Bisphenol A in Dentistry

ABSTRACT

Bisphenol-A, an organic synthetic compound, has been present in many consumer plastic products and food packaging since the 1960s. Nowadays, Bisphenol-A is widely used in the field of dentistry for the manufacturing of resin materials. Several studies have suggested that Bisphenol-A may cause adverse health effects due to its ability to act as an endocrine disruptor chemical which has raised concerns about its widespread use. The aim of this study is to present an overview of the research studies dealing with Bisphenol-A exposure in the field of dentistry. PubMed, Scopus, EMBASE, Europe PMC, Web of Science and reference lists of relevant papers were searched to identify articles for inclusion. Two authors screened literature and extracted data from included studies independently. The evidence supports that Bisphenol A is used in many fields of routine clinical dental practice such as restorative dentistry and orthodontics. Regarding Bisphenol-A exposure from dental materials, the current data concludes that is below the Tolerable Daily Intake levels, but further evaluation is needed to reveal any possible adverse events caused by low-dose BPA exposure.

Keywords

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INTRODUCTION

Bisphenol A (BPA) is a synthetic compound that acts as an endocrine disruptor chemical by binding both oestrogen and androgen receptors. Nowadays, BPA can be found in many consumer products like internal coating of food, drink containers, reusable plastic bottles, medical devices and dental materials.[1] In the field of dentistry, BPA is used for the production of resins.[2]

BPA can be released and migrate to saliva, urine and blood. According to studies conducted in both America and Europe human exposure to BPA is common and the majority of people has detectable levels in urine.[3,4] It is thought that food is the main contributor to the overall BPA exposure, whereas dental surgery contributes to a minor extent.[5] European Food Safety Authority (EFSA) also showed that the contribution from dental sealants was limited to 0.001% compared to the overall BPA exposure.[6] Regarding dental materials, it has been shown that low doses of BPA are released in human saliva and urine, as a result of incomplete polymerization of composite resins or their degradation.[7,8]

The aim of this study is to provide an overview regarding the use of BPA-based materials in the field of dentistry and present data about BPA safety levels and long-term BPA exposure.

EVIDENCE ACQUISITION

Literature search was conducted in PubMed, Scopus, EMBASE, Europe PMC and Web of Science for articles published until February 2019. Two authors (KK and PA) searched both databases independently and extracted the data in pre-specified forms. No limitations for geographic region and no language restrictions were used for the retrieval of articles. The terms used for the PubMed search were: (Bisphenol A OR BPA or chemical disruptor) AND (Dentistry OR Dental OR Sealants). In Scopus, search was limited to 'articles', as regards the study type, using the same terms. Reference lists of relevant reviews and articles selected for inclusion were manually searched. Abstracts submitted in conferences were not eligible for inclusion. Data regarding authors, date of publication, study design and scope of the study were abstracted. Every study type (observational, case series) was considered eligible for inclusion. In vitro and experimental animal model studies were also considered eligible. The review was not registered in any database.

EVIDENCE SYNTHESIS

INTRODUCTION TO BISPHENOL-A

Bisphenol A (BPA) is an organic synthetic compound which belongs to the group of diphenylmethane derivatives and bisphenols, with two hydroxyphenyl groups (4,40-dihydroxy-2,2-diphenylpropane).[9] Initially, it was developed as a synthetic oestrogen in the 1890s. Chemical industries used BPA as a monomer in order to manufacture polymers such as polycarbonate and epoxy resins, as an antioxidant and as an inhibitor of polyvinyl chloride polymerization. Additionally, it was used for the synthesis of a flame retardant.[10]

Nowadays, BPA is massively produced in industry and constitutes a pervasive in our environment and in our daily lives.[11,12] The US Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), based on toxicological in vivo studies, have concluded that human exposure to BPA is under the safe Tolerable Daily Intake (TDI) value of 4 mg per Kg of body weight per day (mg/kg bw/day).[5,6] Similarly, according to the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), both short-term and long-term exposure of BPA from materials used in dentistry was estimated to be under the TDI limit of 4 mg/kg bw/day.[13]

Regarding children exposure, ADA Science Institute found that BPA release from 12 dental sealants, used by dentists in U.S.A., was 0.09 nanograms per day. This amount was below the limit of 1 million nanograms per day proposed for a 6-year-old child (who weighs about 20 kilograms) by the US Environmental Protection Agency.[14] Another study estimated the risk of BPA release after orthodontic bonding to be more than 42 000 times lower than the TDI for children who weigh 30kg.

