REVIEWS

A Systematic Review of Exposure to Bisphenol A from Dental Treatment

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Abstract: Introduction: Dental composite restorations and dental sealants containing bisphenol A glycidyl methacrylate (BisGMA) are commonly used materials in dentistry. Bisphenol A (BPA) is used to manufacture BisGMA and can be a by-product in BisGMA-based dental materials. BPA is an endocrine-disrupting chemical that may affect reproductive, psychological, cognitive, and endocrine-related health. We conducted a systematic review of clinical studies that measured urinary BPA (uBPA) concentrations before and after dental treatment to evaluate the extent to which individuals are exposed to BPA from dental treatment.

Methods: Eligibility included studies that measured uBPA concentrations before and after dental treatment with any type of resin-based dental material. We searched PubMed, Cochrane, Web of Science, Virtual Health Library, Science Direct, ProQuest, and Clinical Trials with no date or language restrictions to identify published studies. We summarized

eligible studies across participant characteristics, amount of treatment, and time of follow-up measures. Because methods of measuring uBPA varied, our primary outcome was the direction and percentage change between baseline and 24 h posttreatment and at later time points as available.

Results: We identified 1,190 abstracts and 7 eligible studies: 4 in children and 3 in adults. In all studies, BPA concentrations increased 24 h after treatment. The 2 studies with the largest sample sizes found statistically significant increases >40% in uBPA concentrations at 24 h posttreatment (both P values <0.01). The 1 study to examine uBPA concentrations beyond 1 mo posttreatment found that concentrations returned to baseline by 14 d after treatment and remained at baseline 6 mo after treatment.

Conclusions: Our findings suggest that uBPA concentrations increase 24 h after dental treatment. One study showed that uBPA concentrations return to baseline by 14 d. Additional

research is needed to determine the magnitude of change from pre- to post-dental treatment and the trajectory of uBPA concentrations posttreatment.

Knowledge Transfer Statement: BPA is an endocrine-disrupting chemical that may have negative human health effects. Our findings suggest that urinary BPA concentrations increase in the short term after dental treatment. The extent to which such an increase may affect the health of patients remains an open question, particularly since there are no established thresholds for safety or harm related to BPA exposure.

Keywords: dental resins, composite resins, bisphenol A-glycidyl methacrylate, chromatography, urine, humans

Introduction

Bisphenol A (BPA) is a synthetic chemical that is used to make a wide range of products, including many types of resin-based dental materials (Geens et al. 2012). BPA is the starting

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ingredient in the manufacturing of BPA glycidyl methacrylate (BisGMA), the most common resin-based oligomer matrix component used in many dental composite restorations, dental sealants, and orthodontic adhesives (Van Noort 2011). Because BPA is used to make BisGMA, it may be present after the manufacture of BisGMA as an impurity or by-product of the manufacturing process (ADA Council on Scientific Affairs 2013). Additionally, leaching of BPA from BisGMA-based restorations may occur due to incomplete polymerization during the initial setting period or over time due to mechanical, bacterial, thermal, or salivary enzymatic biodegradation in the oral cavity (Kang et al. 2011).

Resin-based dental materials have revolutionized the field of aesthetic and preventive dentistry over the past decades, yet BPA exposure from resin-based dental materials has only recently begun to be explored. Safety studies of BisGMA-based dental materials in humans are not typically required by the Food and Drug Administration. Although BisGMA-based dental materials are tested for cytotoxicity, they are not formally evaluated for biological toxicity in humans. Moreover, assays for accurately quantifying BPA exposure have been developed and refined in just the last 15 y (Matsumoto et al. 2003; Ye et al. 2005). Only since then have clinical studies assessing systemic exposure to BPA from dental treatment been conducted.

