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The evolution of Hybrid Prosthesis. Transitioning from Analog to Digital Workflow (3D Printed Vs Zirconia)

Julian Jaramillo Botero*

*Dentist, Oral Rehabilitation, Clinic and Dental Laboratory owner at Dr Julian Jaramillo. Cali/Colombia.

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***Corresponding Author:** Dr. Julian Jaramillo Botero, Dentist, Oral Rehabilitation, Clinic and Dental Laboratory owner at Dr Julian Jaramillo. Cali/Colombia.

Abstract

Since 1965 when Dr Per-Ingvar Branemark, a Swedish Orthopedic surgeon placed the first Osseo integrated implant, dentistry had to wait till 1980's to see the first hybrid prosthesis using a mixture of multiple implants supporting a metal framework and acrylic teeth.

With standardized protocols and advancements in CAD/CAM technologies, combined with cone beam and 3D X-rays, implants can now be placed with greater precision. Digital workflows enhance the predictability of prosthetic outcomes.

Prosthetic materials have evolved significantly, including acrylic teeth, titanium substructures, PEEK, PMMA, and zirconia frameworks. These have progressed from full-to-partial ceramic layering to full-contour zirconia with varying strengths and translucencies. Although 3D-printed technologies offer new possibilities, no consensus exists on the optimal long-term material for hybrid prostheses or whether they should be connected over multi-unit abutments or directly to the implants. [1-12]

With advancements in 3D-printed prostheses and suitable materials, the future looks promising—reducing treatment time while providing excellent aesthetics and functionality. However, long-term validation of these new materials remains necessary.

The digital workflow for planning and execution of predictable functional, prosthetically guided hybrid prosthesis has significant benefits from both the surgical and prosthetic perspectives [10]

HYBRID PROSTHESIS GOALS

When planning a hybrid prosthesis, dentists should be focused in the following while studying the case:

1. Begin with a prosthetic-driven plan.

2. Screw-retained prostheses are preferred for retrievability. However, repeated disconnection of the implant-abutment connection may lead to apical bone migration. [13]

3. For aesthetic and functional reasons, the screw should not emerge through the facial surface or functional cusps. Ideally, it should be positioned in the occlusal area while avoiding cusps or occlusal points.

4. Seek adequate bone for implant placement, preserving as much as possible. Perform bone augmentation only when necessary to reduce time, cost, pain, and patient appointments.

5. Consider the patient's age, health condition, and specific needs.

6. For non-parallel implants, a multi-unit abutment is essential to correct angulations and optimize screw access. This requires more vertical height and increases complexity and cost. However, it distributes forces more evenly, reducing stress on implants and prosthetic components.

7. For parallel implants, screwing directly to the implant simplifies the procedure, requires less vertical height and fewer components, and reduces complications. However, this concentrates stress on the implant-prosthesis interface, increasing the risk of mechanical complications such as screw loosening, and provides fewer options for prosthesis removal. [7]

CASE PRESENTATION

This case highlights the transition from an analog to a digital workflow to demonstrate the benefits of digitalization. An 88-year-old patient had been using an upper implant prosthesis for years and wished for a lower removable prosthesis for improved retention and support.

The upper arch had four external hex implants and an upper right canine supporting an acrylic hybrid prosthesis. The lower maxilla had five root fragments, making a removable prosthesis uncomfortable.

UPPER CASE (Analog Treatment Plan)

After evaluating the patient's medical condition, the treatment plan involved replacing the upper acrylic restoration with a screw-retained 10-unit zirconia fixed hybrid prosthesis. A gold cap was planned for the canine (#13), with distal cantilevers on teeth #14 and #25. The hybrid prosthesis was screw-retained on implants #12, #21, #23, and #24 and cemented with provisional cement on tooth #13 for retrievability.

LOWER CASE (Digital treatment Plan)

The lower arch treatment involved placing 4-Biohorizon tapered internal laser-lok implant supported, surgically guided, immediate loaded implants to support a 3D printed 10-unit hybrid screw retained restoration. (SprintRay Pro2 + ProWash+ NanoCure system and OnX

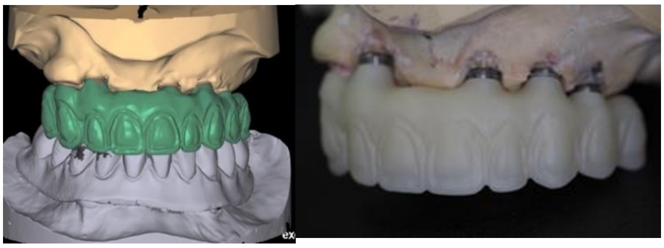
Tough 2, 3D printed resin) (5 -11)

UPPER CASE ANALOGIC WORKFLOW

Upper and lower physical casts were taken to fabricate an upper screw-retained provisional restoration and a lower full denture, which could be converted into the immediate loaded prosthesis once implants were placed.

