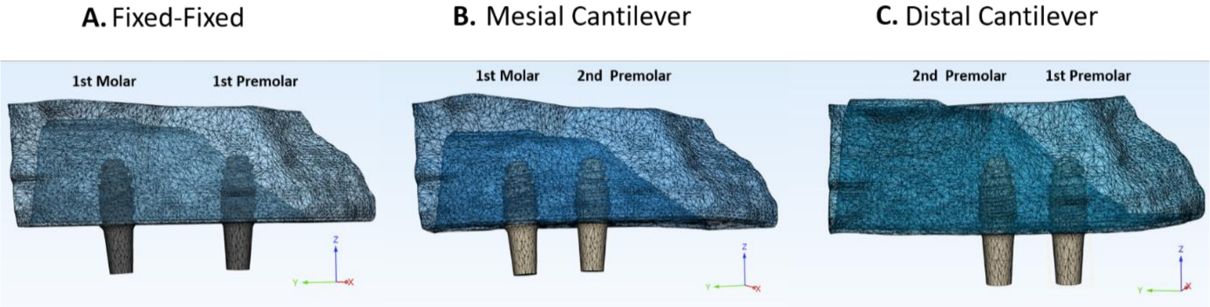

Fig. 3: Boolean-subtracted implant sites in a 3D maxillary FE model for three implant distribution configurations (A) Fixed–Fixed (MF), (B) Mesial Cantilever (MM), and (C) Distal Cantilever (MD).(Modified from Aboelfadl et al., 2024)

Using a Computer-Aided Design (CAD) approach, three implant-supported prosthetic designs were created: fixed-fixed, mesial cantilever, and distal cantilever, corresponding to MF, MM, and MD configurations, respectively. Six implant prosthetic configurations (MF–Zr, MM–Zr, MD–Zr, MF–PEKK, MM–PEKK, MD–PEKK) were generated. STL files were then converted into solid volumetric meshes for finite element analysis (Fig. 4).

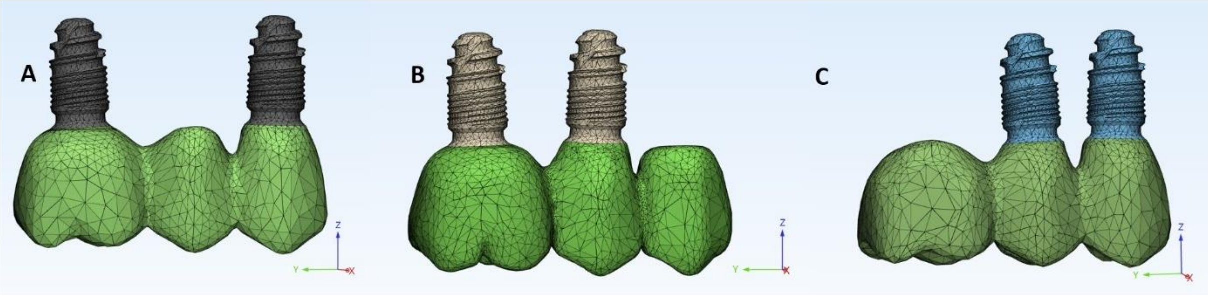

Fig. 4: Finite element models representing three prosthetic configurations over posterior maxillary implants: (A) Fixed-Fixed design with implants at the first premolar and first molar (MF), (B) Mesial Cantilever design with implants at the second premolar and first molar (MM), and (C) Distal Cantilever design with implants at the first and second premolars (MD).(Modified from Aboelfadl et al., 2024)

Creation of Numerical Models

STL models (MF-Zr, MM-Zr, MD-Zr; MF-PEKK, MM-PEKK, MD-PEKK) were converted to CDB format and imported into Marc/Mentat (v2015, MSC.Marc/Mentat, Hexagon, Stockholm, Schweden) for finite element analysis. Meshing employed 10-node tetrahedral elements with six degrees of freedom per node and quadratic interpolation. This element type was chosen to accommodate complex geometries and to offer improved accuracy in capturing real-world loading conditions and nonlinear material behavior. Stress and strain values were computed at a single integration point in every element to ensure accurate directional analysis of mechanical response