An estimated 120 million resin-based dental restorations are placed in patients every year in the United States (ADA Survey Center 2007). More than 40% of children aged 6 to 19 y have at least 1 tooth sealed (Dye et al. 2015). Although there are many sources of BPA, dental treatment may be of high importance given the potential for widespread, direct, acute exposure and the potential for exposure during sensitive periods in childhood development. Despite the widespread use of resin-based dental materials, the extent to which patients are exposed to BPA from these materials is unclear. BPA is an endocrine-

disrupting chemical with potential toxicity in vitro (Wetherill et al. 2007; Machtinger et al. 2013) and in vivo (Perera et al. 2012; Ejaredar et al. 2017). Endocrine-disrupting chemicals perturb normal hormonal processes in the body with harmful downstream health effects. BPA is a known xenoestrogen that can affect the reproductive, psychological, cognitive, or endocrine-related health of children (Perera et al. 2012; Ejaredar et al. 2017) and adults (Ranciere et al. 2015). Specific health conditions that have been associated with BPA exposure include alterations in child behavior (Perera et al. 2012; Ejaredar et al. 2017), diabetes, hypertension, and obesity (Ranciere et al. 2015).

A growing body of research has examined systemic urinary BPA (uBPA) exposure from BisGMA-based dental materials in human clinical studies, which have never been synthesized or systematically reviewed. We conducted a systematic review to assess BPA exposure from dental treatment in humans by evaluating all clinical studies that measured uBPA concentrations in patients before and after dental treatment. Our objective was to evaluate the extent to which uBPA concentrations increase after exposure to BisGMA-based dental restorations, dental sealants, and other BisGMA-based dental materials. Secondly, we explored the degree to which baseline BPA concentrations were associated with prior dental treatment with BisGMA-based dental treatment.

Methods

Eligibility Criteria

Eligible articles included prospective clinical studies that measured uBPA concentrations before and after dental treatment with any type of resin-based dental material in human study participants. BPA may be measured in saliva, blood, or urine. This review was limited to uBPA because it measures systemic exposure likely tied to health impacts and because many of the studies examining BPA in saliva were already incorporated into a review (Kloukos

et al. 2013b). Human studies with abstracts in English were included in this review. Based on review of the English abstracts, studies that appeared eligible but were in a foreign language were translated for further inspection.

There were no restrictions in terms of participant age. We excluded studies that did not measure uBPA before and after dental treatment, since they did not measure change. Studies without original data (e.g., letters to the editors, opinions) were also excluded. Cross-sectional studies and review articles of in vitro and ex vivo studies were excluded, but the reference lists of these types of articles were reviewed to identify potentially eligible studies.

Search Strategy

The following strategy was used to search PubMed: (((bisphenol A[Supplementary Concept] OR bisphenol A[Title/Abstract] OR BPA[Title/Abstract] OR bisphenol A[nm]))) AND (((dental[All Fields] OR Dental Materials[MeSH Terms] OR Dental Restoration, Permanent[MeSH Terms] OR Dental Cements[MeSH Terms] OR Pit and Fissure Sealants[MeSH Terms] OR Composite Resins[MeSH Terms] OR Orthodontic Brackets[MeSH Terms] OR Orthodontic Retainers[MeSH Terms])). The specific search strategies for other databases were equivalent to those used in PubMed and are included in Appendix 1.

One calibrated reviewer (T.M.) performed the electronic search and evaluated studies for eligibility. We obtained article citations through an electronic search of 7 databases and the reference listings of eligible studies. The electronic databases that we used—all for the period through May 1, 2018—were PubMed, Cochrane Central Register of Controlled Trials, Web of Science, Virtual Health Library, and Science Direct. We also searched ClinicalTrials.gov and ProQuest (Fig.).

Review Process

One reviewer (T.M.) screened all abstracts for eligibility. A 25% random sample of initial abstracts identified was

Figure. Flowchart of the selection of studies for the systematic review of the exposure to bisphenol A from dental treatment. A total of 1,190 unique citations were identified through our electronic searches. Following the initial evaluation, 32 citations were indicated for full-text review. After reviewing these articles in-depth, we identified 7 studies that met the inclusion criteria. BPA, bisphenol A; PICO, patient, intervention, comparison, outcome.

reviewed by a second reviewer (C.M.M.). Initial eligibility criteria included the study being of humans, involving dental treatment (e.g., restorative, preventive,

orthodontic), and measuring BPA in urine. There was 99.6% concordance on the 25% random sample reviewed by the 2 reviewers. The reviewers assessed

eligibility independently and resolved the difference by re-review of the abstract. References lists of all eligible studies were reviewed to identify other related

studies not identified through database searches.