After placing and adjusting the horizontal Plane of the upper full acrylic provisional prosthesis, an impression was taken to create a GC pattern duplicate for the final zirconia prosthesis.

A full-contour zirconia framework with a 1.2mm cut-back on the facial surface was designed for improved aesthetics. The incisal edges remained in zirconia (NexxZr T, 3Y-TZP, high flexural strength 1270 MPa, medium translucency 42%) to prevent porcelain cracks or delamination under occlusal forces.



The GC prosthesis was scanned, turned to a digital design, and milled into the zirconia framework, with the facial portion layered in porcelain and the occlusal and lingual areas stained. "T-base-like titanium abutments" were cemented onto the framework for implants #12, #22, #23, and #24. Tooth #13 was retained with a gold coping, and the final prosthesis was screw-retained but temporarily cemented onto #13 for retrievability. (2)

ZIRCONIA FRAMEWORK ESTHETIC TREATMENT

The zirconia framework received the first layer of ZirLiner, then internal stains that will go underneath the layering of the facial portion are applied in conjunction with occlusal and lingual stains.

The Zirconia structure undergoes 4 oven cocktion:

1. ZirLiner.

2. Internal stains.

3. Gingiva, body, incisal & translucent porcelain & layering all at once.

4. Final glaze plus additional stains to end up.

Here is the corrected and better-structured version of your text:

The upper hybrid prosthesis is ready for abutment cementation, which is performed on the stone cast. Before cementation, the zirconia is sandblasted with 50-micron alumina at 10bar. During the blank processing stage, the internal portion of the zirconia is modified by creating small indentations using a round 1/2P bur to enhance inner retention. After this modification, the zirconia is sintered.

Figure: An example of the inner retentions made in the blank zirconia

The prosthesis is now a hybrid full contour zirconia framework. Once secured in place, with the screw access sealed using Teflon and composite, the lower case was ready to proceed.

Zirconia frameworks meet all the needs of these patients, offering excellent esthetic outcomes, resistance to stains and food accumulation, easy maintenance and cleaning, no mucosal irritation, and long-lasting durability. However, opposing hybrid prostheses present challenges, particularly in occlusal force dissipation, due to the absence of a periodontal ligament and pressure proprioceptors. The choice of opposing material can either result in significant material wear or minimal to no wear, accompanied by an unpleasant clenching noise and increased occlusal load. [8 – 9]

OPPOSING HYBRID MATERIAL OPTIONS

Acrylic is just out of the question (the patient wore an acrylic hybrid for many years and had heard of newer more biocompatible materials), as it is a temporary material: as benefits it has the easy of in mouth cheap fast repair, with nice load distribution, gentle noise upon occlusion but disadvantages as high wear, non-biocompatibility, high stains and food accumulation, some kind of mucosa irritation, short term restoration. [12]

And at the other end zirconia offered a very strong opposing antagonist, noisy occlusion and lots of costly lab work. With the appearance of 3D Printed options, with full contoured material with no add-ons (no layered acrylic for gingiva) with the easy of double printing for a second immediate replacement in case of need with just a stain cured esthetic lab work with little polishing to do due to high precision dental printers (newest SprintRay Pro2 DLP printer with NanoCure curing machine). With a possibility of in mouth repair. This is the case of SprintRay next generation Hybrid Ceramic Resin with Nano Fusion technology while increasing the bond between the resin and the filler preventing fractures, water absorption and though reducing material weakening. [3 – 4]

Although with still some question marks and long-term reviews of outcomes with these newest materials as: biocompatibility, wear resistance, esthetic outcome of stains especially pink gingiva over white support.

