Objective: There has been variation reported in literature examining the relationship between dental caries and total antioxidant capacity (TAC) of saliva in children. This study aimed to systematically review the literature and conduct a meta-analysis of the association between dental caries and TAC in children.

Methodology: A systematic review of literature was done using the PubMed, Medline, and EBSCO libraries. Of the total of 68 records found, 11 studies were qualitatively assessed in the final analysis. These studies yielded a total of 13 comparisons to be included in the meta-analysis. The type of dentition of the child and the test used to measure TAC were assigned as moderators. A meta-analysis was done of the mean TAC levels, while a meta-regression was formulated using the moderators. All analyses were performed using OpenMetaAnalyst™ meta-analysis software (Brown University, RI, USA).

Results: The meta-analysis showed significant increase in TAC in children with dental caries when compared to their caries-free counterparts ($P < 0.001$). The meta-analysis showed high levels of heterogeneity ($I^2 = 99.48$). The meta-regression revealed that, while the type of dentition was a significant moderating factor ($P = 0.002$), the method used to assess the TAC was not ($P = 0.053$).

Conclusion: There is a significant increase in TAC in children with dental caries when compared to their caries-free counterparts.

Keywords: Dental caries, early childhood caries, meta-analysis, total antioxidant capacity
Meta-analyses serve as an aid in analyzing secondary data and determining whether the expense and time of further research into a topic are justified.[20] However, biomarkers have been traditionally associated with confounding factors which may result in heterogeneity, or extremely wide confidence intervals that diminish the value of a meta-analysis.[21] Dental caries has long been recognized as a disease with a multifactorial etiology and multiple risk factors.[22] Confounding factors such as age,[15,23] gender,[17] presence of periodontal disease,[16] method and type of antioxidants,[24] and type of dentition[12] studied mean that, despite several studies on the topic, it is difficult to determine the exact role of antioxidants in dental caries in children.

Moderators are factors which when included in meta-analyses can reduce heterogeneity and explain the role of confounding factors.[25] The aim of this study is to systematically review the literature on the relationship between dental caries in children and the TAC of saliva, perform a meta-analysis of the reviewed literature, and identify moderators that can explain the influence, if any, of potential confounding factors.

**Methodology**

Ethical approval for the study was approved from the research center of the Riyadh Elm University with registration number FRP/2016/222.

**Selection criteria**

The literature on the topic was systematically reviewed using the following criteria.

**Studies**

Observational studies conducted after 1967 were included in this systematic review.

**Population**

The study population was defined as children below the age of 14 years with dental caries. No attempt was made to distinguish between the types of dentition in which the caries occurred or to standardize for the severity of caries as these were considered as factors to be evaluated as potential moderators in the meta-analysis.

**Comparison groups**

Only studies comparing between caries-free children and children with dental caries were included in the review.

**Outcome measure**

The outcome was defined as the measurement of salivary TAC. Here, again, studies with differing methods of evaluation of TAC were included in the initial search so as to identify if the method of analysis was a confounding factor during the analysis. Studies measuring the salivary antioxidants were included in the systematic review; however, only those estimating the TAC were included in the meta-analysis.

**Collection of data**

The keywords total antioxidant capacity, saliva, dental caries, and children were used on PubMed, Medline, and EBSCO libraries to identify and collect the relevant literature. PRISMA guidelines were used to plan the systematic review and meta-analysis [Figure 1]. All data were encoded into a spreadsheet (Microsoft Excel, Microsoft Corp., San Jose, CA, USA). The units of record were converted into mmol/l and the moderators such as type of dentition, method of analysis, and type of caries studied were recorded.

**Conducting the meta-analysis**

The analysis of data was performed using the Open-Meta™ meta-analysis software (Brown University, Providence RI, USA).

**Results**

A total of 77 studies were found using the keywords “antioxidants” + “dental caries” + “children” on the PubMed database. The search using the same keywords on EBSCO yielded 34 additional records, while two additional records were found using the Google Scholar database. After removal of duplicates, a total of 68 records were found to match the keyword search. Twenty-three records were excluded as it was clear from the abstract that they did not meet the Patient Intervention Comparator and Outcome (PICO) criteria of the study. Of the 25 articles whose full text was assessed, 11 studies and 13 comparisons were included in the final qualitative synthesis. All these articles were found to be statistically capable of inclusion in the meta-analysis [Figure 1].

Of the studies included, most of the studies looked at early childhood caries,[4,5,13,14,26-28] two studies looked at dental caries in the mixed dentition,[15,29] and one looked at caries in the permanent dentition of schoolchildren.[30] One study looked at both primary and mixed dentition,[28] while one study looked at caries in both mixed and permanent dentition.[15] The studies analyzed are summarized in Table 1.

The meta-analysis showed that overall children with dental caries had significantly higher TAC levels than their caries-free counterparts [Figure 2]. However, the analysis had a significant heterogeneity ($I^2 = 99.8\%, P < 0.001$).

The meta-regression revealed a significant association between the type of the dentition and the difference in TAC between caries-free individuals and those with dental caries. The model showed that differences tended to increase significantly from primary to mixed and from mixed to permanent dentition ($P = 0.011$). The type
of method used to determine the TAC did not seem to significantly influence the difference in TAC between children with dental caries and those without [Table 2].