For each eligible study, we abstracted data on metrics outlined in Tables 1 and 2 (e.g., demographics, type of material, time points when uBPA was measured) to capture results and heterogeneity in methods, to evaluate study design, and to assess potential confounding. Two independent reviewers (T.M. and C.M.M.) assessed all studies for rigor in study methods and for potential threats to validity, including bias and confounding, and summarized findings in a bias risk assessment. Because the identified assessment tools were deemed to not adequately capture study quality (Wells et al. 2009; Moola et al. 2017) and risk of bias for the scope of this type of review, we created a tailored list of assessment criteria to measure relevant study quality metrics deemed appropriate to our specific question (Table 3).

uBPA Outcome Measures

To the extent available, we report original results, including means and medians in BPA concentrations and *P* values comparing BPA concentrations over time. For our primary outcome, we calculated the percentage change from the pretreatment baseline mean to means at 24 h posttreatment and at later time points for each pre- and posttime point when BPA was measured. The reason is that we anticipated variation in absolute measures of uBPA, since studies were conducted over a 12-y period and assays were analyzed in different laboratories. We also report changes in absolute uBPA concentrations as a secondary outcome. For all measures, we report ng/mL as the unit of measurement for BPA concentrations. In 1 study (Moreira et al. 2017), BPA was measured in $\text{ng}\cdot\text{g}^{-1}$, and we converted it to ng/mL. Because of the heterogeneity in type of materials, laboratory methodologies, time points, and reporting of outcomes, we chose not to perform quantitative comparisons and instead performed a qualitative synthesis.

Results

Search Results

We identified 1,190 unique citations through our electronic searches (Fig.). After evaluating titles and abstracts, we identified 32 citations that met initial criteria. After further review, we identified 7 studies that met inclusion criteria. Among the 25 excluded studies, 15 measured BPA in saliva and/or blood; 3 were cross-sectional studies that measured BPA at only 1 point in time; 3 had no dental treatment; and 4 studies did not contain original data (Fig. and Appendix 2). Twelve studies were identified by reviewing the reference lists of studies that met initial criteria, 2 of which were deemed eligible for inclusion (Martin et al. 2005; Kim and Choi 2015).

Summary of Included Studies

In total, the 7 studies that measured uBPA concentration before and after dental treatment involved 348 participants, with sample sizes ranging from 9 to 172 (Table 1). Of the 7 studies, 5 involved <25 participants. Two studies were of adults; 4 were of children; and 1 study included adolescents and adults. Among the 7 studies, 2 examined resin-based sealants; 2, composite restorations; 1, composite restorations and sealants; and 2, orthodontic adhesives (Table 1). All studies had measures just before treatment. All studies had uBPA measured at 24 h posttreatment. Other posttreatment time points when uBPA concentrations were measured ranged from 1 day to 6 mo (Fig.). Only 1 study examined uBPA concentrations >1 mo after treatment.

All but 2 studies that we reviewed had material safety data sheets for the examined products showing that BisGMA was an ingredient (Table 2). Some studies used materials that appeared to include other BPA-derived materials, such as BPA bis(2-hydroxyethyl ether) dimethacrylate. We were not always able to obtain the material safety data sheets active at the time of the study or know what product number was used,

and so the ingredient composition of the materials is uncertain.