FLEXURAL STRENGTH[a] 126 MPa
Higher flexural strength ensures that the restoration does not break during normal use

FLEXURAL MODULUS [a] 4281 MPa
Higher flexural modulus prevents distortion, which can impact accuracy

WORK OF FRACTURE[b] 1033 J/m^2
Measures the adhesion of dental adhesives to a restoration

a-Test Method ASTM D790 b-Test method ISO 20795-1

Figure: SprintRay OnX Tough 2 Material properties

LOWER CASE DIGITAL WORKFLOW

The full digital workflow for planning a hybrid prosthesis should include:(15)

1. Once the medical history is cleared for surgery, we start by scanning the initial restorations. In edentulous patients, first pre-scan the upper and lower prostheses with sufficient margins of the edentulous areas and scan the vertical dimension. When possible, remove the prostheses and erase from the initial scanner just the portion of the prosthesis, leaving the mucosa, to retain the vertical dimension information.

2. Initial X rays.

3. Take two Face pictures: one with mouth retractor and one smiling without it. This is to capture the horizontal planes (intra pupilar- tragus – nose – labial commissure) of the face and match the teeth planes.

4. Design a mock-up or superimposed prosthetic design with radiographic markers. Gutta-percha is a convenient material for wrapping from the facial to the lingual of the teeth and tissue, creating a silhouette of the teeth to visualize their final position, assess the need for tissue regeneration (prosthetically or surgically), and plan the screw access. When possible, remove any metal from the patient and place a provisional restoration in a non-radiographic material, wrapping a flattened gutta-percha point around the missing teeth, always touching the mucosa from the facial to the incisal edge, lingual, and towards the mucosa. This creates a silhouette of the crown and the distance from the bone to the tissue.

Figure: Examples of gutta-percha wrap arround silhouette creation

5. Place the Radiographic mockup in mouth and ask the patient to take a Tomography with it to better understand and design the optimal location for the implants with respect to the prosthetic outcome you expect to deliver.

6. Plan the case prosthetically: Yow will be looking at the silhouette of the teeth and any portion of missing gum tissues, this way you will ideally look for screw retained, prosthesis with implants placed in sound bone, more or less symmetrical and parallel, favoring its placement to clinical outcomes not to photographic cases.

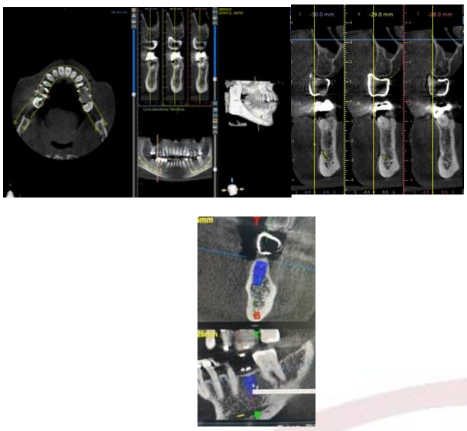


Figure: Examples from other cases, of the silhouette of the gutta-percha.

7. Always aim to achieve the best results with the least complexity. We seem to fall into social media posts and treatments that provide little or no information about the number of surgeries, discomfort or pain experienced by the patient, and the time (months or years) required to finalize the treatment. We must consider not only the surgical or prosthetic outcome but also the patient's age, initial complaints, and treatment expectations. Ask yourself or your team how to deliver their needs in the most predictable, suitable, and least invasive manner, with the fewest appointments in the shortest time.

8. Design the surgical guide, ideally tooth-supported for better stability and precision when possible. In edentulous patients, try to design a replica of the prosthesis the patient is wearing. It should be functional, in occlusion, and have flanges similar to the prosthesis.

Analyze whether it is truly necessary to place stabilizing lateral pins. There is no such thing as minimally invasive dentistry! Every time we enter a patient’s mouth, even for a necessary procedure, we invade their space and alter their natural state. Therefore, having a functional prosthesis as a surgical guide that someone can easily hold in place without movement, and flapless approach, should be the path to follow.

