

Review Article

The Relationship between Salivary Total Antioxidant Capacity and Dental Caries in Children: A Meta-Analysis with Assessment of Moderators

Sharat Chandra Pani

Department of Preventive Dental Sciences, Riyadh Elm University, Riyadh, Saudi Arabia

Received : 26-05-18.

Accepted : 15-06-18.

Published : 08-10-18.

INTRODUCTION

Antioxidant mechanisms of the body are a series of compounds that act to reduce oxidative stress and the effect of free radicals on the human body.^[1,2] It has been suggested that saliva, through salivary antioxidants, could constitute a first line of defense against oxidative stress.^[2-5] Salivary antioxidants are a group of enzymes that comprise of salivary peroxidase, salivary uric acid, and several minor enzymes. The combined ability of these enzymes to counter oxidative stress is often referred to as the total antioxidant capacity (TAC) of the saliva.^[1,6]

Inflammation increases the activity of the antioxidant mechanisms of the body and there have been efforts over the past decade to determine the association between oral

diseases and TAC.^[7-10] The hypothesis that dental caries in children is an inflammatory process, and therefore would cause an increase in the oxidative response of the oral cavity, is one that has recently received a great deal of attention in literature.^[9,11-18] Given the rapid spread of dental caries in children below 6 years of age, early childhood caries and rampant caries in children have received particular focus.^[4,6,19]

Address for correspondence: Dr. Sharat Chandra Pani, Department of Preventive Dental Sciences, Riyadh Elm University, Riyadh, Saudi Arabia. E-mail: sharat@riyadh.edu.sa

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Pani SC. The relationship between salivary total antioxidant capacity and dental caries in children: A meta-analysis with assessment of moderators. J Int Soc Prevent Communit Dent 2018;8:381-5.

ABSTRACT

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

Access this article online

Quick Response Code:



Website: www.jispcd.org

DOI: [10.4103/jispcd.JISPCD_203_18](https://doi.org/10.4103/jispcd.JISPCD_203_18)