Based on EFSA, the amount of BPA released after restorative treatment was also below the safe TDI value and was not hazardous for human health.[16] It was suggested, however, that the EFSA's TDI of 4 mg/kg bw/day did not sufficiently protect the general population.[17] Thus, adverse effects can possibly occur even after low-level BPA exposure.[18,19] While there is considerable concern, when making comparisons between animal and humans, since their physiology and pathophysiology differ substantially, animal studies have also proposed that BPA acts as an endocrine disruptor chemical causing adverse effects even at lower doses.[20] BPA has been associated with several harmful health effects such as hormonal disorders, asthma, diabetes, obesity, behavioural changes, cancer and alterations in immune function and neurodevelopment in children.[21-24] The most common disorders caused by low amounts of BPA are linked with the female reproductive system.[25] Moreover, transfer of BPA through the umbilical cord blood can be succeeded through high placental oestrogen receptor expression.[26] Thus, it can be suggested that embryos can be possibly affected due to maternal BPA exposure during prenatal period.

Therefore, dentists should be encouraged to consider reducing exposure to unpolymerized resin materials due to the possible adverse effects of BPA exposure, especially for high risk populations, such as pregnant women and children.[27]

BISPHENOL-A AS AN ENDOCRINE DISRUPTOR

BPA, due to its phenolic structure, binds to both nuclear oestrogen receptors (ERα and ERβ) but with lower affinity compared to oestradiol. BPA, under different molecular environments can act either as an oestrogen agonist or antagonist.[28,29]

More specifically, BPA is usually concentrated in ovarian follicular fluid, as ovary is a prime target for BPA action. The reason for this is that the ovary is the main site of ER expression and oestrogen production. There, BPA stimulates ovarian theca cells to produce androgens, by affecting 17β-hydroxylase.[30] Moreover, BPA decreases the oestradiol production in the granulosa cells, by the down-regulation of Cyp19a1 activity. Furthermore, the neonatal exposure to BPA may alter gonadotrophin releasing hormone secretion, leading to a luteinizing hormone increase and as a result to ovarian hyperandrogenism and impaired follicular development. BPA may also increase the amount of free testosterone, by displacing the sex steroids from human Sex Hormone Binding Globulin.[31,32]

BPA can also antagonize the androgen receptor (AR) at high concentrations. Furthermore, studies have shown that BPA may affect Leydig cell steroidogenesis, 17α-hydroxylase/17,20 lyase function and aromatase expression.[27,28]

Taken together, these pieces of data suggest many putative mechanisms by which BPA, even in low doses, may affect many different physiological processes. However, its exact molecular effects depend on factors which are not clearly understood yet such as the time and the amount of exposure.

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BISPHENOL-A AND RESIN COMPOSITE

Composite resins are widely used by dentists in order to remove tooth structure in a more conservative way and to restore not only decayed teeth, but also abrasion and other teeth anatomical malformations. BPA is a basic component of composite resins as it offers strength, bulk and rigidity to these materials[16] However, a significant disadvantage of BPA composite materials is their incomplete polymerization, leading the restoration to shrinkage, microleakage, and degradation. During their life in the oral cavity the restorations release BPA and other chemicals. Storage time, mechanical stress and consumption of acidic food and beverage, are linked to the BPA leaching from composites.[8,33-35]

In dentistry, Bisphenol A (BPA) is not a direct element of dental materials. For the manufacturing of resin composites BPA derivatives are used such as bisphenol A diglycidyl methacrylate (bis-GMA), bisphenol A dimethacrylate (bis-DMA) and ethoxylated bisphenol A glycol dimethacrylate (bis-EMA).[7] Also, another BPA derivative called bisphenol A diglycidyl ether (BADGE) has been recently found in different dental resins and sealants *(Figure 1*).[36]