Risk-of-Bias Assessment

Six of the 7 studies reported inclusion and exclusion details for the sample and high rates of follow-up (Table 3). No studies included participants who did not receive dental treatment as a comparison group. Most studies reported the materials used, the material that contained BisGMA, and detailed their laboratory methods. Five studies reported using BPA-free containers for collection and storage. Four studies reported a limit of detection of BPA, but only 2 reported the number of samples below the limit of detection. Four studies analyzed uBPA concentration by demographics and treatment characteristics. Three studies collected information about other sources of BPA, but only 1 study examined other potential sources of BPA in the analysis. All but 2 studies considered urinary dilution as part of their analysis (Table 3). Only 1 study reported that laboratory analysts were blinded to the collection scheme, sample-numbering system, and material brand used (Joskow et al. 2006).

Findings

All 7 studies reported a substantial increase in mean uBPA concentrations 24 h after treatment, with the increase ranging from 43% to 354% compared with pretreatment. The percentage increase varied for the different types of materials. The increase in mean uBPA concentrations 24 h after treatment was between 43% and 51% for dental composite restorations, 30% and 113% for dental sealants, and 95% and 319% for orthodontic adhesives. The 1 small study that combined dental sealants and dental composite restorations is the oldest and reported the highest increase at 354% (Martin et al. 2005). Findings may be affected by outliers. For example, Maserejian et al. (2016) reported that the mean (SD) change in uBPA

Table 1.

Summary of Materials and Methods of Eligible Studies.

Study	Martin (2005)	Joskow (2006)	Kang (2011)	Kingman (2012)	Kim (2015)	Maserejian (2016)	Moreira (2017)
Country	US	US	South Korea	US	South Korea	US	Brazil
Setting	University	Military	University	Military	University	Academic research, private practice and community	University
Participants, <i>n</i>	19	15	22	172	9	91	20
Age group, <i>y</i>	Children (age not specified)	Adults (19 to 42)	Adults (13 to 32)	Adults (mean = 43.9)	Children (6 to 8)	Children (3 to 17)	Children (12 to 18)
Female, %	NR	7.1	54.5	49.7	22.2	45	NR
Race, %	NR	White 35.7; Black 64.2	NR	White 63.7; Black 18.1; Hispanic 6.4; Asian 9.3; other / unknown 2.3	Asian 100	Hispanic 38.4; White 26.3; Black 17.5; other 17.5	NR
Resin-based dental material used	Composite restorations and sealants	Sealants	Orthodontic adhesives	Composite restorations	Sealants	Composite restorations	Orthodontic adhesives
Amount of material	NR	Mean = 40.35 mg of sealant material per participant and 7.36 mg per tooth	NR	Mean = 120 mg of composite material, 2.6 teeth, and 5.3 surfaces with composite restorations	NR	NR	NR
Teeth surfaces restored / other, <i>n</i>	Mean ≥4	Mean = 6	Lingual bonded retainer on mandibular anterior teeth (6 to 8 teeth)	Mean = 1.5	Mean = 5.9	Mean = 2.3	Brackets on buccal surface of 20 teeth
Time of analyses ^a	1 h, 24 h, 7 d, 14 d	1 h, 24 h	24 h, 1 wk, 1 mo	1 h, 1 to 8 h or 9 to 30 h	24 h	24 h, 14 d, 6 mo	30 min, 1 d, 1 wk, 1 mo
BPA measurement method	HPLC-MS	Gas chromatography and high-resolution mass spectrometry	Liquid chromatography / mass spectrometry	Liquid chromatography / mass spectrometry (standard addition method)	HPLC-MS	HPLC-MS	Gas chromatography / mass spectrometry
Laboratory	Environmental Health Laboratory (University of Washington)	CDC Laboratory (Atlanta, GA)	NR	Midwest Research Institute Laboratory (Kansas City, MO)	NR	CDC Laboratory (Atlanta, GA)	NR
LOD, ng/mL	0.25	0.1	0.5	1.1 (male), 1.6 (female)	NR	0.1	NR
Composite / sealant brand	NR	Delton LC, Heliaseal	Filtek Flow, Filtek Z250	Filtek Z250, Tetric Flow, Heliomolar or Heliomolar HB, Esthet-X	TEETHMATE- F-1 2.0	Z100 Restorative and OptiBond Solo Plus bonding agent	Transbond XT light-cure orthodontic adhesive system (3M Unitek)

Characteristics of the studies included in the systematic review of the exposure to bisphenol A from dental treatment. Data were abstracted on a range of metrics (e.g., demographics, type and amount of material used, number of teeth surfaces restored, laboratory, and time points of urinary BPA measurement).

