Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2021 Oct 02; 9(B):1092-1097.
https://doi.org/10.3889/oamjms.2021.6499
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Pediatrics*

Association between Bisphenol A Urine Level with Low-Grade Albuminuria in Egyptian Children and Adolescents

Nermine Mahfouz[1], Ebtissam Salah[1], Ayman Armaneous[1], Mai M. Youssef[1], Mones Mahmoud Abu Shady[1], Sara Sallam[1]*, Mona Anwar[2], Safaa Morsy[3], Jihan Hussein[3]

[1]Department of Child Health, Medical Research Division, National Research Centre, Medical Research Centre of Excellence (MRCE), Dokki, Cairo, Egypt; [2]Department of Basic Sciences and Biomechanics, Faculty of Physical Therapy, Heliopolis University, Cairo, Egypt; [3]Department of Medical Biochemistry, Medical Research Division, National Research Centre, Medical Research Centre of Excellence (MRCE), Dokki, Cairo, Egypt

Edited by: Ksenija Bogoeva-Kostovska
Citation: Mahfouz N, Salah E, Armaneous A, Youssef MM, Shady MMA, Sallam S, Anwar M, Morsy S, Hussein J. Association Between Bisphenol A Urine Level with Low-Grade Albuminuria in Egyptian Children and Adolescents. Open Access Maced J Med Sci. 2021 Oct 02; 9(B):1069-1074. https://doi.org/10.3889/oamjms.2021.6499
Keywords: Bisphenol A; Albuminuria; Pediatrics; Endothelial dysfunction
***Correspondence:** Sara Sallam, Department of Child Health, Medical Research Division, National Research Centre (NRC), (33rd El Bohouthst, former El Tahrirst, PO 12622) and Medical Research Centre of Excellence (MRCE), Dokki, Cairo, Egypt.
E-mail: lara26sara@gmail.com
Received: 21-May-2021
Revised: 01-Sep-2021
Accepted: 22-Sep-2021

Funding: This work is a part of projected funded by National Research Centre, Giza, Egypt.
Competing Interest: The authors have declared that no competing interest exists

Abstract

BACKGROUND: The glomerulus is a window to visualize the endothelial status of the whole body. Minimal decrease of albumin level below cutoff point might be a marker of endothelial dysfunction. Exposure to bisphenol A may be a risk factor of developing low-grade albuminuria (LGA) in pediatrics.

AIM: The aim of this study was to investigate the association of exposure to bisphenol A and the presence of LGA.

METHODS: This was a cross-sectional study enrolling 158 children: 91 boys and 67 girls excluding kids with hepatic disease, kidney disease, and endocrinopathies. Urinary albumin and creatinine were measured. Urinary albumin/creatinine ratio was calculated in mg/g and was stratified into macroalbuminuria of >300 mg/g, microalbuminuria of 30–300 mg/g, and LGA of <30 mg/g. Urinary bisphenol A was measured by high-performance liquid chromatography using fluorescent detector.

RESULTS: LGA was detected in 141 participants (89.24%), while microalbuminuria and macroalbuminuria were detected in 15 (9.5%) and 2 (1.26%) participants, respectively. The total urinary bisphenol A in candidates with LGA was categorized into four quartiles (<0.285, 0.285–0.599, 0.600–1.215, and >1.215) ng/mL and similarly their LGA (<2.0404, 2.0404–4.0385, 4.0386–7.3870, and >7.3870) mg/g. Children with the highest compared to the lowest quartile of urinary bisphenol A had a comparable mean of LGA with insignificant p value.

CONCLUSION: LGA was found in 141 out of 158 children. A direct cause effect of exposure to bisphenol A could not be proved. Further studies are needed to investigate the pathophysiology of LGA and its significance.

Introduction

The increasing environmental chemical exposure to bisphenol A (BPA) is now a daily base concern, especially with the westernized shift in eating practices in Egypt and other countries. Food packing, modern kitchenware, and inner coating of cans and jars heightened the incidence of health hazards of exposure to BPA via the oral route [1]. BPA is an organic synthetic compound found in polycarbonate plastics and epoxy resins. Polycarbonate plastics are often used in containers such as water bottles and tableware. Epoxy resins are present in the inner layer of metal cans, bottle tops, and water supply lines. BPA can seep into foods and beverages through leaching from can liners. Some dental sealants also may contain BPA. In addition, handling thermal sales' paper receipts can be a source of exposure to BPA [2], [3].