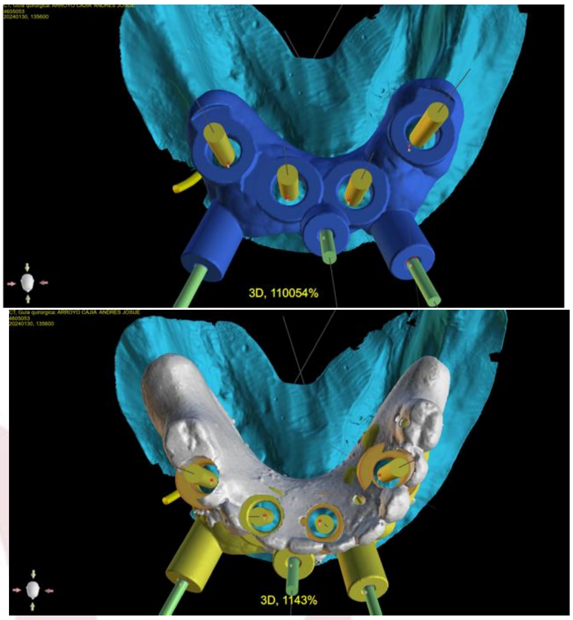
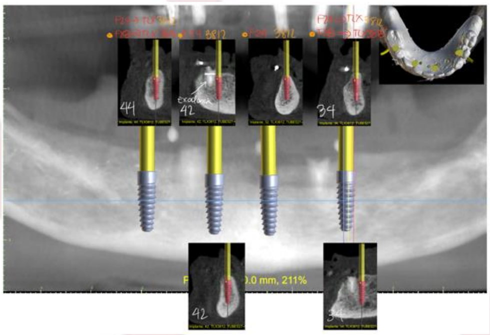


Figure: Upper guide usual without teeth, lower ideal mantaining the teeth from the actual prosthesis, this will allow to place it in the mouth and make the patient bite and double chek if the oclussion and the guide are stable and firm. If the remaining structure plus some of the rooths and firm and stable this cannolso be used to support and maintain the surgical guide firm and inmobile without the use of the fixation tubes.



9. Once the surgical plan is established, ensure you know the type of prosthesis you will deliver and the number of surgeries required to place the implants in accordance with the functional and aesthetic design of the prosthesis. Plan for potential failures to achieve success. Yes, as strange as this might sound, prepare for any possible surgical treatments that may not go as planned. Inform the patient about this contingency plan, as it is part of the diagnostic and treatment plan. Any changes may lead to misinformation or, worse, treatment failure. For example, if you plan to deliver an immediate prosthesis but the bone hardness and insertion torque of the implant are not adequate, inform the patient in advance that this may occur, but you already have a plan B for the temporary prosthesis, including how much longer it will take and the benefits and drawbacks.

10. Proceed to the implant placement surgery. Ideally, you should have the provisional design of the final prosthesis, including both the functional and aesthetic positions of the teeth.

The "Hybrid Prosthesis" (HP) term has been used since Dr Per-Ingvar Branemark, the term was introduced to describe a full arch screw retained implant supported prosthesis, combining or blending elements from fixed and removable prosthesis. That is when the term "Hybrid Prosthesis" was adopted.

HP METAL SUBSTRUCTURES AND ACRILIC PROSTHESIS

Initially, HPs were a combination of metal structures wrapped or covered with acrylic. The evolution of technology and materials in HPs has progressed as follows: we have transitioned from cast metal substructures with wrapped acrylic teeth and gum tissues to machine-milled titanium substructures, in search of more biocompatible, lighter, and more stable (passive fit) prostheses.

Subsequently, acrylic was replaced with light-cured composites for gum tissues, which provided aesthetically pleasing results but faced long-term issues with stain accumulation and material wear, leading to a loss of aesthetic and functional characteristics. Cast metal structures with layered porcelain mimicking traditional full mouth porcelain-fused-to-metal reconstructions were then utilized. This approach is highly labor-intensive and employs non-biocompatible materials, with difficulties in achieving passive fit due to the wobbling of structures introduced for several porcelain layers. Anyone who has worked with a porcelain-fused-to-metal (PFM) hybrid prosthesis faces a common problem: when the initial trial of the metal framework is stable, once the porcelain is layered, it often wobbles. This is due to the number of times the substructure is placed in the oven, as the fusion temperature of the layering porcelain is typically very close to that of the metal, even in non-precious metals with higher temperature ranges. This creates a contraction in the metal, preventing passive adaptation. Solutions include sealing the gap from disadaptation and correcting the occlusion, making post-soldering adjustments, or seeking a more stable material that ensures passive fit, such as zirconia or 3D printed hybrids.

HP ZIRCONIA RESTORATIONS

For some time, machine milled PMMA was thought as a right material, but still the need for stronger substructures (titanium milled) was a limitation, as it is more considered as a provisional material.