Interface Conditions

All materials used in the models were considered as being homogeneous, isotropic, and linear elastic. The implant–bone junction was represented as a rigidly fused boundary, reflecting complete osseointegration with no relative displacement or frictional interaction (Güzelce, 2023; Pisani et al., 2018). The prosthesis-abutment assembly was modeled as cement-retained. The abutments were assumed to be perfectly bonded to the prostheses to simulate clinical cementation conditions (Kaleli et al., 2018; Mosavar et al., 2017).

Loading Simulation and Material Property Assignment

Finite element analyses were performed in Marc/Mentat (v2015) using nonlinear geometric analysis. Material properties (elastic modulus, Poisson’s ratio) were assigned to model components based on values from established literature (Table 1).

Table 1: Finite Element Model material characteristics.

Structure	Elastic Modulus in GPa	Poisson’s Ratio	Reference
Bone	13.7	0.30	Ramos Verri et al., 2015
Implants	110	0.34	Schwitalla et al., 2015
Zirconia (Zr)	200	0.26	Al-Zordk et al., 2020
PEKK	3.5	0.36	Heimer et al., 2017

At the maxillary base, boundary constraints were imposed to rigidly inhibit both translational and rotational movements, thereby emulating anatomical fixation. Additional constraints were applied at the lateral edges of the bone to prevent deformation, particularly due to its asymmetrical geometry.

A static axial load of 300 N was applied to each numerical model. This load was distributed across the central fossae of the prosthetic units, with 100 N applied to each fossa to simulate occlusal loading under functional conditions (Fig. 5).

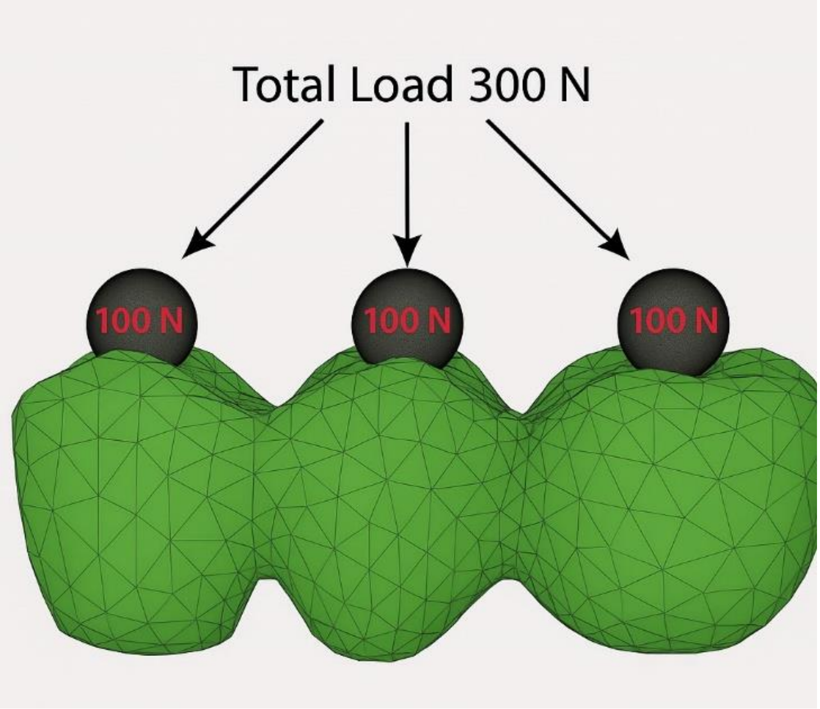

Fig. 5: Application of a static axial load of 300 N distributed evenly as 100 N on each central fossa of the prosthetic units to simulate functional occlusal loading conditions in the numerical models. (Modified from Aboelfadl et al., 2024)

Static structural analysis was conducted to calculate von Mises stresses within the prosthesis, implant, and surrounding bone structures. Due to the use of a single model per group, statistical comparisons were not feasible in this finite element study.