Since the 1960s till 2012, BPA had been used to make hard plastic baby bottles, cups for toddlers, and the linings of cans that hold infant formula. By June 2012, the Food and Drug Administration [4] ended the use of BPA in baby bottles and children's drinking cups. The hazardous potential of BPA is due to its estrogenic mimicking effects, its ability to induce reactive oxygen species, and its disruption to endocrinal functions. BPA can imitate the body's hormones, and it can interfere with the production, secretion, and action of natural hormones, as well as affecting their transport, function, and elimination [5]. The scope of notorious impact of BPA on health is getting wider every day. Multiple researches suggest a possible link between BPA and chronic non-communicable diseases [6]. Studies point out the association between BPA and low-grade albuminuria (LGA) among children and adults [3], [7].

LGA is defined as urinary albumin–creatinine ratio (UACR) <30 mg/g, i.e., below the range of conventional microalbuminuria (UACR: 30–300 mg/g). The LGA points to a leaky glomerular tuft and is a marker of renal endothelial barrier malfunction. This local endothelial dysfunction is just a mirror reflecting a

generalized endothelial dysfunction. Therefore, LGA is related to cardiovascular morbidity and mortality in the general population [8].

In view of the potential risks of LGA and in the light of the universal exposure to BPA in early life, we conducted the current study to explore the probable relation between LGA and BPA in a sample of Egyptian children.

Subjects and Methods

This was a cross-sectional study enrolling 158 children: 91 boys and 67 girls randomly selected from nurseries and primary, preparatory, and secondary schools in Giza, Egypt, during the period from September 2018 to September 2019. As for randomization, boys and girls present in class at time of our presence on Tuesday and Wednesday of each week and whose guardian accepted to enroll them and signed the consent are numbered by order and then we select odd numbers in each class for enrollment.

Exclusion criteria

Children with hepatic disease, kidney disease, and endocrinopathies were excluded from the study.

Ethical considerations

This study was a part of a large project, which investigated the different health hazards of BPA exposure in children and adolescents. The Research and Ethical Committee of National Research Centre of Egypt cleared the study protocol with ethical approval code number 14039. The study was also approved by the Egyptian Ministry of Education as well as schools and nurseries from which we enrolled the children. Written consent was signed by the legal guardian of each participant.

Each participant in this study was subjected to:

1. Food frequency questionnaire: A specific food frequency questionnaire was designed to identify the sources of BPA exposure, which enlisted the canned food and beverage consumed per month, e.g., fruits, vegetables, soft drinks, and fast food [9]
2. Anthropometry: Height was noted to the nearest 0.1 cm using a Holtain portable anthropometer, while weight was documented to the nearest 0.01 kg using a Seca scale balance with the candidate minimally dressed and shoes taken off
3. Laboratory investigation:

- Urine sample was collected from participants. It was the first-morning urine passed by the child collected directly in sterile plastic cups and stored immediately within 1 h at −20°C
- Blood sample was taken for measuring fasting blood glucose, total cholesterol (TC), triglycerides (TGs), high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

Techniques

Total and conjugated BPA levels were estimated using reversed-phase high-performance liquid chromatography (RP-HPLC) and quaternary pump Agilent Technologies 1100 series, Quat. pump, G131A model as described in our previous [10].

Sample extraction

Thirty μl from sodium acetate (2.0 M, pH 5.0) was added to 500 μL urine sample and hydrolyzed with β-glucuronidase/sulfatase for 3 h in shaking water bath that was adjusted at 37°C and then 100 μL hydrochloric acid was added. Then, the hydrolysate was extracted with ethyl acetate and centrifuged. Four ml from the supernatant was transferred to a clean tube for evaporation under nitrogen stream gas (N2 gas). The produced residue was then dissolved in 200 μL acetonitrile/water (60/40) v/v; finally, 40 μL of this solution was injected onto the HPLC [11]. The mean value of BPA was then divided on urinary creatinine concentration to correct the dilution of urine samples [12].

Urinary creatinine was measured by kinetic method according to Bartel, 1972 [13]. The kit was purchased from high-performance diagnostic reagents (Pointe, Scientific Inc., USA).

