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Long-Term Side Effects of Clear Aligner- A Review Article

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ABSTRACT
Introduction: Clear aligner materials are exposed to degradation in the oral environmentdue to extreme changes of temperature, mechanical wear, changes in pH and enzymatic, bacterial and salivary activity,raising the issue of toxic material release. The biocompatibility of clear aligners is a topic of debate due to the lack of scientific literature thus there is a need to assess the cytotoxicity of the materials used by different brands.**Materials&methods:**An extensive literature search was performed in multiple electronic databases such as PubMed, Medline, Embase, ScienceDirect, and ProQuest which included articles published from 2004 to 2022 in the English language. **Conclusion:** The aligners are subject to mechanical and chemical assault continuously in the oral environment. The results of in-vitro studies showed mixed results but majority of the studies concluded that the clear aligner materials showed only a low level of cytotoxicity, and the clinical use could be considered safe.
Key words: Aligners, Invisalign, Cytotoxicity, mandible, BPA

I. INTRODUCTION

Clear aligners are an orthodontic treatment method based on the usage of removable, clear semi elastic polyurethane aligners.[1]Reinforced by the patients' request for less visible aesthetic orthodontic devices and a systematic promotion policy of aligner companies, an increased demand for clear aligner treatment has taken place in the last decade.[2-4] This upward rise in the demand and use of clean aligners has occurred due to the advantages offered by clear aligners like aesthetics, easy to maintain oral hygiene, less traumatic to gingiva and soft tissues and shorter in-office appointments.

Fig 1

Biocompatibility of the thermoplastic materials and material safety are pivotal aspects of long-lasting treatments.[5]In the mouth, these materials are exposed to degradation due to extreme changes of temperature, mechanical wear, changes in pH and enzymatic, bacterial and salivary activity, thus raising the issue of toxic material release.[6]Bisphenol A (BPA) is the most common cytotoxic agent. The other cytotoxic agents are methyl methacry- late (MMA), triethylene glycol dimethacrylate (TEGDMA), 2-hydroxyethyl methacrylate (HEMA), and bisphenol A glycidyl methacrylate (Bis-GMA).Degradation and metabolization of these monomers can cause irreversible damage to cellular DNA.[7]

The cytotoxicity of clear aligners is still a topic of debate due to the lack of scientific literature and the conflicting results in the few available studies. Additionally, in the last decade, several new aligners appeared on the market and there is a need to assess the cytotoxicity of the different materials used by different brands.

HISTORY

In 1945, Dr. Harold Dean Kesling first proposed a clear, vacuum-formed tooth-positioning appliance for minor tooth movement – 'Positioner'.[8]Dr. Henry Nahoum (1964) described a method to change tooth contours using thermoformed plastic sheets – Vacuum formed dental contour appliance.[9]In 1971, Robert J Pontiz introduced a thermoformed plastic appliance called the "invisible retainer" made on a master model that repositioned teeth with base-plate wax.[10]James

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A McNamara Jr. in 1985 also described, using invisible retainers to achieve minor tooth movement.[11]

FIGURE 2: TOOTH POSITIONER APPLIANCE

John J Sheridan and colleagues (1993) developed a technique involving interproximal tooth reduction and progressive alignment using clear Essix appliances.[12]Align technology, Inc.-Invisalign (Align Technology, Inc., Santa Clara,CA) took the principles of Kesling, Nahoum and others and used CAD-CAM technology to fabricate a series of custom appliance that are aesthetic, removable and can move teeth. Invisalign is a proprietary orthodontic technique that uses a series of computer generated custom plastic aligners to gradually guide the teeth into proper alignment. Launched commercially in 2013, Align's proprietary SmartTrack material is free of bisphenol-A (also known as BPA), as well as free of latex, gluten, and BPS.[13, 14]

CYOTOXIC PROPERTIES OF THE MATERIALS USED IN ALIGNERS

The polymers used for such long term treatment should not leach any potential toxins that may produce adverse local or systemic reactions, should not be carcinogenic or produce developmental defects.[15]Aligners and some retainers need to be worn continuously, except during eating and oral hygiene procedures. As a rule, aligners are replaced every 14 days during treatment and, thus, each aligner is in the mouth for approximately 308 hours. During this period the aligner is continually exposed to salivary enzymes, introduced liquids, inhaled and exhaled air and trauma caused by swallowing, speech and bruxism.[16]

The components of almost all the aligners are synthetic polymers like polyurethanes, polyamides, polycarbonates, polyethylene family but most commonly used aligners use polyurethane due to colour stability and its characteristic shape memory. Other concerning by-product of chemical and mechanical wear of aligners is Bisphenol-A.