1.3 Results

von Mises stress distributions on the prosthesis, implant fixture, and adjacent bone were visualized using a red-to-blue color scale (red = highest stress, blue = lowest stress), and the peak stress values from each model were extracted and presented in a summary chart (Fig. 6).

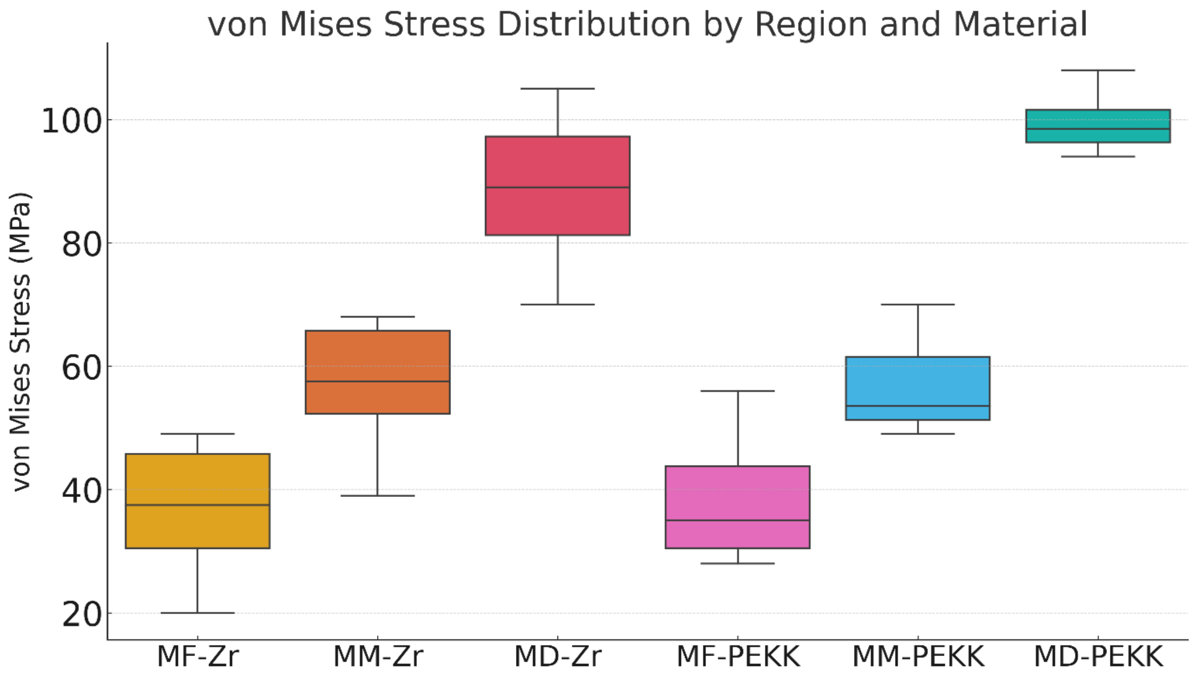

Fig. 6: Boxplot representation of von Mises stress distribution across implants, prostheses, and bone components. For Zirconia (Zr) : MF-Zr: Prosthesis: 42.4 MPa, Implant: 48.9 MPa, Bone: 19.6 MPa ,MM-Zr: Prosthesis: 65.9 MPa, Implant: 66.3 MPa, Bone: 38.9 MPa ,MD-Zr: Prosthesis: 105.0 MPa, Implant: 88.9 MPa, Bone: 67.8 MPa.For PEKK :MF-PEKK: Prosthesis: 35.4 MPa, Implant: 56.6 MPa, Bone: 26.5 MPa ,MM-PEKK: Prosthesis: 50.6 MPa, Implant: 70.7 MPa, Bone: 49.4 MPa ,MD-PEKK: Prosthesis: 93.3 MPa, Implant: 111.6 MPa, Bone: 100.0 MPa

Overall, both mesial and distal cantilever configurations (MM and MD) exhibited significantly higher von Mises stresses compared to the fixed-fixed configuration (MF) under axial loading. Peak stress values (in MPa) in the prosthesis, implant, and compact bone for both zirconia and PEKK materials are presented in Table 2.