Urinary microalbumin was detected using enzyme-linked immunosorbent assay (ELISA) according to the method of Mogensen, 1984 [14] (Orgentec, Diagnostika, Hamburg, Germany).

The degree of albuminuria was determined according to the value of ACR. Three grades were described: A high grade, namely macroalbuminuria of >300 mg/g; an intermediate grade, namely microalbuminuria of 30–300 mg/g; and a LGA of <30 mg/g.

Blood samples were withdrawn from the participants after 12-h fasting. Blood was left to clot at 37°C and then centrifuged to separate serum which was then stored at −80°C. Fasting blood glucose was estimated immediately using the routine glucose oxidase method via Olympus 400 autoanalyzer (Olympus, Tokyo, Japan) [15].

Serum TC and TGs were estimated by the enzymatic calorimetric method according to Titez, 1982, and Fossati and Prencipe, 1982, respectively [16], [17].

HDL was estimated by precipitation method described by Lopez *et al*., 1977 [18].

Whereas, LDL was calculated by the Friedewald formula.

Statistical analysis

The ratio of BPA/creatinine and its log were calculated. Urinary BPA and BPA/creatinine levels were log transformed to obtain a better normality of the distribution. The data were presented as mean + standard deviation and were compared by student's t-test. Pearson's correlation analysis was used to assess the correlation between the different variables with normal distribution, while Spearman's correlation was used for the variables lacking normal distribution. SPSS version 21 (SSPS Inc., Pennsylvania, USA) was the software in use. Two-sided $p < 0.05$ was counted as statistically significant.

Results

The study group included 158 children, 91 (57.6%) males and 67 (42.4%) females; the age ranged between 2.12 and 18.8 years. LGA was the predominant finding. It was detected in 141 participants (89.24%), while microalbuminuria and macroalbuminuria were much less commonly detected in 15 (9.5%) and 2 (1.26%) participants, respectively. Hence, we focused our study on the candidates with LGA. Those 141 children were 82 males (58.2%) and 59 females (41.8%). Their age ranged from 2.12 to 18.8 years, with a mean of 11.03 years. All descriptive data (clinical and laboratory) are noted in Table 1.

Table 1: Descriptive statistics

Variable	Mean ± SD
Age in years	11.02 ± 3.281
Body mass index-z score	1 ± 1.59044
Systolic BP	110.97 ± 10.72
Diastolic BP	73.10 ± 7.93
Log total bisphenol A	−0.1987 ± 0.45
Log bisphenol A/creatinine	2.62 ± 0.53
Blood glucose	88.32 ± 15.36
Serum cholesterol	174.44 ± 39.88
Serum triglyceride	74.59 ± 32.13
HDL	39.91 ± 7.61
LDL	118.37 ± 39.07
Urine albumin mg/creatinine g ratio	5.89 ± 5.64

SD: Standard deviation, HDL: High-density lipoprotein, LDL: Low-density lipoprotein.

Childhood obesity was diagnosed according to body mass index z-score (BMI z-score) cutoff points settled by the Centers for Disease Control and Prevention. Forty-two children were obese (29.8%) with BMI z-score above +2 SD.

The total urinary BPA was categorized into four quartiles (<0.285, 0.285–0.599, 0.600–1.215, and >1.215) ng/mL and similarly their LGA (<2.0404, 2.0404–4.0385, 4.0386–7.3870, and >7.3870) mg/g, as shown in Tables 2 and 3, respectively.

Table 2: Bisphenol A quartiles

Bisphenol A quartile	Frequency (%) *n*=141
Valid	
Quartile 1 (<0.285)	33 (23.4)
Quartile 2 (0.285–0.599)	32 (22.7)
Quartile 3 (0.600–1.215)	34 (24.1)
Quartile 4 (>1.215)	33 (23.4)
Total	132 (93.6)

Missing (6.4%) as 9 children did not give urine sample.

Table 3: Quartiles of albumin mg/creatinine g

Albumin/creatinine quartile	Frequency (%) *n*=141
Quartile 1 (<2.0404 mg/g)	35 (24.8)
Quartile 2 (2.0404–4.0385 mg/g)	36 (25.5)
Quartile 3 (4.0386–7.3870 mg/g)	35 (24.8)
Quartile 4 (>7.3870 mg/g)	35 (24.8)

Females had a significantly higher level of LGA compared to males, of 7.3533 mg/g and 4.8417 mg/g, respectively, with $p = 0.009$. While, a similar urinary BPA value was found in both sexes. Both urinary BPA and LGA were significantly higher in non-obese compared to obese children with $p = 0.018$ and 0.01, respectively. Otherwise, non-significant difference was detected as regards lipid profile parameters and fasting blood glucose level on both urinary BPA and LGA values in Table 4.