For some time, machine-milled PMMA was considered a suitable material, but the need for stronger substructures (titanium milled) remained a limitation, as PMMA is primarily regarded as a provisional material. The evolution of zirconia—from the initial type requiring veneering or layered porcelain to achieve a biomimetic appearance—has led to today's softer, full-contour, stainable zirconia, which avoids issues such as microfractures or delamination of porcelain. This advancement has made zirconia one of the preferred materials. [14]

We tend to designate "gold standards" in dentistry when years of sustained achievements have been reached. In the context of HPs, this has not yet been fully realized. However, if the cost of zirconia restorations were not an issue, it is likely that full contour zirconia restorations with minimal facial layering or just staining, would achieve the status of "Gold Standard." [14]

We still need to evaluate the latest 3D printed products and printers, which are now providing faster, easier, and more precise hybrid prostheses.

BIOCOMPATIBILITY AND BIOMIMETIC MATERIALS: CAD/CAM MACHINE MILLED MATERIALS (PMMA & Zirconia)

Biocompatibility in dental materials is a reality thanks to the appearance and wide use of different titanium implants, but the search of such materials has gone more towards the prosthetic portion.

Figure: Initial Casted Framework wrapped around with acrylic; a second zirconia framework with layered gingiva and individual E-max press crowns cemented to produce a screw retained hybrid prosthesis; initial patient results showing high aesthetics, with staining observed after six years of continuous use.

In the quest for more biomimetic materials (those that mimic nature) and the advent of CAD/CAM dentistry, zirconia has emerged as a superior long-term option due to its strength, aesthetics, and biocompatibility.

It requires less maintenance due to low bacterial adherence, has a long lifespan due to its strength, and exhibits minimal wear and staining. Although it has a higher initial cost, it ultimately offers better aesthetics and durability, provided skilled dentists and technicians are involved.

In constructing the hybrid prosthesis, there are essentially two screw-retained prosthetic options:

a. **Directly to the implant**

Figure: 4 Screw retained Scan-bodies

b. To a prosthetic component (multi-unit abutment)

In a fully digital workflow, we expect to place the scan bodies (elements that capture the exact position, angulation, depth, and orientation of the implant and its specific type of connection). The ideal scan bodies should be screw-retained to ensure complete seating.

In theory, you should be able to decide on an implant base scanning regardless of the type of abutment chosen. However, in most multi-unit cases (and across most implant companies), this cannot be achieved due to the absence of digital multi-unit abutments. Typically, there is only one scan body for any height or angulation of multi-unit abutments. [6 – 7]

Consequently, you must select the correct angulation and tissue height of the abutment in the mouth before placing the scan body on top of this multi-unit abutment to design your hybrid prosthesis digitally.

IMPLANT BASE IMPRESSION

In a fully digital workflow, we should seek to take implant-based digital impressions (scanning directly to the implant, not to the prosthetic abutment). This allows you to digitally select the ideal abutment based on screw access, tissue depth, angulation, and abutment-crown ratio. You can also digitally visualize the most suitable prosthetic abutment for the desired outcome.

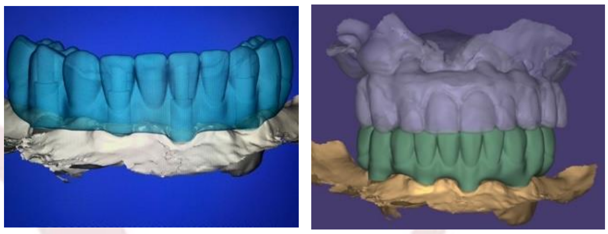


Figure: Hybrid digital design, functional occlusion.

Once digitally accepted, you can choose the material for printing; in this case, it was SprintRay OnX Tough 2 ceramic hybrid resin. The SprintRay Pro2 and NanoCure 3D printer require minimal post-processing. The positioning of the hybrid on the printing platform shows the number and position of supports; the flatter they are, the faster the printing process and the more stable the result. Always avoid placing supports on the inner abutment or preparation connections, typically located on the occlusal surfaces.