Table 2: von Mises stress (MPa) observed in prosthesis, implant, and bone across zirconia and PEKK Configurations under axial loading.

Component	Location	Zirconia in MPa	PEKK in MPa	Difference in MPa
Prosthesis	Fixed (MF)	42.4	35.4	7.0
	Mesial (MM)	65.9	50.6	15.3
	Distal (MD)	105.0	93.3	11.7
Implant	Fixed (MF)	48.9	56.6	7.7
	Mesial (MM)	66.3	70.7	4.4
	Distal (MD)	88.9	111.6	22.7
Bone	Fixed (MF)	19.6	26.5	6.9
	Mesial (MM)	38.9	49.4	10.5
	Distal (MD)	67.8	100.0	32.2

Prosthesis Stress Analysis

The MD-Zr model produced the highest von Mises stress in the prosthesis (105.0 MPa), with stress concentration observed at the abutment–prosthesis interface adjacent to the distal cantilever. This was followed by the MD-PEKK model, which recorded 93.3 MPa. The MF-PEKK model demonstrated the lowest prosthetic stress value (35.4 MPa), with more uniform stress distribution along the implant–prosthesis interface (Fig. 7).

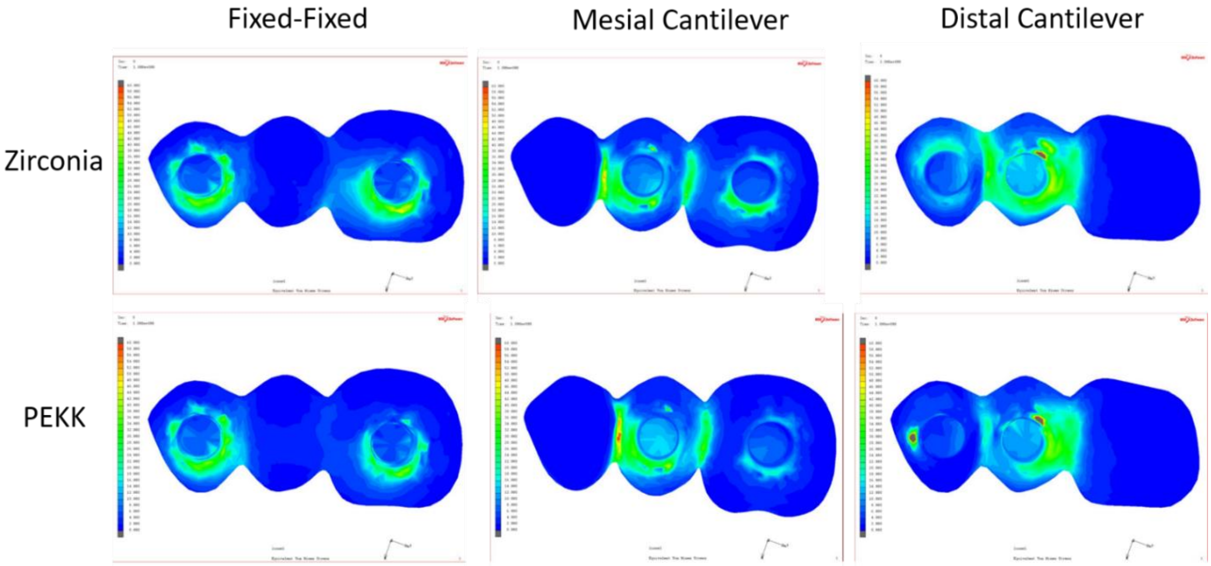

Fig. 7: von Mises stress in prostheses: top row: zirconia, bottom row: PEKK; columns :fixed–fixed, mesial cantilever, distal cantilever. Modified(Aboelfadl et al., 2024).