In orthodontics, potential candidates for BPA (Bisphenol A) release include plastic materials and auxiliaries such as adhesives, polycarbonate brackets and aligners. The release of BPA has shown to be increased in alkaline environments and at high temperature; intraoral conditions might expose the aligners to transient heat shock during consumption of hot liquids.[8] However, all the materials used in the manufacturing of aligners have substances which are strongly associated with leaching and have estrogenic properties.

In the mouth, these materials are exposed to degradation due to extreme changes of temperature, mechanical wear, changes in pH and enzymatic, bacterial and salivary aggression, thus raising the issue of possible BPA release. Using the detection threshold of most standard analysis techniques, BPA has been reported to produce biological effects at very low concentrations.[7]This is due to the fact that natural hormones such as 17b-estradiol induce effects at strengths well below those at which their receptors are activated. This has led public health authorities in several countries to adopt restrictive measures regarding products containing BPA.

BPA has been classified as a category 3 toxic substance and a significant risk factor in human fertility. A recently published warning stated that exposure to BPA derivate-based composite resins can affect the psychosocial health of children. Increased levels and a long exposure period (5 years) to composites evidence higher levels of anxiety, depression and social stress in children.[17] Moreover, it should be noted that many cases of allergic contact dermatitis have been reported among dental staff.[17-19] Reports of allergic contact dermatitis reactions to BPA during manufacture of fixed retainers have also been made.

Hougaardet al[20] found that the incidence of infertility among women working in the plastics industry has increased while Jelnes et al[21]concluded that working in the manufacture of reinforced plastics could lead to abnormal sperm counts among male workers. According to the United States Environmental Protection Agency reference dose and the Food and Drug Administration's acceptable daily intake dose, the presumed ''safe'' dosage for BPA is 50 µg/ kg/day.[7,22,23] However, adverse effects have been documented with BPA doses below the above-mentioned daily level.

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Despite the generally accepted polyurethane (PU) biocompatibility, several safety concerns regarding each step of PU synthesis remain such as

(i) Toxic polyisocyanate synthetic pathway uses phosgene, a highly toxic gas at room temperature[24]
(ii) Impurities in the prepared polyols and polyisocyanates, and
(iii) The residual unreacted polyisocyanate monomer.[25]

FIGURE 3 INFLAMMATION AND ERYTHEMA CAUSED BY ALIGNER USE

FIGURE 4 : CONTACT DERMATITIS OF LIPS AND TONGUE

Polyethylene essentially causes health impacts like mild dermatitis, burning sensation in eyes, dryness and irritation in nose and throat,itching and irritation of the skin,asthma and hormone disruption.[26] Polypropylene and polycarbonate resins based aligners have the same or similar by-products released due to chemical and mechanical wear having estrogenic and inflammation of the cells especially giant cells.

Invisalign aligners have surged the market in comparison to the other types of aligners. In 2013 Align Technology introduced the new aligner material Smart Track. Primary goal of transitioning the Invisalign System to the Smart Track material was to optimize control of tooth movement.[8] Smart Track material is primarily composed of thermoplastic Polyurethane [PU] with some modifications. Although the colour stability of the PU-based aligners is relatively less stable (particularly after coffee exposure as reported after a study), the soft PU elastomer aids in improving the elasticity and is able to produce continuous light forces to the teeth, which is beneficial for orthodontic tooth movement.[27]

The new generation of Invisalign® aligner material is SmartTrack, a thermoplastic polyurethane with an integrated elastomer.[28]Some significant morphological differences have been found in the used Invisalign® aligners in relation to the new ones involving abrasion at the cusp tips, adsorption of integuments at stagnation sites, and localized calcification of the biofilm developed during intraoral use. Similarly, their mechanical properties were adversely affected during intraoral aging.[29] Regarding leaching of biologically active substances, neither a traceable amount of substances in an ethanol aging solution after immersion of aligner specimens for two weeks at 23° C was detected nor any cytotoxic and estrogenic activity of the device materials when tested in vitro were found.[29,30]