BPA, bisphenol A; CDC, Centers for Disease Control and Prevention; HPLC-MS, high-performance liquid chromatography and mass spectrometry; LOD, limit of detection; NR, not reported.

^aAfter placement of resin-based materials.

Table 2.

Compilation of Key Findings of Eligible Studies.

Study	Martin (2005)	Joskow (2006)	Kang (2011)	Kingman (2012)	Kim (2015)	Maserejian (2016)	Moreira (2017)
Mean BPA concentration, ng/mL							
Before treatment	0.26	2.41	0.561	1.67	2.88	3.33	2.20
After treatment							
~1 h		20.1		1.05 (0 to <1 h), 2.24 (1 to 8 h)	3.74		5.11
~24 h	1.18	5.14	2.351	2.38 (9 to 30 h)		5.04	4.28
7 d	1.21		2.083				3.10
14 d	0.73					2.95	
1 mo			1.805				2.20
6 mo						3.36	
Median, ng/mL							
Before treatment		2.35				1.98	
After treatment		6.75 (1 h), 3.75 (24 h)				2.25 (24 h), 1.98 (14 d), 1.95 (6 mo)	
<i>P</i> value, pre- vs posttreatment			0.13 (24 h); 0.21 (7 d); 0.28 (1 mo)	<0.0005 (1 h); <0.0005 (9 to 30 h)	0.99 ~24 h	<0.002 (24 h); 0.64 (14 d); 0.35 (6 mo)	<0.05 (1 h); <0.05 (24 h); <0.05 (7 d); >0.05 (1 mo)
Change, %							
After 24 h vs baseline	354	113	319	43	30	51	95
In mean at later time, %	365 (7 d), 181 (14 d)		271 (7 d), 222 (1 mo)			-15 (14 d), <1 (6 mo)	41 (7 d), 0 (1 mo)

Compilation of the key findings of eligible studies included in the systematic review of the exposure to BPA from dental treatment. Values reported include original results (e.g., means and medians in BPA concentrations and *P* values comparing BPA concentrations over time) and percentage change from the pretreatment baseline to ≥24 h posttreatment (means). Urine-specific gravity ranges from 1.00 to 1.03. We used the value of 1.015 to change ng·g⁻¹ to ng/mL (ng·g⁻¹ × 1.015 = ng/mL).

BPA, bisphenol A.

concentrations between baseline and 24 h was 1.71 (9.94) ng/mL, and after the exclusion of 1 participant with 8 surfaces restored in a single visit, the mean changed to 0.87 (5.98) ng/mL (Table 2).

Three studies did not measure uBPA beyond a day. Among the 4 studies that examined uBPA at further time points, 3 reported uBPA concentrations at 7 d. All these studies found that uBPA concentrations 7 d posttreatment were higher than pretreatment uBPA concentrations, with the percentage

increase ranging from 21% to 210% (Table 2).

Maserejian et al. (2016) conducted the only study that examined uBPA at 14 d posttreatment and beyond 1 mo. In this relatively large study, uBPA concentrations returned to pretreatment concentrations 14 d posttreatment and remained at pretreatment concentrations 6 mo after treatment (Table 2). Consistent with Maserejian et al. (2016), Moreira et al. (2017) found that uBPA concentrations were similar to

pretreatment levels

1 mo after treatment (in both studies, *P* > 0.05). In contrast, Martin et al. (2005) and Kang et al. (2011) found that concentrations 14 d to 1 mo after treatment remained high relative to pretreatment concentrations. There was no evidence of this increase being statistically significant in either study. Both had relatively small sample sizes.

To further examine the results, we assessed uBPA concentration before and after treatment beyond 24 h by

Table 3.
Results of Risk-of-Bias Assessment.