Implant Stress Analysis

The highest von Mises stress in the implant was observed in the MD-PEKK model (111.6 MPa), localized near the distal offset extension. Conversely, the MF-Zr model recorded the lowest implant stress at 48.9 MPa (Fig. 8).

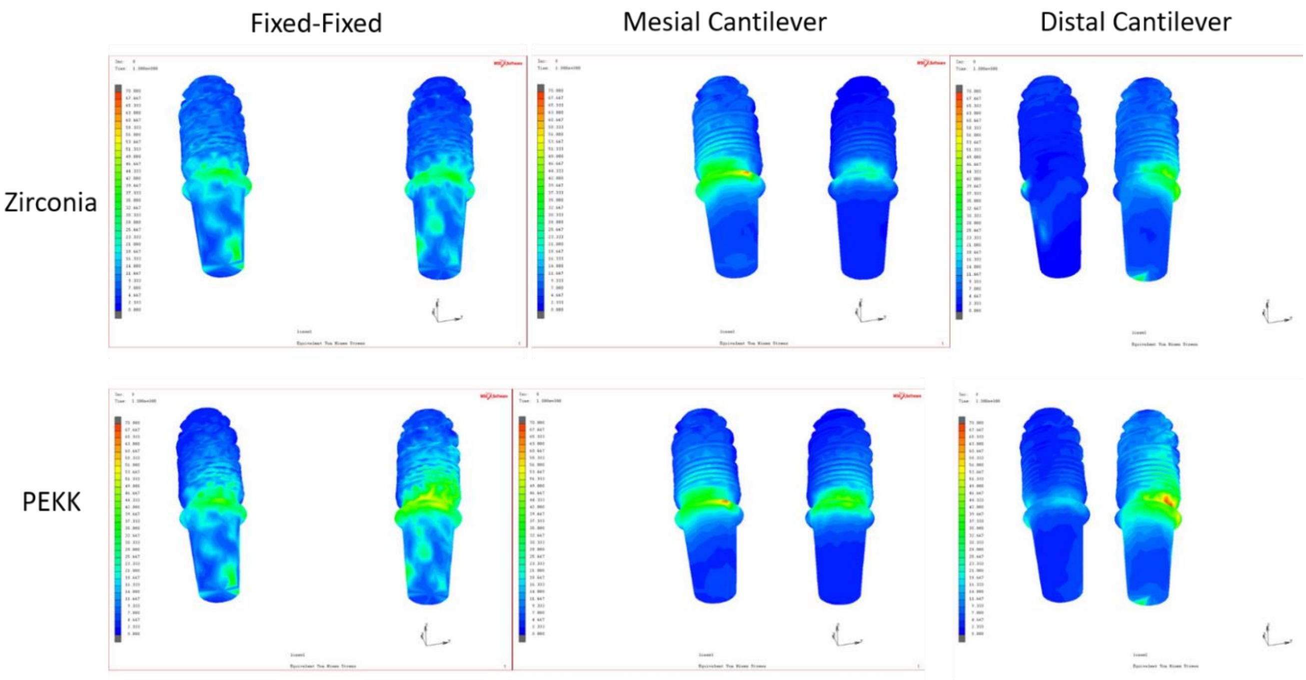

Fig. 8: Von Mises stress in implants: top row: zirconia, bottom row: PEKK; columns: fixed–fixed, mesial cantilever, distal cantilever. Modified(Aboelfadl et al., 2024).

Bone Stress Analysis

von Mises stress within the compact bone was generally higher in PEKK models than in zirconia models. The MD-PEKK model produced the highest bone stress (100.0 MPa), while the MF-Zr model yielded the lowest stress value (19.6 MPa) under vertical loading conditions (Fig. 9).