However, in a qualitative analysis of composite resins' and sealants' components it was demonstrated that bis-GMA and different oligomers of bis-EMA were frequently present in dental materials but were not always reported on product safety sheets.[36] Additionally, according to a survey conducted in 2016, 112 of 130 studied composites were based on BPA derivatives, whereas only 18 of the composite resins marketed in Europe, did not contain BPA derivatives. Pure BPA was not reported in any type of composites.[7]

BISPHENOL-A EXPOSURE IN RESTORATIVE DENTISTRY

Many studies have examined the presence of BPA in patients' saliva, urine and blood after receiving restorative treatment with BPA-based materials. Most of these studies concluded that there are detectable amounts of BPA, mainly in saliva and urine, after the treatments and that these amounts can be affected by many factors.[37,38]

BPA exposure has been associated with the presence of multiple and large resin fillings.[39] A survey of Korean children, showed that there was a positive association between the number of surfaces restored with sealants or resin composites and BPA concentration in children's urine.[40] Also, a similar study concluded that children who had at least 7 restorations, had 20% higher mean urinary BPA concentration than the children with no restorations (p=0,13).[33] On the contrary, there is only one study conducted in U.S. which found no relationship between the number of sealants and fillings and the amount of urinary BPA.[41] Moreover, a recently published systematic review concluded that baseline urinary BPA levels are not associated with the number of the pre-existing resin-based restorations.[42]

Apart from the total surface of resin restorations, it was suggested that there is also a correlation between physicochemical conditions and BPA exposure levels. Firstly, changes in the PH can affect the release of BPA. The detected amounts of BPA released from seven polymerized bis-GMA-based composites and one sealant, before and after *in vitro* polymerization, were altered depending on PH based on a Spanish study.[43]

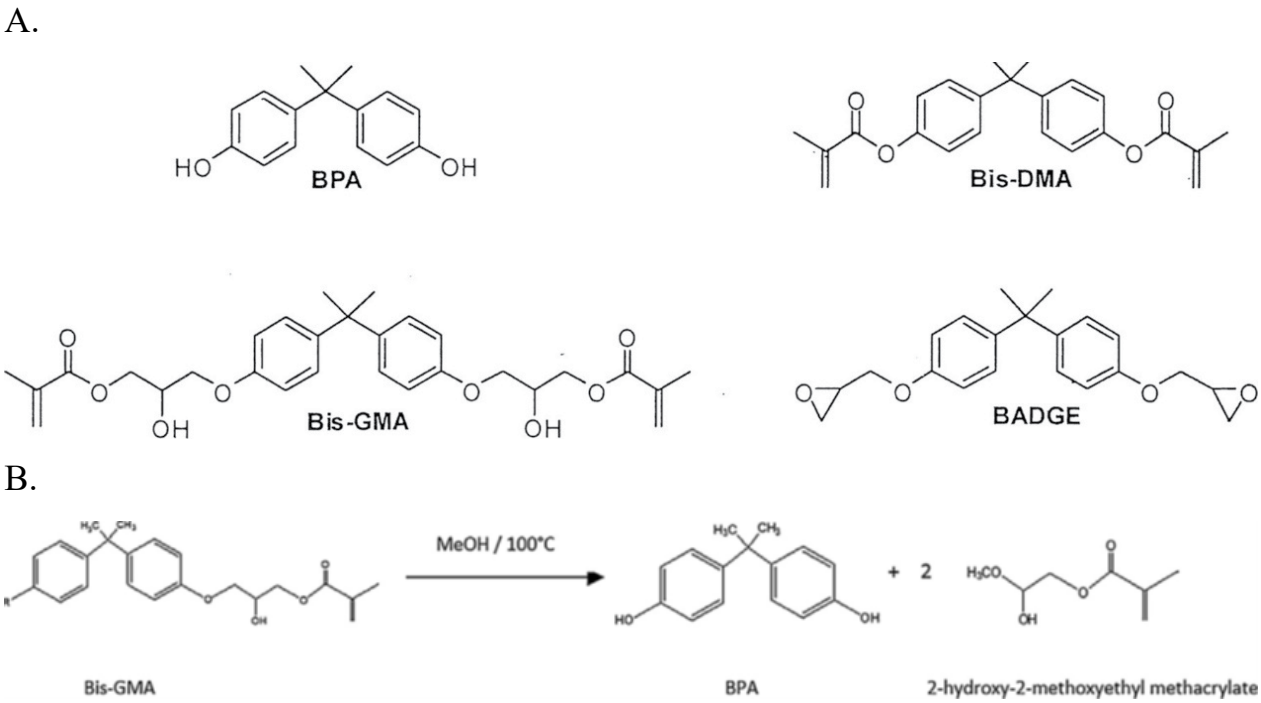

Figure 1: (A) Chemical structures of BPA, Bis-DMA, Bis-GMA, BADGE.46 (B) Transformation of bis-GMA in BPA.13