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

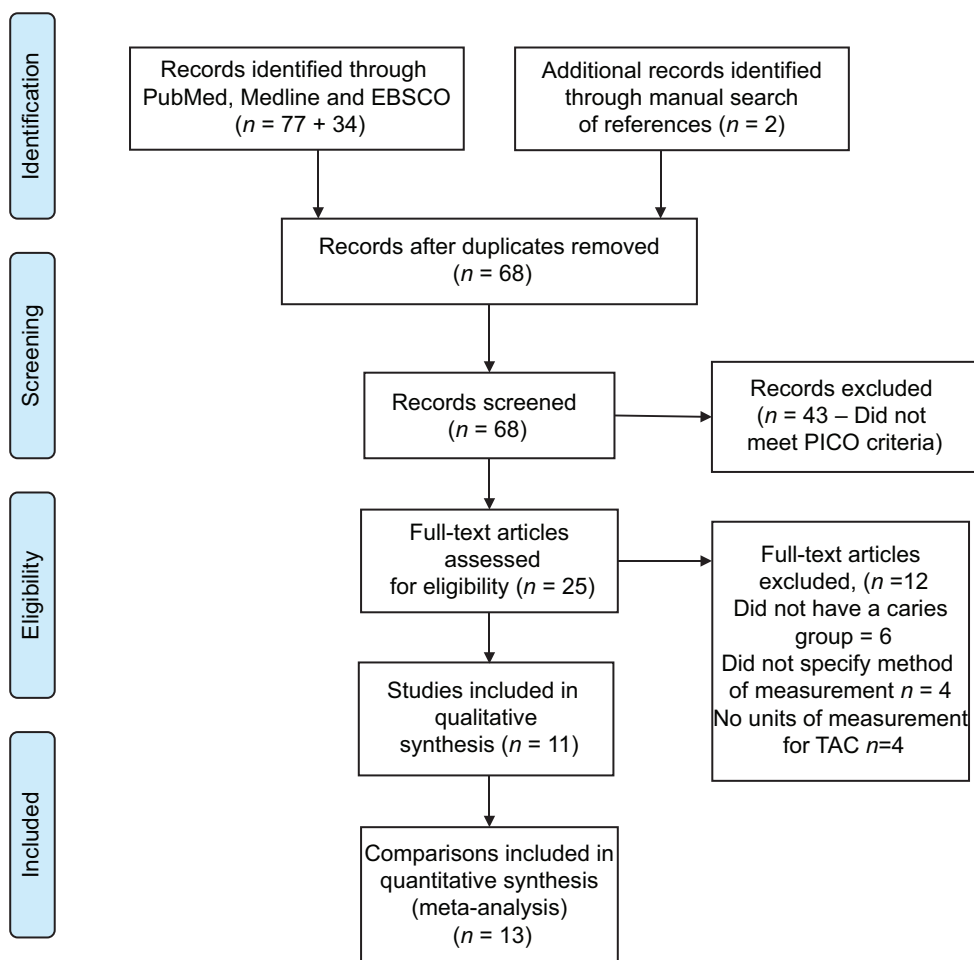


Figure 1: PRISMA flowchart of the article selection process

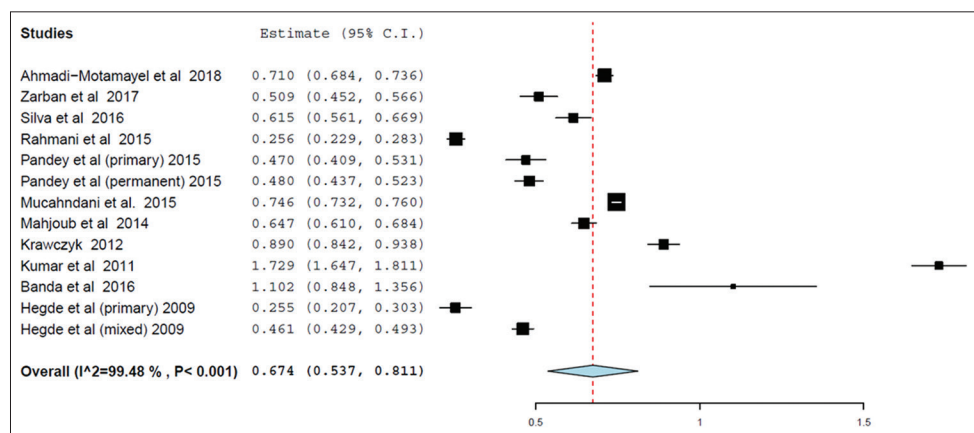


Figure 2: Overall meta-analysis of studies

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
Ahmedi-Motamayel <i>et al.</i> , 2018	Spectrophotometry	ECC	Primary
Zarban <i>et al.</i> , 2017	Ferric-reducing antioxidant	ECC	Primary
Silva <i>et al.</i> , 2016	Ferric-reducing antioxidant	ECC	Primary
Rahmani <i>et al.</i> , 2015	ELISA	Dental caries	Mixed
Pandey <i>et al.</i> , 2015	Ferric-reducing antioxidant	Dental caries	Mixed
Pandey <i>et al.</i> , 2015	Ferric-reducing antioxidant	Dental caries	Permanent
Mucahndani <i>et al.</i> , 2015	Spectrophotometry	ECC	Primary
Mahjoub <i>et al.</i> , 2014	Ferric-reducing antioxidant	ECC	Primary
Krawczyk, 2012	ELISA	Dental caries	Permanent
Kumar <i>et al.</i> , 2011	ABTS assay	ECC	Primary
Banda <i>et al.</i> , 2016	Ferric-reducing antioxidant	Dental caries	Mixed
Hegde <i>et al.</i> , 2009	Spectrophotometry	ECC	Primary
Hegde <i>et al.</i> , 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.^[35] 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.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES

- Battino M, Ferreiro MS, Gallardo I, Newman HN, Bullon P. The antioxidant capacity of saliva. *J Clin Periodontol* 2002;29:189-94.
- Greabu M, Battino M, Mohora M, Totan A, Spinu T, Totan C, *et al.* Could constitute saliva the first line of defence against oxidative stress? *Rom J Intern Med* 2007;45:209-13.
- Limón-Pacheco J, Gonsebatt ME. The role of antioxidants and antioxidant-related enzymes in protective responses to environmentally induced oxidative stress. *Mutat Res* 2009;674:137-47.
- Ahmadi-Motamayel F, Goodarzi MT, Mahdavezhad A, Jamshidi Z, Darvishi M. Salivary and serum antioxidant and oxidative stress markers in dental caries. *Caries Res* 2018;52:565-9.
- Zarban A, Ebrahimpour S, Sharifzadeh GR, Rashed-Mohassel A, Barkooi M. Comparison of salivary antioxidants in children with primary tooth abscesses before and after treatment in comparison with healthy subjects *Asian Pac J Cancer Prev* 2017;18:3315-8.
- Banda NR, Singh G, Markam V. Evaluation of total antioxidant level of saliva in modulation of caries occurrence and progression in children. *J Indian Soc Pedod Prev Dent* 2016;34:227-32.
- Abdolsamadi H, Rafeian N, Goodarzi MT, Feradmal J, Davoodi P, Jazayeri M, *et al.* Levels of salivary antioxidant vitamins and lipid peroxidation in patients with oral lichen planus and healthy individuals. *Chonnam Med J* 2014;50:58-62.
- Cağlayan F, Miloglu O, Altun O, Erel O, Yilmaz AB. Oxidative stress and myeloperoxidase levels in saliva of patients with recurrent aphthous stomatitis. *Oral Dis* 2008;14:700-4.
- Giebułtowiec J, Wroczyński P, Samolczyk-Wanyura D. Comparison of antioxidant enzymes activity and the concentration of uric acid in the saliva of patients with oral cavity cancer, odontogenic cysts and healthy subjects. *J Oral Pathol Med* 2011;40:726-30.
- Miricescu D, Totan A, Calenic B, Mocanu B, Didilescu A, Mohora M, *et al.* Salivary biomarkers: Relationship between oxidative stress and alveolar bone loss in chronic periodontitis. *Acta Odontol Scand* 2014;72:42-7.
- Hegde AM, Neekhra V, Shetty S. Evaluation of levels of nitric oxide in saliva of children with rampant caries and early childhood caries: A comparative study. *J Clin Pediatr Dent* 2008;32:283-6.
- Hegde AM, Rai K, Padmanabhan V. Total antioxidant capacity of saliva and its relation with early childhood caries and rampant caries. *J Clin Pediatr Dent* 2009;33:231-4.
- Kumar D, Pandey RK, Agrawal D, Agrawal D. An estimation and evaluation of total antioxidant capacity of saliva in children with severe early childhood caries. *Int J Paediatr Dent* 2011;21:459-64.
- Mahjoub S, Ghasempour M, Gharage A, Bijani A, Masrouroudsari J. Comparison of total antioxidant capacity in saliva of children with severe early childhood caries and caries-free children. *Caries Res* 2014;48:271-5.
- Pandey P, Reddy NV, Rao VA, Saxena A, Chaudhary CP. Estimation of salivary flow rate, pH, buffer capacity, calcium, total protein content and total antioxidant capacity in relation to dental caries severity, age and gender. *Contemp Clin Dent* 2015;6:S65-71.
- Tóthová L, Celecová V, Celec P. Salivary markers of oxidative stress and their relation to periodontal and dental status in children. *Dis Markers* 2013;34:9-15.
- Tulunoglu O, Demirtas S, Tulunoglu I. Total antioxidant levels of saliva in children related to caries, age, and gender. *Int J Paediatr Dent* 2006;16:186-91.
- Uberos J, Alarcón JA, Peñalver MA, Molina-Carballo A, Ruiz M, González E, *et al.* Influence of the antioxidant content of saliva on dental caries in an at-risk community. *Br Dent J* 2008;205:E5.
- Syed M, Sachdev V, Chopra R. Intercomparison of salivary nitric oxide as a biomarker of dental caries risk between caries-active and caries-free children. *Eur Arch Paediatr Dent* 2016;17:239-43.
- Blettner M, Sauerbrei W, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol* 1999;28:1-9.
- Lewington S, Bragg F, Clarke R. A review on meta-analysis of biomarkers: Promises and pitfalls. *Clin Chem* 2012;58:1192-204.
- Reich E, Lussi A, Newbrun E. Caries-risk assessment. *Int Dent J* 1999;49:15-26.
- Hegde MN, Hegde ND, Ashok A, Shetty S. Biochemical indicators of dental caries in saliva: An *in vivo* study. *Caries Res* 2014;48:170-3.
- Bayindir YZ, Polat MF, Seven N. Nitric oxide concentrations in saliva and dental plaque in relation to caries experience and oral hygiene. *Caries Res* 2005;39:130-3.
- Cumming G. The new statistics: Why and how. *Psychol Sci* 2014;25:7-29.
- Silva PV, Troiano JA, Nakamune AC, Pessan JP, Antoniali C. Increased activity of the antioxidants systems modulate the oxidative stress in saliva of toddlers with early childhood caries. *Arch Oral Biol* 2016;70:62-6.
- Muchandi S, Walimbe H, Bijle MN, Nankar M, Chaturvedi S, Karekar P. Comparative evaluation and correlation of salivary total antioxidant capacity and salivary pH in caries-free and severe early childhood caries children. *J Contemp Dent Pract* 2015;16:234-7.
- Hegde AM, Raj K, Shetty S. Relation of caries status on the salivary total antioxidant levels in asthmatic children. *Contemp Clin Dent* 2012;3:402-5.
- Rahmani M, Ghorchi V, Rezaei F, Vaisi-Raygani A. Evaluation of total antioxidant capacity of saliva in high school students. *Glob J Health Sci* 2015;8:89-94.
- Krawczyk D, Sikorska-Jaroszyńska MH, Mielnik-Błaszczak M, Pasternak K, Kapeć E, Sztanke M. Dental caries and total antioxidant status of unstimulated mixed whole saliva in patients aged 16-23 years. *Adv Med Sci* 2012;57:163-8.
- Oldfield JE. The selenium story: Some reflections on the "moon-metal". *N Z Vet J* 1974;22:85-94.
- Hadjimarkos DM. Selenium in relation to dental caries. *Food Cosmet Toxicol* 1973;11:1083-95.
- Hadjimarkos DM, Bonhorst CW. The trace element selenium and its influence on dental caries susceptibility. *J Pediatr* 1958;52:274-8.
- Conn VS, Valentine JC, Cooper HM, Rantz MJ. Grey literature in meta-analyses. *Nurs Res* 2003;52:256-61.
- Khan SQ, Khan NB, Arrejaie AS. Dental caries. A meta-analysis on a Saudi population. *Saudi Med J* 2013;34:744-9.