Invisalign® aligners did not present any cytotoxic effect on human gingival fibroblasts, did not show any noticeable estrogenic effects when tested on MCF-7 breast cancer cell line, and no measurable Bisphenol-A (BPA) release was traced in a trial of various orthodontic materials.[31] On the contrary, a relatively recent investigation found undesirable effects when epithelial cells were treated with eluates obtained from soaking Invisalign® plastic in saline solution.[32]This study was the first to report the adverse effect of contact with Invisalign® plastic on oral keratinocytes.[28]

The crucial concern regarding the use of plastic- based materials is the leaching of chemical substances called xenoestrogens into the immediate environment surrounding the plastic. Those substances have the ability to produce a biological reaction comparable to that of estrogen hormones, which are capable of inducing estrogenic signals that modify gene expression.[33-35]

Shaima R Al Naqbi et al.[28] conducted a study to investigate the cytotoxicity and estrogenicity of Vivera® retainers by assessing their biological behavioural effects as-received from the manufacturer, after it was retrieved from patients and the effects of the two sterilization procedures while the third one served as a control. None of the samples tested, at any concentrationInduced the proliferation of MCF-7 cells compared to the negative control, in contrast to the pronounced stimulation by all three b-

estradiol concentrations. However, after gamma-irradiation, the appearance of the retainers was altered, acquiring a yellowish colour reminiscent of the effect of ultraviolet light on plastic materials. Hence, it was considered that the sterilization through gamma-irradiation could potentially damage the plastic and the authors concluded that Vivera® retainers demonstrated no cytotoxic or estrogenic action.

Kopperud et al (2011)[36] conducted an in-vitro study to analyse leachable monomers, additives, and degradation products from polymer-based orthodontic base-plate materials. One heat-cured resin (Orthocryl), one light-cured (Triad VLC), and three thermoplastic materials (Biocryl C, Essix A+, and Essix Embrace) were investigated. Elution was performed in water at 37°C for 10 days. Chromatographic methods were used to identify and quantify the leachable. Monomers and additives leached from the materials polymerized in situ and from the thermoplastic PMMA-based material. Minimal leaching was found from the thermoplastic materials, while leaching of methacrylates and formaldehyde was observed from the powder-and-liquid type and the paste material.

Schuster et al.[29] investigated the effects of exposure to the oral environment on Invisalign aligners and reported substantial alterations in their morphology, but not in their composition, over two weeks. They concluded that no definitive consensus on the reactivity and biological properties can be established.

Gracco et al.[16] conducted a study to show the molecular and structural changes caused in Invisalign. The specimens showed free disordered hydrogen-bonded carbonyl (C=O) in urethane. A gas chromatography-mass spectrometer equipped with an electron impact ionisation detector (GC-MS) revealed that no substances were released from the aligner (A) into artificial saliva over 14 days. Scanning electron microscopy and energy dispersive X-ray analysis (SEM-EDX) revealed that there was no surface damage or detectable loss of elements from the as-received (N) aligner.

Martin et al.[37] conducted a study to investigate the in vitro cytotoxicity of different thermoplastic materials for clear aligners on human primary gingival fibroblasts (HGFs). Four materials for clear aligners were considered in this study: Duran (Scheu-Dental GmbH, Iserlohn, Germany), Biolon (DreveDentamid GmbH, Unna, Germany), Zendura (Bay Materials LLC, Fremont, CA, USA), and SmartTrack (Align Technology, San Jose, CA, USA). Three out of four materials (Duran, Biolon, Zendura) were assessed as thermoformed and non-thermoformed, whereas the SmartTrack was assessed only as thermoformed. In conclusion, under the experimental conditions, all materials for clear aligners showed slight cytotoxicity after 14 days. The thermoforming process increased the cytotoxicity of Polyethylene terephthalate glycol materials. Since materials for clear aligners have only shown a slight level of cytotoxicity, their clinical use may be considered safe.

Kurzmann C et al.[38] conducted a study to evaluate resins with composition of clear resin (FLGPCL02)and dental SG resin (FLDGOR01) in direct and indirect contact with tissues on L929 cell line (Human Gingival Fibroblasts). The results showed that when exposed to the materials, the cellular activity of L929 cells and gingival fibroblasts was observed. The impact of Clear and Dental SG resins depends on the processing stage of the material.