Table 4: Effect of different variables on bisphenol A level and on albuminuria

Variables	Log BPA/creatinine			Albumin/creatinine ratio		
	Mean ± SD	t-test	p-value	Mean ± SD	t-test	p-value
Sex						
Male	2.64 ± 0.58	0.336	7.737	4.84 ± 4.23	−2.66	0.009*
Female	2.61 ± 0.46			7.35 ± 6.95		
Body mass index						
Non-obese	2.70 ± 0.53	2.393	0.018*	6.73 ± 6.32	2.60	0.01*
Obese	2.47 ± 0.51			4.07 ± 2.96		
Blood glucose						
<100	2.60 ± 0.54	−0.394	0.696	5.63 ± 4.60	−1.89	0.064
>100	2.52 ± 0.39			9.33 ± 9.84		
Cholesterol						
<200	2.48 ± 0.49	−1.412	0.164	6.47 ± 6.03	0.41	0.68
>200	2.74 ± 0.62			5.64 ± 6.11		
HDL						
>35	2.59 ± 0.33	1.757	0.085	6.96 ± 6.35	1.75	0.085
<35	2.29 ± 0.33			3.51 ± 2.87		
LDL						
<130	2.46 ± 0.47	−1.35	0.182	6.20 ± 5.48	0.227	0.821
>13	2.68 ± 0.64			5.83 ± 5.68		

*p < 0.05 is significant. HDL: High-density lipoprotein, LDL: Low-density lipoprotein.

Children with the highest compared to the lowest quartile of urinary BPA had a comparable mean of LGA with insignificant P value. Also no significant p value was found between low grade albuminuria quartiles, as illustrated in Tables 5 and 6, respectively.

Table 5: Comparison of low-grade albuminuria according to bisphenol A quartiles

Quartiles of bisphenol A	Mean	Std. Deviation	p-value
Albumin/creatinine ratio			
Quartile1(<0.285) (Reference)	6.0203	6.05326	
Quartile 2 (0.285–0.599)	5.8019	6.07727	0.863
Quartile 3 (0.600–1.215)	4.1241	3.44623	0.129
Quartile 4 (>1.215)	5.9336	4.28215	0.945

*p<0.05 is significant.

Discussion

It was suggested that BPA exposure during childhood may contribute to early vascular damage in children and adolescents [19]. LGA could be attributed to oxidative stress and generalized endothelial dysfunction induced by BPA [20]. In the current study, we examined the association between LGA as an early indicator of endothelial dysfunction and BPA exposure in a sample of Egyptian children.

Table 6: Comparison of bisphenol A according to quartiles of low-grade albuminuria

Low-grade albuminuria (quartiles)	Mean	Std. Deviation	p-value
Log bisphenol A/creatinine			
Quartile 1 (Reference)	2.5804	0.55726	
Quartile 2	2.6386	0.47786	0.655
Quartile 3	2.7218	0.54193	0.279
Quartile 4	2.5532	0.56932	0.841

In this study, LGA was detected in 89.24% of participants. There was a significantly higher level of LGA in females compared to males, of 7.3533 mg/g and 4.8417 mg/g, respectively, with p = 0.009. This may be explained by the greater muscle bulk in boys compared to girls in adolescence. Consequently, a gender-related difference in mean serum creatinine levels of 16.7% in favor of male sex is detected [21]. While ACR is inversely related to serum creatinine levels [22], a lower range of LGA is expected in males. These results are similar to those found by Trasande *et al*. [3].

Similarly, the muscle bulk discrepancy clarifies the reason for the significantly higher level of LGA in non-obese children as compared to those who have obesity, of 6.73 mg/g and 4.07 mg/g, respectively, with p = 0.01. The low muscle mass of the normal weight children might present with the decreased excretion of urinary creatinine, thus resulting in an overestimation of ACR [23].

Another possibility is, the lean children might have increased physical activity than the obese children and the active exercise might lead to physiological microalbuminuria [24].

