Research Article

http://journals.sbmu.ac.ir/jpn
DOI: https://doi.org/10.22037/jpn.v7i2.26038

A Comparative Evaluation of Salivary Changes and Oral Indices in Pediatric Patients Having Chronic Kidney Disease and Juvenile Diabetes with Healthy Controls

Chaudhary Shweta[1], Shimpi Manasi[2]*, Shimpi Rajendra[3], Lakade Laxmi[1], Jajoo Shweta[4], Desai Sneha[4]

[1] MDS. Associate Professor, Dept. of Pediatric Dentistry, Bharati Vidyapeeth Dental College and Hospital, Pune, India.
[2] MDS III, Dept. of Pediatric Dentistry, Bharati Vidyapeeth Dental College and Hospital, Pune, India.
[3] M.Ch. Professor and Head of Department, Dept, Of Urology, Ruby Hall Clinic, Pune, India.
[4] MDS. Assistant Professor, Dept. of Pediatric Dentistry, Bharati Vidyapeeth Dental College and Hospital, Pune, India.

***Corresponding Author**
Manasi Shimpi, MDS
Email: manasi.shimpi92@gmail.com

Abstract:

Background and Aim: Chronic Kidney disease is a common condition seen in Juvenile diabetes with 90% of renal impairment patients displaying a wide spectrum of oral manifestations in the hard and soft tissues including changes of the salivary composition and flow rate. There is an increase in the serum cystatin-C, urea and creatinine levels in these patients, which is reflected in the saliva. This study was conducted to assess the changes in salivary levels of cystatin-C, urea, and creatinine as well as oral – Decayed, Missing and Filled Teeth Index (DMFT) and gingival indices in pediatric patients suffering from chronic renal disease and juvenile diabetes and compare them with healthy individuals.

Methods: Fifteen patients with juvenile diabetes suffering from chronic renal disease and 15 healthy controls aged 2-18 years were included in the study. Their saliva was analyzed for creatinine, cystatin-C and urea levels using an auto-analyzer and correlated with their existing serum levels. DMFT, gingival index, gingival bleeding and gingival enlargement indices were also assessed.

Results: Increased levels of salivary cystatin C, urea (p value <0.001) and creatinine (p value =0.001) were seen in the cases. The deft value was significantly lower (p value <0.001) while the gingival index, gingival bleeding index, and gingival enlargement index were significantly higher in the subjects with renal impairment.

Conclusion: Chronic Kidney disease results in many metabolic changes in the body, necessitating frequent biochemical blood analysis. Saliva, being a non-invasive, simple and rapid adjunctive tool, can be used for diagnosing and staging the disease and to check the progression of the condition.

Keywords: Chronic Kidney Disease; Renal Dysfunction; Saliva; Cystatin-C; Diagnosis.

Received: March,2019
Revised: April,2019
Accepted: April,2019

Please Cite This Article as: Shweta C, Manasi S, Rajendra S, Laxmi L, Shweta J, Sneha D. A Comparative Evaluation of Salivary Changes and Oral Indices in Pediatric Patients Having Chronic Renal Disease and Juvenile Diabetes with Healthy Controls. J Ped Nephrol 2019;7(2)
DOI: https://doi.org/10.22037/jpn.v7i2.26038

Introduction

With technological advances in the fields of healthcare and medicine, oral health care professionals also have to adopt a holistic approach to the management of patients with complex medical problems.

Amongst all the systemic disorders, diseases of the renal system contribute to the increased morbidity and mortality rates worldwide (1), as the kidneys are vital organs for maintaining homeostasis in the body (2). India is now

becoming a major reservoir of chronic diseases like diabetes.

Chronic Kidney disease (CKD) is a common complication of type 1 (juvenile) diabetes that affects nearly 30% of such patients. Previous studies identified this condition as a risk factor for mortality in type 1 diabetes (3). This burden is expected to rise and thus, health care professionals need to address this matter, as 25-40% of these subjects may develop CKD and end-stage renal disease (ESRD). CKD is the 12th leading cause of death and the 17th cause of disability worldwide (4).

Chronic Renal Disease is defined as structural or functional abnormalities of the kidney, with or without decreased GFR (Glomerular Filtration Rate), which may be manifested by pathological abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine or on in imaging tests. (GFR <60ml/min/1.73m2 for three months or more, with or without kidney damage) (5).

There are several causes that may lead to CKD, including hypertension, diabetes, glomerular nephritis, interstitial nephritis, pyelonephritis, etc (1). Progressive loss of the renal function ultimately results in a clinical syndrome known as uremia. The systemic signs of renal failure and uremia such as hematological changes, bone metabolism alterations, and changes in the immune status can be significant to the dental practitioner (6).