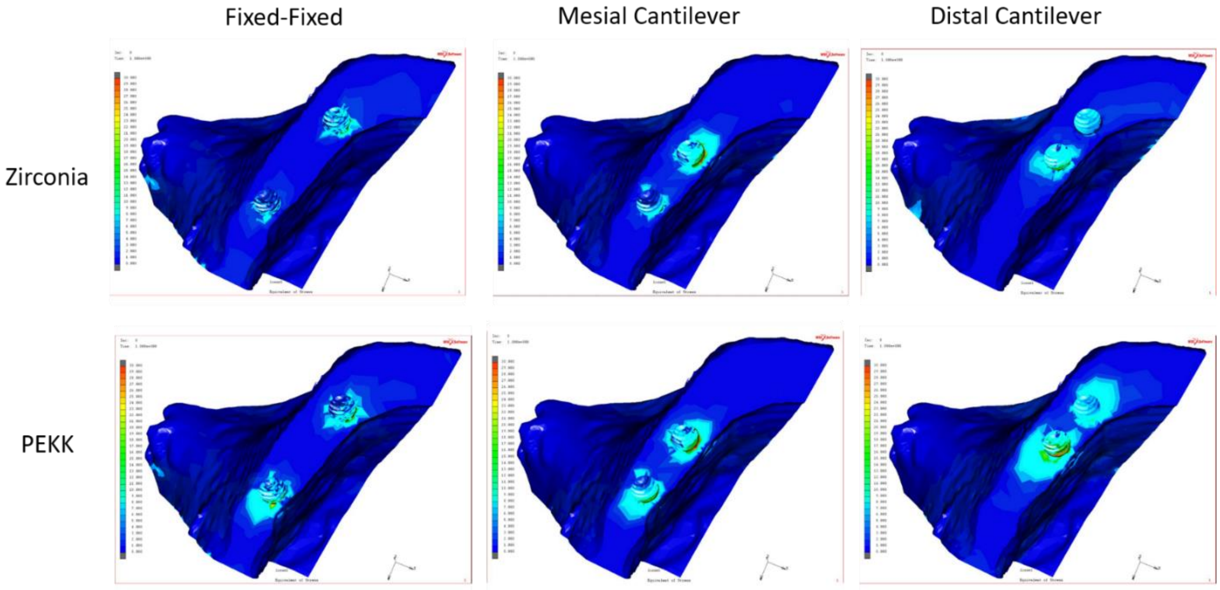

Fig. 9: Von Mises stress in bone: top row: zirconia, bottom row: PEKK; columns: fixed–fixed, mesial cantilever, distal cantilever.Modified (Aboelfadl et al., 2024).

1.4 Discussion

In this study, the findings showed that prosthetic bridge design affects the biomechanical behavior of implant-supported prostheses, thus rejecting the first null hypothesis. Offset-extension setups generated higher stress magnitudes than fixed-fixed models. The distal-cantilever arrangement produced the highest implant stresses, 111.6 MPa in distal cantilever group of PEKKTON and 88.9 MPa in distal cantilever group of zirconia focused chiefly at the distal offset.

Conversely, bridge designs without cantilever demonstrated better biomechanical performance with evenly distributed stress, recording the lowest stresses (56.6 MPa for MF-PEKK; 48.9 MPa for MF-Zr). The differences in observed stresses result from biomechanical factors: cantilever designs produce increased bending moments and rotational forces distally, causing stress concentrations due to lack of support. Conversely, fixed-fixed designs evenly distribute occlusal loads, reducing implant interface stress and lowering the risk of implant failure or bone resorption (Schmid et al., 2020). Several studies support these findings, highlighting that distal cantilever prostheses, particularly under overload or bruxism, significantly increase biomechanical risks and stress at implants and bone due to elevated bending and rotational forces (Kim et al., 2014; Kobari et al., 2016; Kreissl et al., 2007).