To avoid the spuriously elevated ACR, we tried to space the sample collection far from exertion and longstanding upright posture, this rise in albumin excretion was mentioned in two different studies [25], [26].

Our finding that ACR was lower in the overweight children is consistent with what Nguyen concluded [26], but still, it merits further researches as several studies revealed the opposite [27].

Our study results showed that there is a significantly higher level of urinary BPA in non-obese children as compared to obese, of 2.7 and 4.27, respectively, with p = 0.018. This finding is contrary to what is reported in many other studies [3], [27], [28]. On the other hand, some studies showed no association between urinary BPA and overweight or obesity [29], [30].

The results we obtained could be explained by the lipophilic tendency of BPA. BPA was previously detected in human adipose tissue [31]. This is why blood level can be lower in obese subjects as it is stored more in adipose tissues.

Normal BMI does not guarantee healthy eating behaviors [32]. Many lean children and adolescents are exposed to high levels of BPA through consumption of canned food and beverages leading to an increment in urinary BPA [7].

The higher level of BPA in non-obese candidates, could result from a multitude of sources as the consumption of canned foods [33], dental materials [34], air, soil [35], plastic water bottles [36], and thermal paper [37]. Furthermore, gestational and lactational exposures are proved in humans [38], [39].

Our data failed to prove an association between urinary BPA levels and LGA. This result is against to what was found in many other studies like what was found by Trasande *et al*. They confirmed the association of urinary BPA and LGA in US adults, and documented the same association in a population of US children [3]. Another large population study demonstrated a significant association between urinary excretion of BPA concentration and albuminuria [7]. This association persisted independently of sex, diabetes, smoking status, hypertension, or chronic kidney disease. However, the non-monotonic dose–response relationships of BPA render the results unpredictable and widely variable [40].

Our results revealed that urinary concentration of BPA and the levels of ACR were not affected by the blood levels of other variables, such as lipid profile and FBG, whether low or high values. These results are similar to those of a recent Egyptian study [2].

The cross-sectional design of the current study might not reflect the long-term effect of BPA on endothelium. The small sample size was a confounding factor. Inadequate data about sources and routes of exposure to BPA make the interpretation difficult and non-conclusive. Dependence on BMI alone cannot precisely differentiate between lean and obese subjects.

Conclusion

BPA exposure as detected by cross-sectional urinary assay was not correlated to the predominant LGA of the study group. However, long-term researches are needed to provide more data about this association and to confirm whether urinary BPA-associated changes in LGA could or could not serve as an alarm for future development of metabolic syndrome and glomerular disease. This would lend support to our suggestion that BPA promotes generalized endothelial dysfunction.

Contemporary researches announce that even LGA accompanying BPA exposure could induce podocytopathy. This mandates the re-evaluation of the cutoff value of pathological albuminuria. Furthermore, it renders the use of BPA a forbidden issue rather than restricted one.

Acknowledgment

We would like to thank all children enrolled in this study together with their parents who showed interest and collaboration although our interview and examination session. Acknowledgment is also offered to our institute “National Research Centre” that gave us the opportunity to undergo this project.