Secondly, thermal conditions during manufacturing of polycarbonate denture bases may lead to polymer decomposition and BPA leaching. Data indicate that BPA can be released from polycarbonate-based materials after the immersion in water or organic solvents.[44] Furthermore, in an investigation of 4 contemporary resin composites, BPA amounts were detected in 2 of them when they were stored in ethanol 75%, and there was a significant effect of time, storage solution, and material on the release of BPA.[45]

While increased concentrations of BPA in saliva and urine have been found after the use of fissure sealants, resin composite materials and bonding agents, other dental materials may not lead to BPA demonstration in saliva and urine, given that the release of BPA depends on the material characteristics.[2] BPA concentration in saliva, released from resin composites, depends on their monomers' solubility in the water.[15] In other words, there is a different susceptibility of BPA derivatives to hydrolysis by esterases in saliva. For example, bis-GMA's chemical structure prevents hydrolysis and BPA might be present as an impurity during bis-GMA manufacturing if the polymerization is not complete.[46,47] On the contrary, bis-DMA undergoes hydrolysis and leaches BPA as a product of its degradation.[48,49] As a result, higher amounts of BPA are released from bis-DMA degradation compared to bis-GMA degradation.[50] Factors such as number and size of sealants, physicochemical conditions and material's characteristics are important for the release of BPA, but BPA exposure due to polymer dental fillings is low compared to the overall BPA exposure.[38] In other words, despite the consistent results about the release of BPA from restorative dental materials, BPA-based materials are considered as safe and are widely used in daily clinical practise.

BISPHENOL-A EXPOSURE IN ORTHODONTICS

BPA is a basic element of resins and adhesives used at fixed orthodontic treatments in order to succeed bracket or lingual fixed retainers' bonding. The available data demonstrates that amounts of BPA and its derivatives are released by most of the orthodontic adhesive resins of the European market.[51]

Different types of orthodontic composites used for bracket bonding release different BPA amounts in saliva and urine which peak within one month after their use.[52] A study conducted in Brazil showed a significant increase of BPA levels within 24 hours and 1 week after bracket bonding.[53] Similarly, Kloukos *et al*, detected an increase in BPA concertation immediately after bonding of fixed orthodontic appliances with BPA-based adhesives during the early post-bonding period.[54] Also, Manoj *et al*, concluded that there was a constant BPA release from light- and chemical- cured orthodontic resins after bracket bonding, for 1 month, but in lower levels compared to the initial 30 minutes release. However, the increase in the level of BPA, immediately after bracket bonding, was below the TDI limits.[55]

The placing of lingual bonded orthodontic retainers is also related with an immediate increase of BPA concentration in saliva, with nanohybrid flowable composite resins releasing lower BPA amounts compared to the conventional hybrid ones. Eliades *et al*, in a study of light-cured orthodontic adhesive bonded to lingual fixed retainers, observed that BPA was released at detectable amounts and the highest level was observed within 1 month after the retainers' placement (2.9 μg/L), compared to the control group concentration (0,16μg/L). However, once again studies demonstrate that orthodontic bonded retainers release BPA amounts below the TDI limit.[56,57]

Interestingly, saliva BPA concentrations are higher in patients treated with vacuum-formed retainers compared to Hawley retainers. Vacuum-formed retainers and Hawley retainers are composed of polypropylene/polyethylene and polymethylmethacrylate/hydroquinone respectively. All of these products contain BPA. Thus, different orthodontic retainers could release BPA and affect the saliva BPA levels.[58]

Moreover, a relation between BPA release from orthodontic adhesives and the degree of polymerization has been proposed. More specifically, an increase in tip distance of both light-emitting diode device (LED) and halogen light-curing unit (HLC), led to the reduction in the degree of conversion and as a result to greater BPA release.[59] However, there are studies demonstrating the absence of significant link between BPA release and curing distance.[60]

LONG-TERM BISPHENOL-A EXPOSURE

While BPA release immediately after the use of dental materials is common knowledge the amount of long-term exposure still constitutes a matter of debate. Several studies conclude that there is a detectable amount of BPA in saliva only within 1 hour from the composite placement, and thereafter this amount decreases rapidly. The in vivo studies examining long-term BPA exposure from dental materials are summarized in Table 1.