**DISCUSSION**

**HISTORICAL PERSPECTIVE**

The role of antioxidants in the etiology and progression of dental caries has been a topic of debate for the past two decades. Early studies on antioxidants and dental caries focused on the role of trace elements such as selenium and the possible antioxidant effects that they may have.\[^{31-33}\]

It was not until the late 1990s that researchers began to explore the role of salivary antioxidant capacity with an emphasis on salivary nitric oxide.\[^{22,24}\] By the early 2000s, researchers were actively looking into the TAC of saliva and its influence on different oral conditions.\[^{8,12,17}\]
Table 1: Summary of studies included in the meta-analysis

| Study                        | Method                | Condition | Dentition |
|------------------------------|-----------------------|-----------|-----------|
| Ahmadi-Motamayel et al., 2018| Spectrophotometry     | ECC       | Primary   |
| Zarban et al., 2017          | Ferric-reducing antioxidant| ECC     | Primary   |
| Silva et al., 2016           | Ferric-reducing antioxidant | ECC     | Primary   |
| Rahmani et al., 2015         | ELISA                 | Dental caries | Mixed   |
| Pandey et al., 2015          | Ferric-reducing antioxidant | Dental caries | Mixed   |
| Pandey et al., 2015          | Ferric-reducing antioxidant | Dental caries | Permanent |
| Mucalhdani et al., 2015      | Spectrophotometry     | ECC       | Primary   |
| Mahjoub et al., 2014         | Ferric-reducing antioxidant | ECC     | Primary   |
| Krawczyk, 2012               | ELISA                 | Dental caries | Permanent |
| Kumar et al., 2011           | ABTS assay            | ECC       | Primary   |
| Banda et al., 2016           | Ferric-reducing antioxidant | Dental caries | Mixed   |
| Hegde et al., 2009           | Spectrophotometry     | ECC       | Primary   |
| Hegde et al., 2009           | Spectrophotometry     | ECC       | Mixed     |

ECC=Early childhood caries, ELISA=Enzyme-linked immunosorbent assay, ABTS=2,2’-Azino-bis (3-ethylbenzthiazoline-6-sulfonic acid)

Table 2: Meta-regression examining the influence of covariates on total antioxidant capacity values

| Covariate                | Coefficients | Lower bound | Upper bound | SE  | P   |
|--------------------------|--------------|-------------|-------------|-----|-----|
| Intercept                | 0.889        | 0.283       | 1.494       | 0.309| 0.004|
| Type of dentition        | 0.462        | 0.174       | 0.75        | 0.147| 0.002*|
| Type of method used      | −0.455       | −0.813      | −0.097      | 0.183| 0.053|
| Omnibus P                | 0.005*       |             |             |      |     |

*Influence significant at P<0.05. SE=Standard error

Total antioxidant capacity and dental caries

The relationship between TAC and dental caries has been studied in detail and most studies show that TAC levels are elevated in children with dental caries. There have been a few studies that have shown that children with dental caries have lower TAC levels than caries-free children. Four of the 13 comparisons used in this meta-analysis showed a greater TAC than the control group.\[6,13,27,30\] One of the objectives of this meta-analysis was to identify the cause of this discrepancy.

Role of moderating factors

Heterogeneity refers to differences among the studies included in a meta-analysis.\[34\] Conventionally, heterogeneity has been considered to be a sign that the studies included in the analysis are not a homogeneous group and therefore indicative of a flaw in the construction of the meta-analysis.\[20\] While this is true of analyses of controlled factors such as those observed in in vitro studies, meta-analyses of dental caries typically show large heterogeneity.\[34\] This has been attributed to the multifactorial nature of dental caries. In general, deviations from a pattern can occur either due to the presence of an outlier or a moderating factor.\[34\]

Outliers refer to studies that do not fit into the pattern of the meta-analysis and should be excluded from the meta-analyses.\[34\] Moderating factors on the other hand refer to factors which can explain the reason for the shift or heterogeneity in the meta-analysis.\[34\]

In the current study, we based our selection of moderating factors on the qualitative assessment of the systematic review. It was observed that older children tended to have higher levels of salivary TAC; however, given that most studies only mentioned a mean age, it was decided to use the type of dentition as a more reliable covariate.

It was observed that studies used different methods to measure salivary TAC. While spectrophotometry\[4,12,27\] and ferric-reducing antioxidant power\[5,6,14,15,26\] were the most commonly used methods, some studies also utilized the 2,2’-azino-bis 3-ethylbenzthiazoline-6-sulfonic acid\[13\] or the enzyme-linked immunosorbent assay.\[29,30\] Thus, we also decided to examine the role of the type of test used on the variation in the TAC levels.

The results of the meta-regression demonstrated that, while the type of dentition studied had significant influence on the outcome of the meta-analysis, the type of test used did not seem to influence the outcome. This seems to suggest that each of the different tests used to assess salivary TAC levels was valid.

The study did notice that the studies done by Kumar et al.\[13\] and Banda et al.\[6\] showed a marked difference from the other studies in the meta-analyses. While it is possible to consider these two studies as outliers in the context of the current meta-analysis, the qualitative assessment of the studies was unable to find any obvious fault in either methodology or difference in the selected sample.
CONCLUSION

Within the limitations of the current meta-analyses, we can conclude that there is a definite association between salivary TAC and dental caries. Most studies suggest that there is an increase in TAC with dental caries and that this increase is more marked in the permanent dentition than in the primary or mixed dentition. The type of test used to measure TAC has no impact on the association between TAC levels and dental caries.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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