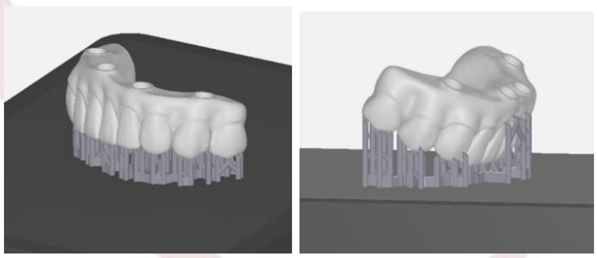
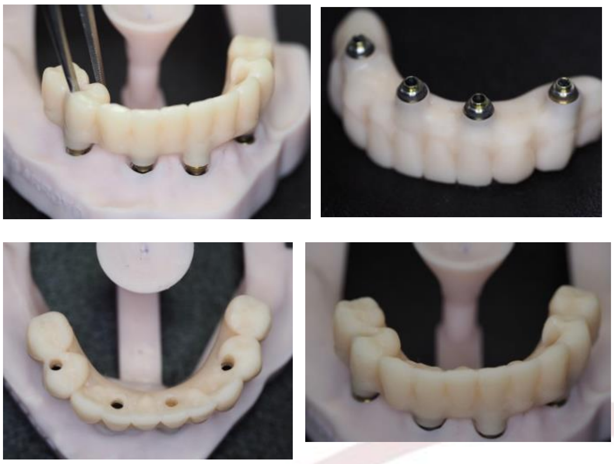


Figure: Left: ideal support placement. Right: non ideal

After printing, clean and cure the hybrid, checking the passive fit of the abutments to the prosthesis and the passivity of the hybrid to the final cast.



Proceed to the staining of the teeth and gum tissues; in this case GC Optiglaze light cure stains were used to mimic the upper zirconia prosthesis and natural teeth. Verify the passivity of the fit in the patient's mouth, with just one screw and check occlusion before final cementation. Use aluminum oxide micro etcher at 10 bar pressure in the inner portion of the abutment seating position, followed by isopropyl alcohol and ultrasound cleaning and final cementation with 3M relyx Universal. Clean the implant sites with chlorhexidine, rinse and dry, apply chlorhexidine gel inside the implant inner part and screw the hybrid to the final torque. Close the chimney access with Teflon and apply a small amount of the same OnX Tough 2 liquid resin to seal the access.

CONCLUSIONS

Digital dentistry is essential when considering a machine milled or 3D printed prosthesis.

Analog dentistry offers predictable results when performed step-by-step but requires many appointments, and material setting and availability can take longer. Errors often necessitate repetition or restarting the process, making it impossible to reproduce the exact product. This method is time-consuming and costly.

Digital dentistry workflows provide faster, more predictable outcomes that are easier to duplicate and export. Some errors can be corrected by simply undoing the latest changes. While the initial investment in equipment is high, it quickly pays off due to increased speed and reduced material use (eliminating the need for trays, impression materials, bite registration materials, and stone for models and articulators). Digital cases can be sent anywhere for design or consultation, making remote dentistry a feasible reality.

REFERENCES

1. Vatika Agarwal, Deepak Nallaswamy Veerayan,Suresh Vengopalan, Dhanraj Ganapathy, Subhabarta Maiti, Sanjog Agarwal (2022). Institute of medical and technical science. The Ideal Hybrid Framework Material? - A Literature Review. *Journal of Pharmaceutical Negative Results*, 534-538. https://doi.org/10.47750/pnr.2022.13.S07.072
2. Cinquini, C., Alfonsi, F., Marchio, V., Gallo, F., Zingari, F., Bolzoni, A. R., Romeggio, S., & Barone, A. (2023). The Use of Zirconia for Implant-Supported Fixed Complete Dental Prostheses: A Narrative Review. *Dentistry journal*, *11*(6), 144. https://doi.org/10.3390/dj11060144
3. Prakash, J., Shenoy, M., Alhasmi, A., Al Saleh, A. A.,

C, S. G., & Shivakumar, S. (2024). Biocompatibility of 3D-Printed Dental Resins: A Systematic Review. *Cureus*, *16*(1), e51721. https://doi.org/10.7759/cureus.51721