Ahmed et al. (2022a) confirmed that cantilever prostheses, especially distal types, produce higher stress than fixed-fixed designs. Although cantilevers simplify treatment of thin ridges, they pose biomechanical risks under high occlusal forces. Fixed-fixed designs thus provide better stability and stress distribution (Roccuzzo et al., 2023). Ahmed et al. (2020b) using finite element analysis also reported superior stress distribution with fixed bridges (PEEK frameworks and zirconia crowns). Differences between this study and ours in prosthesis retention (screw vs. cement-retained) and applied load (100 N vs. 300 N) likely contributed to varied results, highlighting the need for careful clinical consideration in material and design selection

The prosthetic material positively influences stress distribution due to favorable mechanical properties, reducing stress transfer to bone (Mohseni and Soufi, 2023). In this study, distal cantilever designs showed the highest bone stress (100.0 MPa MD-PEKK; 67.8 MPa MD-Zr), while fixed-fixed models displayed significantly lower stresses (26.5 MPa MF-PEKK; 19.6 MPa MF-Zr), reflecting superior force distribution. These results align with Doganay and Kilic who observed higher stress in cantilever designs, particularly with tilted implants (129 MPa), while eliminating cantilevers with implants placed vertically significantly reduced stresses (~25 MPa) (Doganay and Kilic, 2020).

Yu et al. (2022) and Zhong et al. (2020) provided consistent FEA-based evidence that eliminating cantilevers improves stress distribution, reduces implant and bone stress, and enhances restoration longevity. This study aligns with those findings, emphasizing the value of proper implant and prosthetic planning. However, Ebadian et al. (2016) found that longer offset extensions did not cause significant increase in stress levels, possibly due to the flexible nature of overdentures compared to fixed prostheses. Their findings suggest that stress distribution may vary with prosthesis type.

A comprehensive review by Jensen et al. (2025) and Roccuzzo et al. (2023) proved that cantilever extensions in fixed bridges on implants can be reliable, particularly when clinical considerations are addressed. Cantilevers with mesial offset are often favored because of better force direction and reduced bending moments, whereas distal cantilevers generate higher mechanical stresses. This study supports our findings on mesial cantilevers, where von Mises stresses were lower (66.3 MPa MM-Zr;

70.7 MPa MM-PEKK) than those in distal designs (88.9 MPa MD-Zr; 116 MPa MD-PEKK). While both cantilever types can be used, mesial cantilevers tend to yield more favorable stress profiles, making them biomechanically preferable in many clinical scenarios.

Rejection of the second null hypothesis was concluded, as prosthetic material significantly influenced stress distribution. Zirconia, with its high modulus of elasticity, generated higher prosthetic stresses reaching 105.0 MPa in the distal cantilever zirconia group. However, lower stresses were noted in the implant (48.9 MPa) and in the bone (19.6 MPa) in fixed fixed zirconia group.

Conversely, PEKK, known for its resilience, demonstrated minimal prosthetic stress (35.4 MPa) in fixed fixed PEKKTON group, but induced maximal implant (111.6 MPa) and bone stress (100.0 MPa) in distal cantilever PEKKTON group.

These results align with previous findings that rigid materials like zirconia transmit forces more uniformly, reducing stress on the peri-implant bone (Jameel and Al-Khafaji, 2024; Meriç et al., 2011). In contrast, PEKK's flexibility may lead to stress mismatches at the abutment-implant interface (De Kok et al., 2015; Soares et al., 2021).

The present results indicate that materials, like PEKK, with low modulus of elasticity alleviate prosthetic stress while increasing stress transfer to the implant-bone interface. This is supported by studies indicating that shock-absorbing polymeric frameworks can lead to increased deformation and micromotion, elevating stress on surrounding bone and implants (Bankoğlu Güngör and Yılmaz, 2016; Lee et al., 2017; Sirandoni et al., 2019; Yu et al., 2022). Consequently, such materials may contribute to complications like bone loss and implant instability. A FEA study comparing PEEK, Zantex, and CoCr alloys in overdenture models found CoCr-supported prostheses delivered the lowest stress values, while flexible PMMA-based systems generated the highest. Metal frameworks consistently provided better stress distribution regardless of implant size, affirming that rigid materials resist deformation and protect the implant-bone complex (Güzelce, 2023). Thus, using high-modulus materials like zirconia or CoCr alloys may enhance biomechanical performance and long-term success by minimizing stress transmission to critical peri-implant structures.