References

1. Gabr AA, Mahfouz NN, Abu Shady MM, Youssef MM, Salah El-Din EM, Kamhawy AH, *et al*. Socioeconomic position as a risk factor for BPA exposure in a sample of Egyptian child. J Appl Pharm Sci. 2017;7(12):84-9.
2. Mohsen MA, Zaki ST, Youssef MM, Salah El-Din EM, AbuShady MM, Hussein J, *et al*. May detectable urinary bisphenol-a among children be associated with cardiovascular risk factor? Biosci Res. 2018;15:1243-50.
3. Trasande L, Attina TM, Trachtman H. Bisphenol a exposure is associated with low-grade urinary albumin excretion in children of the United States. Kidney Int. 2013;83:7418. http://doi.org/10.1038/ki.2012.422
   PMid:23302717
4. Avalable from: https://www.fda.gov/food/food-additives-petitions/bisphenol-bpa-use-food-contact-application#summary
5. Gassman NR. Induction of oxidative stress by bisphenol a and its pleiotropic effects. Environ Mol Mutagen. 2017;58(2):60-71. http://doi.org/10.1002/em.22072
   PMid:28181297
6. Boscha RJ, Quirogab B, Olea-Herreroa CM, Arenasc MI, González-Santanderd M, Reventúne P, Zaragozaf C, *et al*. Bisphenol A: An environmental factor implicated in renal vascular damage. Nefrologia. 2016;36(1):5-9. http://doi.org/10.1016/j.nefro.2015.08.007
   PMid:26565939
7. Li M, Bi Y, Qi L, Wang T, Xu M, Huang Y, *et al*. Exposure to bisphenol a is associated with low- grade albuminuria in Chinese adults. Kidney Int. 2012;81(11):1131-39.
   PMid:22398408
8. Tanaka F, Komi R, Makita S, Onoda T, Tanno K, Ohsawa M, *et al*. Low-grade albuminuria and incidence of cardiovascular disease and all-cause mortality in nondiabetic and normotensive individuals. J Hypertens. 2016;34(3):506-12. http://doi.org/10.1097/HJH.0000000000000809
   PMid:26820477
9. Shehata MA, Youssef MM, El-Din EM, El Mammoon SM, Megahed H, Abou Shady MM, *et al*. Potential sources of exposure and urinary bisphenol a concentration in children. J Clin Diagn Res. 2019;13(5):14-8.
10. a. Youssef MM, El-Din EM, Abu Shady MM, El-Baroudy NR, Abd el Hamid TA, Armaneus AF, *et al*. Urinary bisphenol a concentrations in relation to asthma in a sample of Egyptian children. Hum Exp Toxicol. 2018;37(11):1180-6.
    PMid:29441827.
    b. Youssef MM, El-Din EM, Abu Shady MM, Hussein J, Medhat D, Abdel Latif Y, *et al*. Profile of urinary bisphenol a (BPA) in association with age, sex and socio-economic standard in a sample of Egyptian children and adolescents. Biosci Res. 2018;15(4):3404-14.
11. Available from: http://www.meadowshplc.com/sites/default/files/products/attachments/1100pump.pdf
12. Barr D, Wilder L, Caudill S, Gonzalez AJ, Needham LL, Pirkle JL. Urinary creatinine concentrations in the U.S. population: Implications for urinary biologic monitoring measurements. Environ Health Perspect. 2005;113(2):192-200. http://doi.org/10.1289/ehp.7337
    PMid:15687057
13. Bartels H. Serum creatinine and creatinine clearance. Clin Chim Acta. 1972;8(23):961-3.
14. Mogensen, CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity onset diabetes. N Engl J Med. 1984;310(6):356-60. http://doi.org/10.1056/NEJM198402093100605
    PMid:6690964
15. Burrin JM, Price CP. Measurement of blood glucose. Ann Clin Biochem. 1985;22(4):327-42. http://doi.org/10.1177/000456328502200401
    PMid:3898972
16. Titez NW. Fundamentals of Clinical Chemistry. Philadelphia, PA: USA Publisher W.B., Saunders Company; 1982. p. 492-503.
17. Fossati P, Prencipe L. Serum triglycerides determined colorimetrically with an enzymethat produces hydrogen peroxide. Clin Chem. 1982;28(10):2077-80.
    PMid:6812986
18. Lopez-Virella MF, Stone P, Ellis S, Colwell JA. Cholesterol determination by three different methods. Clin Chem. 1977;23(5):882-4.
    PMid:192488
19. Melzer D, Gates P, Osborne NJ, Henley WE, Cipelli R, Young A, *et al*. Urinary bisphenol a concentration and angiography defined coronary artery stenosis. PLoS One. 2012;7:e43378. http://doi.org/10.1371/journal.pone.0043378
    PMid:22916252
20. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanismunderlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. Arterioscler Thromb Vasc Biol. 2004;24(5):816-23. http://doi.org/10.1161/01.ATV.0000122852.22604.78
    PMid:14976002
21. Groesbeck D, Köttgen A, Parekh R, Selvin E, Schwartz GJ, Coresh J, *et al*. Age, gender, and race effects on cystatin c levels in US adolescents. Clin J Am Soc Nephrol. 2008;3(6):1777-85. http://doi.org/10.2215/CJN.00840208
    PMid:18815241
22. Danziger J. Importance of low-grade albuminuria. Mayo Clin Proc. 2008;83(7):806-12. http://doi.org/10.4065/83.7.806
    PMid:18613997
23. Cirillo M, Laurenzi M, Mancini M, Zanchetti A, De Santo NG. Low muscular mass and overestimation of microalbuminuria by urinary albumin/creatinine ratio. Hypertension. 2006;47(1):56- 61. http://doi.org/10.1161/01.HYP.0000197953.91461.95
    PMid:16344360