In terms of short-term exposure, Kloukos *et al* concluded that the highest BPA amounts were found in saliva immediately and within 1 hour after sealants placement.[37] Moreover, Becher *et al* showed that leaching of BPA in artificial saliva was highest the first day after curing resin composites and small amounts of BPA continued to leach onwards.[18] A similar study conducted by Lee *et al*, demonstrated that the salivary BPA level was much higher 5 minutes after the filling procedure, compared to the level of BPA in saliva 7 days after the composite placement.[16] Furthermore, Berge *et al*., showed that one week after sealant treatment the BPA level in saliva was only marginally higher than before treatment.[61]

As far as urinary BPA is concerned, Maserejian *et al*. showed that placement of bis-GMA composites in children and adolescents resulted to a transient increase of BPA concentration. However, there were no detectable urinary BPA amounts 14

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Table 1. In vivo studies of long-term BPA exposure.

Date	Author	Study	Number of patients	Sample	Collection time after Composite placement	Outcome
2017	Lee[14]	in vivo	30	saliva	5 minutes, 7 days	Higher levels at 5 minutes, than 7 days, but within safe levels
2016	Maserejian[30]	in vivo	91	urine	1 day, 14 days, 6 months	Higher levels the 1rst day, not detectable after 14 days
2012	Kingman[60]	in vivo	151	saliva	1 hour,9 hours, 30 hours	Higher levels within 1 hour until 8 hours
			171	urine	1 hour,9 hours, 30 hours	Higher levels from 9 to 30 hours
2006	Joskow[59]	in vivo	14	saliva	immediately, 1 hour	Higher levels immediately
			14	urine	1 hour, 1 day	Higher levels after 1 hour. Levels remained elevated until 1 day.
2000	Fung[58]	in vivo	40	saliva	1 hour, 3 hours, 1 day, 3 days and 5 days	Higher levels after 1 and 3 hours compared to 1,3,5 days
				blood	1 hour, 3 hours, 1 day, 3 days and 5 days	Not detectable amounts

days or 6 months after composite placement.[33] Joskow *et al*, found that BPA levels in urine peaked 1 hour after sealant placement and then reduced significantly by 24 hours.[62] Kingman *et al*, concluded that placement of resin composite restorations was linked to an increase of BPA levels in urine 9 to 30 hours after restoration placement.[63] This might be explained by the fact that urinary clearance of BPA takes 4 to 9 hours in adults, as studies have shown.[64]

Thus, it can be concluded that there is a low-level BPA release from composite resins in saliva and urine, but only in short-term after restoration placement.[46] Additionally, long-term BPA release from dental materials has little or no estrogenic effects.[65]

CONCLUSION

The use of dental materials, especially bis-GMA composite resins, is associated with BPA exposure. However, while the exact contribution of dental materials to the overall BPA exposure and the patterns of BPA release are not well established, the available data suggests that long-term BPA exposure due to dental materials is unlikely to happen. Thus, dental BPA exposure seems to have no relation with the potential adverse events of BPA.

Despite the above-mentioned assumption, dentists should consider minimizing BPA release from dental materials. Indirect and CAD/CAM resin composites increase the degree of polymerization and thus reduce the release of BPA. The use of rubber dam, prolonged curing time and additional curing for 20 seconds after covering the restoration with glycerine, are some typical measures, which can be taken by dentists in order to control the release of free monomers during the placement of direct resin composites.[7]

Finally, further research is needed to clarify the exact impact of BPA on human physiology and the possible hazardous effects of low-dose BPA exposure, in order to eliminate any remaining concerns regarding the use of BPA-based dental materials.

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