Study	Criteria ^a											
	1	2	3	4	5	6	7	8	9	10	11	12
Joskow (2006)	+	+(80)	+	+	+	–	+	–	+	–	–	+
Kang (2011)	+	+(100)	+	+	+	+	+	–	+	–	–	+
Kim (2015)	+	+(90)	+	–	–	+	–	–	–	+	–	+
Kingman (2012)	+	+(99.4)	+	+	+	+	+	–	+	+	–	+
Martin (2005) ^b	–	–	–	–	+	–	–	–	–	–	–	–
Maserejian (2016)	+	+(80.5)	+	+	+	+	+	+	+	+	+	+
Moreira (2017)	+	+(100)	+	+	+	+	–	–	–	–	–	–

Risk-of-bias assessment of the studies included in the systematic review of the exposure to BPA from dental treatment. A tailored list of assessment criteria was created to measure relevant study quality metrics (e.g., whether the study reports inclusion/exclusion criteria, follow-up percentage, the material used, laboratory methods, limit of detection, and whether the study measured nondental sources of BPA).

BPA, bisphenol A.

^a1) Study reports inclusion/exclusion criteria. 2) Study reports the follow-up percentage. 3) Study describes material used in treatment. 4) Material used reported to contain bisphenol A glycidyl methacrylate. 5) Study details laboratory methods used for BPA analysis. 6) Study reported using BPA-free collection and storage containers. 7) Study reported a limit of detection. 8) Study reported percentage of samples below the limit of detection. 9) Study examined BPA across other factors (examined BPA concentration across demographic and/or treatment characteristics; e.g., rubber dam, material type). 10) Study measured nondental sources of BPA. 11) Study evaluated nondental sources of BPA in analysis. 12) Study considered impact of urinary dilution in analysis by either accounting for urinary dilution with specific gravity or creatinine or providing justification for not accounting for urinary dilution.

^bAn abstract that contained less detail than the others, all of which were manuscripts.

grouping studies by type of dental material used. Two studies that examined dental sealants and/or composite restorations had follow-up beyond 24 h. Maserejian et al. (2016) in their study of 91 children reported little change in uBPA from baseline at 14 d (–15%) and 6 mo (<1%). In contrast, Martin et al. (2005) examined dental sealants and composite restorations in 19 children and reported sustained increases in BPA concentrations at 7 and 14 d, with both exceeding 200% of pretreatment concentrations. Both studies of orthodontic adhesives reported uBPA concentrations at 7 d and 1 mo after treatment. At 7 d, uBPA concentrations were 41% and 271% higher. At 1 mo, uBPA concentrations were 222% in 1 study and the same as baseline in the other study (Kang et al. 2011; Moreira et al. 2017; Table 2).

In terms of changes in absolute uBPA concentrations, the amount of change 1 h after treatment ranged from –0.62 to 17.7 ng/mL (calculated from Table 2). At 24 h after treatment, the amount of change

ranged from 0.71 to 2.73 ng/mL. Beyond 7 d, the amount of change ranged from –0.38 to 1.24 ng/mL (Table 2).

Two studies reported the association between the number of prior composite restorations and uBPA concentrations at baseline (Kingman et al. 2012; Maserejian et al. 2016), and neither found an association between the number of preexisting resin-based restorations and baseline uBPA concentrations.

Discussion

This is the first comprehensive assessment of systemic BPA exposure from dental treatment in humans. Across all studies, we observed an increase in uBPA concentrations 24 h after treatment. There was also some suggestion of an increase at 7 d posttreatment. Beyond 1 wk of treatment, the evidence is mixed. The largest study of children that examined resin-based dental composites found that uBPA concentrations returned to baseline by 14 d posttreatment and remained at baseline at 6 mo after treatment.

Despite the heterogeneity in study design and methods, results show a consistent increase in uBPA between baseline and 24 h following dental treatment. This consistency suggests the release of BPA during dental treatment from resin-based dental materials. This finding is consistent with reviews of BPA exposure that focused on in vitro and ex vivo studies, which found that BPA release is a common phenomenon in oral conditions (Kloukos et al. 2013a, 2013b; Halimi et al. 2016). However, some reported that BPA release from dental materials is negligible (Jaffer et al. 2002).