24. Hirschler V, Molinari C, Maccallini G, Aranda C. Is albuminuria associated with obesity in school children? Pediatr Diabetes. 2010;11(5):322-30.
PMid:19968814

25. Hogg RJ. Adolescents with proteinuria and/or the nephrotic syndrome. Adolesc Med Clin. 2005;16(1):163-72.
PMid:15844389

26. Nguyen S, McCulloch C, Brakeman P, Portale A, Hsu CY. Being overweight modifies the association between cardiovascular risk factors and microalbuminuria in adolescents. Pediatrics 2008: 121: 37–45.

27. Carwile JL, Michels KB. Urinary bisphenol a and obesity: NHANES 2003-2006. Environ Res. 2011;111(6):825-30.
PMid:21676388

28. Takeuchi T, Tsutsumi O, Ikezuki Y, Takai Y, Taketani Y. Positive relationship between androgen and the endocrine disruptor, bisphenol-a, in normal women and women with ovarian dysfunction. Endocr. J. 2004;51(2):165-9. http://doi.org/10.1507/endocrj.51.165
PMid:15118266.

29. Galloway T, Cipelli R, Guralnik J, Ferrucci L, Bandinelli S, Corsi AM, *et al*. Daily bisphenol a excretion and associations with sex hormone concentrations: Results from the in CHIANTI adult population study. Environ. Health Perspect. 2010;118(11):1603- 8. http://doi.org/10.1289/ehp.1002367
PMid:20797929

30. Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, Wallace RB, *et al*. Association of urinary bisphenol a concentration with medical disorders and laboratory abnormalities in adults. JAMA. 2008;300:1303-10. http://doi.org/10.1001/jama.300.11.1303.
PMid:18799442

31. Fernandez MF, Arrebola JP, Taoufiki J, Navalón A, Ballesteros O, Pulgar R, *et al*. Bisphenol-a and chlorinated derivatives in adipose tissue of women. Reprod Toxicol. 2007;24(2):259-64. http://doi.org/10.1016/j.reprotox.2007.06.007
PMid:17689919

32. Abd El-Shaheed A, Mahfouz NN, Moustafa RS, Elabd, MA. Alarming eating behaviors among adolescents in Egypt. Open Access Maced J Med Sci. 2019;7(13):2189-93. https://doi.org/10.3889/oamjms.2019.583
PMid:31456850

33. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: A systematic review. Am J Clin Nutr. 2006;84(2):274-8.
PMid:16895873

34. Todirica D, Santini A, Curticapean A, Varlam CM, Melinda S, Aldossary MS. Bisphenol-A a possible health issue arising from dental restoratives: A review. Dent Oral Biol Craniofac Res. 2018;2018:1-7.

35. Kang JH, Kondo F, Katayama Y. Human exposure to bisphenol a. Toxicology. 2006;226(2-3):79-89. http://doi.org/10.1016/j.tox.2006.06.009
PMid:16860916

36. Cooper JE, Kendig EL, Belcher SM. Assessment of bisphenol a released from reusable plastic, aluminium and stainless steel water bottles. Chemosphere. 2011;85(6):943-7.
PMid:21741673

37. Geens T, Goeyens L, Kannan K, Neels H, Covaci A. Levels of bisphenol-a in thermal paper receipts from belgium and estimation of human exposure. Sci Total Environ. 2012b;435-436:30-3.
PMid:22846760

38. Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, Calafat AM, *et al*. Prenatal bisphenol a exposure and early childhood behavior. Environ Health Perspect. 2009;117(12):1945-52.
PMid:20049216

39. Fenichel P, Dechaux H, Harthe C, Gal J, Ferrari P, Pacini P, *et al*. Unconjugated bisphenol a cord blood levels in boys with descended or undescended testes. Hum Reprod. 2012;27(4):983-90. http://doi.org/10.1093/humrep/der451
PMid:22267833

40. Fabien L, Claire B, Scott MB, Luc PB, Claude E, Michel G, *et al*. Non-monotonic dose-response relationships and endocrine disruptors: Qualitative method of assessment. Environ Health. 2015;14:13. http://doi.org/10.1186/1476-069X-14-13
PMid:25971433