Kotyk et al.[31]conducted a study to quantitatively determine the bisphenol-A (BPA) leached from orthodontic materials during simulated intraoral exposure. Samples of orthodontic materials (thermoformed BiocrylEssix (prethermoformed and thermoformed); Biocryl Retainer (prethermoformed and thermoformed); Dentsply Raintree Essix (pre-thermoformed), Dentsply Essix (thermoformed), Invisalign aligner (unused and used)) were subjected to simulated abrasion, immersion in artificial saliva, thermal shock via temperature cycling, and simulated intraoral exposure. The Chemical analysis eluted in artificial saliva and Bisphenol-A (BPA) leached from orthodontic materials were evaluated. While the quantities of leached BPA were below the reference dose for daily intake, existing data of low-dose effects and medical disorders associated with elevated urinary BPA levels suggest that the use of the leaching materials, should be reduced or eliminated.

A study was conducted by Raghavan et al.[39] to evaluate and compare the bisphenol A (BPA) levels in saliva in patients using vacuum-formed retainers or Hawley retainers. The study concluded that increased BPA levels were found in saliva in all the groups after placement ofthe retainers. BPA levels were found to be larger in VFRs, followed by Hawley retainers by chemical cure, and finally Hawley retainers by heat cure.

Condo et al (2021)[40] conducted an in-vitro study to investigate and compare the morphological features and the chemical stability in weight of two different polyurethane-based blends, Smart Track (LD30) and Exceed30 (EX30), used for orthodontic aligners manufacture before and after the oral usage. The study concluded that LD30 is the

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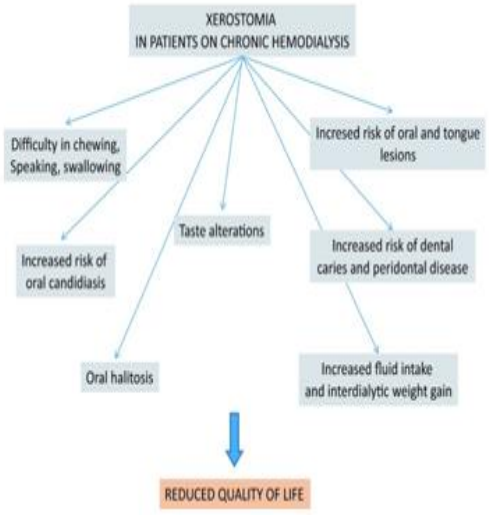
expression of the technological evolution of EX30, this is made evident its morphological architecture, more homogeneous and defined but also by the chemical stability that can be appreciated even in evident critic situations.

N. Olety et al (2022)[41] conducted an in-vivo study to evaluate the possible cytotoxic damage to the oral mucosal cells in healthy patients undergoing orthodontic treatment with clear aligners. 20 patients who required orthodontic treatment were included in the study. The study concluded that PETG material used for fabrication of aligners resulted in a change in the nature of buccal mucosal cells with an increase in the number of micronuclei which is an indicator for cytotoxicity. The PETG material may have a cytotoxic effect on the cells of the oral mucosa.

CYTOTOXIC EFFECTS ON SOFT TISSUES

LOCAL EFFECTS

- Inflammation
- Erythema
- Contact dermatitis
- Xerostomia
- Burning mouth



SYSTEMIC EFFECTS

- Estrogenicity
- Mutagenicity
- ➢ Insulin tolerance through the disruption of beta-pancreatic cells' physiologic activity,
- ➢ disruption of physiologic prostate development or increased risk for prostate cancer in men and breast cancer in women
- ➢ alterations in the physiology of mammary gland development.
- Infertility in women & abnormal sperm counts in men
- Respiratory symptoms

▪ PSYCHOLOGICAL EFFECTS

Higher levels of anxiety, depression and social stress in children.