Our review was limited to studies that examined BPA in urine. Urine is the optimal matrix in which to measure BPA exposure because it measures systemic exposure, which is likely more closely tied to health outcomes. Unlike saliva, there are well-established, widely used methods for measuring BPA concentrations in urine. For these reasons, we did not include studies or results that measured BPA exposure in saliva. Because blood is a poor matrix for

measuring BPA concentrations (Calafat et al. 2013), we did not include studies or results that measured BPA from dental treatment in blood.

The source of the BPA in the reported studies is unclear. Whether or not BPA exposure is due to the unpolymerized material and/or unreacted monomers (potentially due to oxygen inhibition), residual BPA from the manufacturing process, some other ingredient, or some nonmaterial source related to treatment is unknown. All but 1 study that we reviewed had material safety data sheets for the examined products showing that BisGMA was an ingredient (Kim and Choi 2015). Two systematic reviews and a new study reported detecting BPA from BisGMA-based dental materials (Kloukos et al. 2013a, 2013b; De Nys et al. 2018). Given that an estimated 86.2% of dental resin composites are based on BPA derivatives and 74.7% are based on BisGMA (Dursun et al. 2016), BisGMA is a potential source of BPA. Other BPA-derived materials may be responsible for eluting BPA, but less is known about their role.

Data are limited on if and when uBPA concentrations return to baseline after 24 h posttreatment. The only study with uBPA measures beyond 1 mo is the largest of children ($N = 91$). This study supports the finding that BPA concentrations return to baseline by 14 d posttreatment and remain near baseline at 6 mo (Maserejian et al. 2016). The variation observed across other studies makes it unclear when values return to baseline. Aside from Maserejian et al. (2016), all the studies examining uBPA between 7 d to 1 mo involved <25 participants and may have had limited power to detect differences. Thus, the extent to which uBPA from dental treatment is sustained over time is still unclear.

Large percentage increases do not mean large absolute amounts of exposure to BPA. Comparisons of absolute levels of exposure are difficult to interpret for several reasons. BPA exposure from other sources or the dental materials may have declined

over the time. After initial *in vitro* studies (e.g., Olea et al. 1996) showed BPA exposure from dental materials, companies may have altered their dental material formulations to minimize BPA exposure. We speculate that over time, manufacturers may have paid closer attention to eliminate BPA from the manufacturing process, thereby reducing exposure. As a result, uBPA concentrations may have declined over the 12-y period when the studies in this review were conducted.

The 2 studies that examined the number of preexisting resin-based restorations and uBPA concentrations at baseline found no association (Kingman et al. 2012; Maserejian et al. 2016). This finding suggests, albeit in a preliminary and indirect way, that uBPA concentrations may not be affected by a slow, continued release of BPA from degradation of BisGMA-based restorations or sealants or from unpolymerized BisGMA-based dental material. If this were the case, one would expect higher uBPA concentrations among those with a greater number of preexisting resin-based restorations, and this was not observed.

There was substantial heterogeneity among the studies included in this review, and a limitation is that we were not able to combine estimates across studies. The methodologically most rigorous studies (Kingman et al. 2012; Maserejian et al. 2016) examined uBPA related to restorative treatment with BisGMA-based dental composites. These studies were the largest, and 1 had the longest period of follow-up. This review included studies with other types of treatment, different brands of resin-based dental material, different amounts of treatment material, and thus potential differences in skill or technique during application. Additionally, a given urine measurement is representative of only the past few hours to few days of BPA exposure because the half-life of BPA is short and varies over time with exposure from food and sources of BPA. This may have resulted in misclassification and bias for study participants who

happened to be exposed to BPA through food before urine samples were taken. Overall, this would bias results toward the null.