The prevalence of CKD is increasing worldwide. Routinely encountered renal disorders in children include congenital nephropathies, Chronic Renal Failure (CRF), glomerulonephritis, nephrotic syndrome, hydronephrosis, and multicystic renal dysplasia, which ultimately lead to ESRD (7).

The incidence of CRF is known to be increasing globally. Recently, there has been a rise in the Indian population suffering from this disease. Only 2 community- based studies were carried out in patients with CRF in India. Mani et al screened a total population of 25,000 in Chennai and reported a prevalence of 0.16% for CRF and found other renal diseases (short of CRF) in 0.7% of the patients (8).

A study by Agrawal et al showed that of 0.79% patients with CRF, 41% were due to diabetes, 22% due to hypertension, and 16% due to chronic glomerulonephritis (9).

With increased awareness about the mutual relationship between dental and medical problems, the role of a dental practitioner has become indispensable in improving the overall health of patients with CKD and also to render services for the oral findings of such diseases.

Children with CKD develop many metabolic changes in their blood that often necessitate frequent biochemical analysis. Serum analysis is an invasive and painful procedure, due to which simple non-invasive diagnostic tests with minimal risk that can accurately evaluate the disease status need to be identified as they would be of tremendous value to patients and clinicians (10).

The gold standard of determining renal function is the estimation of the GFR rate and the levels of serum creatinine and serum urea. Recently, cystatin C has been identified as one of the earliest markers for renal impairment. It has been observed that changes in the serum concentrations of these biomarkers are reflected in the saliva. Hence, this study was conducted to investigate the salivary levels of cystatin-C, urea and creatinine as a non-invasive method of diagnosing chronic renal disease and evaluating the progression of the condition in the pediatric population.

This study also aimed at investigating oral manifestations of chronic renal disease in children and adolescents aged 2-18 years, including the dmft/DMFT index, the Gingival Index developed by Löe and Silness, and the Gingival Bleeding Index developed by Ainamo and Bay.

Methods

This study was conducted after obtaining the approval of the Ethics Committee of Bharati Vidyapeeth Dental College and Hospital, Pune. The participants included in the study were those patients reporting to Bharati Hospital (Pediatric Ward), Department of Pediatric Dentistry, Bharati Vidyapeeth Dental College and Hospital, Pune, and S.K Medical Centre, Pune who were 2-18 years old and were known cases of chronic renal disease with juvenile diabetes or those with juvenile diabetes having proteinuria, edema of feet and ankles. Healthy subjects who were free from any systemic conditions were recruited as controls. Subjects having developmental

anomalies, undergoing treatment for CKD, dialysis and those with known systemic diseases other than CKD with juvenile diabetes were excluded from the study. Informed consent was obtained from all participants.

The saliva collection method was similar to that followed by Rahime et al (11) in which saliva was collected between 10:00 am and 4:00 pm following fasting for 2 hours in order to prevent any bias in the concentration of the saliva due to the circadian rhythm. Whole saliva samples were collected via the spitting method in order to collect unstimulated saliva. After rinsing the mouth with distilled water, the participants were asked to pool the saliva in the floor of their oral cavity and spit into a sterile calibrated vial every 60s until about 3mL of saliva was obtained. Saliva samples were stored at -20°C until laboratory analysis. Samples were thawed at room temperature and then centrifuged at 3000rpm for 10 min in order to remove contaminants before analysis.

Salivary creatinine, cystatin- C and urea levels were measured using an auto-analyzer. Furthermore, the salivary levels of the CKD cases were also correlated with the serum levels.

The oral status of the individuals was assessed in broad daylight using a mouth mirror, straight probe and a William's Graduated probe while following a strict sterilization protocol.

To assess the dental status, the DMFT/dmft index was measured.

To assess the gingival status, the Gingival Index as given by Löe and Silness was recorded as 0= normal, 1= mild, 2= moderate, 3= severe (12).

the gingival bleeding index proposed by Ainamo and Bay (13) was performed to assess bleeding on probing and the drug induced gingival enlargement index developed by Ingles was also investigated (14).

The data were collected, compiled and entered in an MS Office Excel sheet. Statistical analysis was carried out using IBM SPSS software 20.

Student's t test was used to analyze the difference between the salivary levels of the biomarkers and the oral indices- def (decayed, exfoliated, filled teeth), DMFT (Decayed Missing Filled Teeth), gingival index, and gingival bleeding index while Chi Square test was used to analyze the difference in gingival enlargement between cases and controls.

The correlation between the serum and salivary levels of the biomarkers was investigated using Pearson's correlation coefficient.