RECENT ADVANCES IN THE MATERIALS USED

- Newer aligners make use of attachments to improve tooth movements. Clinicians could request composite buttons to be placed on the teeth and could also start to use inter maxillary elastics.[42]Recently the attachments are now placed automatically by the manufacturer's software where extrusion, de-rotation and root movements are required. Indentations in the aligners are fabricated where root torque is needed.[42] Altered aligner geometries include the use of pressure points within the aligner to deliver forces instead of bonded resin attachments.
- Since 2010, Align Technology has produced a series of improved attachment designs, pressure points, Power Ridges, bite ramps and other altered aligner geometries which have increased the effectiveness of force delivery by the Invisalign appliances. Generally, these improvements have yet to be replicated in any other commercially available Clear Aligner system.[42]
- In aligners produced by CAD-CAM technology, the individual teeth are sectioned and repositioned sequentially using a wax setup. Once a working cast is obtained, teeth are removed from cast and moved into the planned position, with aligners sheets moulded onto the realigned models using pressure moulding or vacuum machine. The digital models are then analysed for inter proximal reduction (IPR) and expansion requirements and the teeth are sectioned digitally.The force bumps, attachments, or auxiliaries are then planned for aiding tooth movements.[43]
- When Clear Aligners are manufactured via the use of 3D scanning technology,more accurate models are producedand more precise tooth movement prediction is done.[44] 3D printing techniques directly build printed aligners using techniques such as selective laser sintering (SLS), laser sintering melting (SLM), stereolithography (SLA). However, 3D printing by photo-polymerisation of clear liquid resin seems to be the most suitable procedure (Tartaglia et al., 2021).[45] Material

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employed through 3D printing in orthodontics can be very different. Among those, we can find acrylonitrile- butadiene-styrene plastic, stereolithography materials (epoxy resins), polylactic acid, polyamide (nylon), glass-filled polyamide, silver, steel, titanium, photopolymers, wax, and polycarbonate.[46]

- NovoAlign was conceptualised in US in 2016, after two years of R and D by a team of orthodontist, engineers, dental technicians and IT professionals. These aligners are made up of USFDA approved medical grade flexible plastic material and are designed to fit each individual's mouth.
- Gold Nanoparticle-Modified Dental Aligners are now used for periodontal therapy.[47] The aligners coated with gold nanoparticles determine favourable antibacterial activity against P. gingivalis, one of the bacteria responsible for the onset of periodontal disease. P. gigivalis has recently been identified in the brains of patients with Alzheimer's disease (Kaye et al., 2010; Dominy et al., 2019). This finding could lead to considerations of using aligners as a means of long-term drug delivery in patients with P. gingivalis infection.

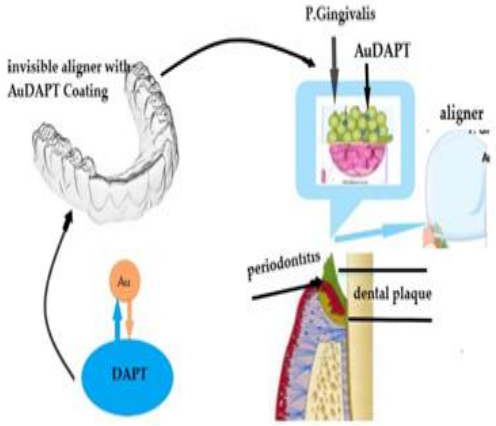

FIGURE 5 : GOLD NANOPARTICLE-MODIFIED DENTAL ALIGNER WITHAUDAPT

The antibacterial action of gold nanoparticles (NPs) has opened up new research fields. Studies indicate the gold NPs exert their antibacterial action in different ways, such as reducing membrane potential, inhibiting ATPase activity, inhibiting the binding of ribosomes to tRNA. Aligners coated with AuDAPT could slow biofilm formation showing favourable biocompatibility. This system could be used for the treatment of systemic infections related to periodontal disease.[47]

II. CONCLUSION

The biocompatibility of clear aligners is still an open research field due to the lack of scientific literature and the few studies performed. Most of the 3D printable materials are resin and Bisphenol-A, one of the by-products resulting from degradation of such resins, can act as a steroid hormone and cause biological effects, such as premature puberty in girls, ovarian cancer, or disruptive maturation of male reproductive organs. The aligners are subject to mechanical and chemical assault continuously in the oral environment. The results of in-vitro studies showed mixed results but majority of the studies concluded that the clear aligner materials showed only a low level of cytotoxicity, and the clinical use could be considered safe.

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