Our risk-of-bias assessment suggests that the studies included had methodologic limitations that could have influenced findings. The small sample sizes of most studies make it difficult to assess associations. Moreover, studies were carried out in different settings, including university, military, academic, research, private practice, and community dental clinics. The potential health implication of an increase in uBPA concentrations may vary among different populations. For example, children are more vulnerable to the impacts of BPA because they have developing organ systems that are susceptible to changes in developmental programming and future health. Other groups that may warrant study regarding BPA exposure from dental treatment include pregnant women, whose fetuses may be sensitive to the effects of BPA exposure.

Study findings may have been affected by laboratory methodologies and the lower limit of detection of the assays. Different laboratories and methods were used to measure uBPA, and interlaboratory variation in uBPA assessments exists. It is unclear how experienced some laboratories were in analyzing uBPA, which is important because rigorous methods are needed to prevent laboratory contamination. BPA is used in numerous consumer products, including plastics, and is found in dust and air. Therefore, background contamination of laboratory equipment/analysis can easily occur without attention to details and thorough quality control measures. Among those who reported it, the limit of detection varied, which likely affected the estimated means. The 2 studies that reported medians reported values below the means, suggesting skewed data with some participants having particularly high values of uBPA (Joskow et al. 2006; Maserejian et al. 2016). The impact of outliers on means can be substantial, as described by Maserejian et al. (2016),

and this may have affected results. Additionally, concentrations of uBPA may differ per the amount or type of dental material, as noted by Joskow et al. (2006), who reported that exposure to Delton LC results in considerably higher uBPA concentrations as compared with Helioclear F.

Because all studies compared pre- and posttreatment uBPA concentrations among the same individuals, the potential for confounding by factors among individuals was eliminated. Primary sources of potential bias in these studies include unmeasured factors that are part of dental treatment and time-varying covariates—for example, exposure to other sources of BPA (canned food) in the period between uBPA measurements. Only 1 study accounted for potential confounders (Maserejian et al. 2016). Studies with a comparison group with no dental treatment but with uBPA measures at the same time points would strengthen inference, but no such studies have been conducted. However, even with a comparison group, studies would still be limited by potential bias in measurement of uBPA.

uBPA concentrations may be affected by pretreatment behavior or advice given in the study. For example, in 1 study, uBPA decreased 0 to 1 h after treatment but increased incrementally at 1 to 8 h and 9 to 30 h (Kingman et al. 2012). It may be that participants consumed no food or beverages before treatment, causing BPA concentrations to decline before they were detectable from dental treatment. This is consistent with the pharmacokinetics of BPA, which shows that excretion of BPA after exposure—in our case, due to dental treatment—does not occur until after 1 h (Volkel et al. 2005). This suggests that uBPA values measured immediately after treatment do not likely reflect BPA exposure from dental treatment.

Given the widespread use of resin-based dental materials and the growing body of knowledge regarding the health effects of BPA, particularly for children, it is necessary to understand

the extent of systemic exposure to BPA from resin-based dental treatment, even if potential outcomes from these exposures are unknown. Overall, the weight of the current evidence suggests that higher concentrations of BPA are associated with significant adverse health impacts (Ranciere et al. 2015; Ejaredar et al. 2017). In this systematic review, we synthesized the evidence base related to dental treatment. We observed a consistent increase in uBPA concentrations 24 h after treatment across different types of resin-based materials. Initial evidence suggests that uBPA concentration may remain elevated at 7 d. There are no known safe levels of BPA for adults or children. Exposure from dental procedures is only one of many potential sources of BPA. However, it is important to understand the extent of exposure from potentially modifiable sources of BPA, such as dental products. Additional research with a follow-up >7 d and among individuals with higher levels of treatment is needed. Future studies should inform how long BPA levels in urine remain elevated after exposure to resin-based dental materials, to more accurately quantify the absolute amount of BPA exposure that occurs and to determine if negative health effects can result from such exposure.

Author Contributions

T. Marzouk, C.M. McKinney, contributed to conception and design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; S. Sathyanarayana, A.S. Kim, A.L. Seminario, contributed to data interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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