4. Upender Punia, Ashish Kaushik, Ramesh Kumar Garg, Deepak Chhabra, Anmol Sharma, 3D printable biomaterials for dental restoration: A systematic review, Materials Today: Proceedings, Volume 63, 2022, Pages 566-572, ISSN 2214-7853, https://doi.org/10.1016/j.matpr.2022.04.018. (https://www.sciencedirect.com/science/article/pii/S2214785322021320)
5. TaeHyun Kwon, Paul A. Bain, Liran Levin, Systematic review of short- (5–10 years) and long-term (10 years or more) survival and success of full-arch fixed dental hybrid prostheses and supporting implants, Journal of Dentistry, Volume 42, Issue 10, 2014, Pages 1228-1241, ISSN 0300-5712, https://doi.org/10.1016/j.jdent.2014.05.016. (https://www.sciencedirect.com/science/article/pii/S0300571214001638)
6. Catapano, S., Ferrari, M., Mobilio, N., Montanari, M., Corsalini, M., & Grande, F. (2021). Comparative Analysis of the Stability of Prosthetic Screws under Cyclic Loading in Implant Prosthodontics: An In Vitro Study. *Applied Sciences*, *11*(2), 622. https://doi.org/10.3390/app11020622
7. Samuel Sami Bekhit, Ahmed M. Abdelhamid, Nayrouz Adel Metwally, Evaluation of prosthetic screw loosening in all-on-four implant-supported restorations with two different connection systems, The Journal of Prosthetic Dentistry, 2023, ISSN00223913. https://doi.org/10.1016/j.prosdent.2023.05.022. (https://www.sciencedirect.com/science/article/pii/S0022391323003669
8. Haroun, F., & Ozan, O. (2021). Evaluation of Stresses on Implant, Bone, and Restorative Materials Caused by Different Opposing Arch Materials in Hybrid Prosthetic Restorations Using the All-on-4 Technique. *Materials (Basel, Switzerland)*, *14*(15), 4308. https://doi.org/10.3390/ma14154308
9. Yomna H. Shash, Mohamed T. Elwakad, Mohamed A. A. Eldosoky, Mohamed M. Dohiem, Evaluation of stress and strain on mandible caused by changing the bar material in hybrid prosthesis utilizing “All-on-Four” technique, Alexandria Engineering Journal, Volume 62, 2023, Pages 129-143, ISSN 1110-0168, https://doi.org/10.1016/j.aej.2022.07.030.
10. Guentsch, A., Bjork, J., Saxe, R., Han, S., & Dentino, A. R. (2023). An in-vitro analysis of the accuracy of different guided surgery systems – They are not all the same. Clinical Oral Implants Research, 34, 531–541. https://doi. org/10.1111/clr.14061.
11. Kalaivani, G., Balaji, V. R., Manikandan, D., & Rohini, G. (2020). Expectation and reality of guided implant surgery protocol using computer-assisted static and dynamic navigation system at present scenario: Evidence-based literature review. *Journal of Indian Society of Periodontology*, *24*(5), 398–408. https://doi.org/10.4103/jisp.jisp_92_20
12. De Araújo Nobre, Miguel & Guedes, Carlos & Almeida, Ricardo & Silva, António & Sereno, Nuno. (2020). Hybrid Polyetheretherketone (PEEK)–Acrylic Resin Prostheses and the All-on-4 Concept: A Full-Arch Implant-Supported Fixed Solution with 3 Years of Follow-Up. Journal of Clinical Medicine. 9. 2187. 10.3390/jcm9072187.
13. Mourad, Khloud & Rashed, Noha & Altonbary, Gilan & Hegazy, Salah. (2024). Five years of radiographic evaluation for the peri-implant bone changes of all-on-four implant prostheses constructed from different framework materials using different digital construction techniques. BMC Oral Health. 24. 10.1186/s12903-024-04642-7.
14. Cinquini, Chiara & Alfonsi, Fortunato & Marchio, Vincenzo & Gallo, Francesco & Zingari, Francesco & Bolzoni, Alessandro & Romeggio, Stefano & Barone, Antonio. (2023). The Use of Zirconia for Implant-Supported Fixed Complete Dental Prostheses: A

Narrative Review. Dentistry Journal. 11. 144. 10.3390/dj11060144.

15. Venezia, P., Torsello, F., Santomauro, V., Dibello, V., & Cavalcanti, R. (2019). Full Digital Workflow for the Treatment of an Edentulous Patient with Guided Surgery, Immediate Loading and 3D-Printed Hybrid Prosthesis: The BARI Technique 2.0. A Case Report. International Journal of Environmental Research and Public Health, 16(24), 5160. https://doi.org/10.3390/ijerph16245160