Yu et al. (2022) conducted an FEA study on mandibular full-arch implant prostheses comparing materials like titanium, CoCr, gold alloy, zirconia, PEEK, and CFR-PEEK. Rigid materials showed higher internal framework stress but better stress control at the implant-bone interface. In contrast, polymeric materials reduced prosthetic stress but transmitted more to the bone due to greater deformation. Güzelce et al. (2023) reported similar results in maxillary overdentures. Overall, while some studies downplay material influence, current evidence supports that in full-arch restorations, rigid frameworks yield more favorable biomechanical outcomes.

Although this study contributes to understanding biomechanical behavior in posterior edentulous regions, it has limitations. The use of static, axial loading does not replicate dynamic, multidirectional masticatory forces, limiting real-world applicability. The assumption of zero friction at the implant-bone interface also oversimplifies clinical conditions, where surface treatments and biological tissues influence stress transfer. Furthermore, idealized assumptions - such as material homogeneity, isotropy, linear elasticity, and perfect contact - do not account for the complex behavior of bone and restorative materials (Güzelce, 2023; Lee et al., 2017; Radi and Elmahrouky, 2016). These factors highlight the need for future research using more clinically realistic models.

To enhance the clinical relevance of FEA studies, future research should incorporate dynamic loading, variable friction coefficients, and realistic material properties, such as viscoelastic behavior for bone and polymers. Including implant surface treatments would further improve model accuracy. In vitro testing can validate computational data and assess long-term performance of materials and configurations under conditions that mimic the oral environment.

Additionally, clinical studies are essential to evaluate how different implant designs and materials influence outcomes like implant survival, bone resorption, mechanical complications, and patient satisfaction. Such studies will bridge the gap between simulation and real-world application.

1.5 Summary

This study evaluated the biomechanical behavior of fixed–fixed, mesial cantilever, and distal cantilever implant-supported prosthetic designs in the posterior maxilla fabricated from monolithic zirconia or polyetherketoneketone (PEKK) using three-dimensional finite element analysis. Patient-specific maxillary models reconstructed from cone-beam computed tomography scans were used to simulate three implant configurations restored with zirconia or PEKK prostheses. Models were created using Mimics Innovation Suite and analyzed in Marc/Mentat under a 300 N vertical load, with von Mises stresses assessed in the prosthesis, implants, and surrounding bone. Fixed–fixed zirconia prostheses showed the lowest stress values in implants (48.9 MPa) and bone (19.6 MPa), whereas distal cantilever PEKK designs produced the highest stresses (implants: 111.6 MPa; bone: 100.0 MPa). Prosthetic stress was highest in the distal cantilever zirconia model (105 MPa) and lowest in the fixed–fixed PEKK model (35.4 MPa). Overall, rigid non-cantilevered designs, particularly zirconia prostheses, provided the most favorable stress distribution, while PEKK reduced internal prosthetic stress but increased stress transmission to the bone–implant interface, especially in cantilevered designs. These findings highlight the need to balance material selection and prosthetic design, and further clinical studies are recommended to validate the results.

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2. Publication

This dissertation is based on the following peer-reviewed publication:

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3. Statement on personal contributions

I, Ahmad Khaled Mohammad Aboelfadl, hereby declare that the work presented in this thesis is the result of my own independent research and effort, except where otherwise acknowledged. All sources of information and data have been appropriately referenced.

I confirm that I have written this doctoral thesis independently and that I have listed all sources and resources used.

I confirm that this work has not been submitted previously, in whole or in part, for any degree or qualification at any other academic institution. The experimental design, data analysis, interpretation, and writing have been completed by myself under the supervision and guidance of my academic mentors.

This declaration is made in good faith and in accordance with the academic integrity policies of Faculty of Medicine of the Rheinische Friedrich-Wilhelms-Universität Bonn.

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