Results

Salivary Levels of the Biomarkers: (Table 1)

In our study, according to the student's t-test, the mean salivary urea level was 21.86 ±10.91 in the cases and 7.26±1.57 in the controls, showing a t value of -5.127 and a p value of < 0.001 (highly significant difference)

The mean salivary creatinine level was 0.23±0.14 in the cases and 0.1 in the controls with a t value of -3.568 and a p value of 0.001 (significant difference).

Student t test showed a mean cystatin-C level of 1.06 ±0.55 in the renal impairment patients and 0.44±0.05 in the controls with a t value of -4.324 and a p value of < 0.001 (highly significant difference)

On co-relating the salivary and serum levels of the biomarkers, the creatinine levels showed a Pearson's correlation r value of 0.476 while the p value was 0.043 (significant difference). The serum and salivary urea levels showed an r value of 0.961 and a p value of < 0.001 (highly significant difference). The serum and salivary creatinine levels on co-relation showed an r value of 0.594 and a p value of 0.019 (significant difference). (Table 2)

Oral Indices:

Comparison of the deft index of the subjects and the controls using the student's t-test showed that the mean level was 0.09±0.1 in the cases and 0.39±.25 in the controls with a p value of <0.001, indicating a highly significant difference with a lower rate of caries in the subjects with renal dysfunction as compared to that of the controls. The DMFT of the cases and controls was 0.022±0.048 and 0.0027 ± 0.010 respectively with a p value of 0.142, showing no significant difference. (Table 3)

The mean gingival index of the cases and controls was 1.4±0.73 and 0.0 with a p value of < 0.001 (highly significant difference). The mean gingival bleeding index score of the cases and controls was 4.137±4.47 and 0.0 in the controls with a p value of 0.001(significant difference) (Table 3).

Table 1. Distribution and Comparison of the Salivary Biomarkers in the Controls and Subjects with Chronic Renal Disease and Juvenile Diabetes

Biomarker	Subjects	Mean	SD	Student's t-Test	p Value*
Urea	Healthy Controls	7.26	1.57	t = -5.127	p < 0.001 highly significant difference
	Chronic Kidney Disease + Juvenile Diabetes	21.86	10.91		
Creatinine	Healthy Controls	0.1	0.0	t = - 3.568	p =0.001 significant difference
	Chronic Kidney Disease + Juvenile Diabetes	0.23	0.14		
Cystatin C	Healthy Controls	0.44	0.05	t = - 4.324	p < 0.001 highly significant difference
	Chronic Kidney Disease + Juvenile Diabetes	1.06	0.55		

*p > 0.05 – not significant, p < 0.05 – significant difference, p < 0.001 – highly significant

Table 2. Distribution and Comparison of the Oral Indices in the Controls and Subjects with Chronic Renal Disease and Juvenile Diabetes

Oral Index	Subjects	Mean	SD	Student t Test	p Value; significance
deft	Healthy Controls	0.39	0.25	t = -4.202	p < 0.001 highly significant difference
	CKD + Juvenile Diabetes	0.09	0.10		
DMFT	Healthy Controls	0.0027	0.10	t = - 1.512	p =0.142 no significant difference
	CKD + Juvenile Diabetes	0.022	0.48		
Gingival Index	Healthy Controls	0	0	t = - 7.359	p < 0.001 highly significant difference
	CKD + Juvenile Diabetes	1.4	0.73		
Gingival Bleeding Index	Healthy Controls	0	0	t = -3.579	p =0.001 significant difference
	CKD + Juvenile Diabetes	4.137	4.47		

Our study also showed a higher gingival enlargement index in the subjects with Renal dysfunction when compared to the controls.

All 15 controls had a gingival enlargement score of 0 according to the scoring criteria given by Innes, while 6.7% of the subjects with Chronic Kidney Disease showed Score 0, 60% showed score 1 and 33.3% showed score 2 (Table 4).

Discussion

Improper kidney function is reflected in every organ system of the body (15). In children, renal impairment can result in a plethora of oral manifestations in the hard and soft tissues such as poor oral hygiene, pale oral mucosa, enamel hypoplasia, dental calculus, xerostomia, a relatively lower caries rate, and uremic stomatitis. These complications can lead to excessive bleeding, anemia, increased susceptibility to infections, drug intolerance, enamel defects, adrenal crisis, and renal osteodystrophy in children and may cause changes in the salivary composition and flow rate (7).

Saliva offers an attractive alternative to blood samples, particularly in children and the elderly in whom blood sample collection often reduces compliance to follow-up.

With the increase in the levels of biomarkers in the blood, there is a synchronous increase in the salivary biomarker levels where the biomarkers are either passively diffused or actively transported directly from the serum into the saliva through the oral mucosa and/or the gingival crevicular fluid. This was observed in our study as well (Table 4). Nandan et al reported that the normal salivary urea level (SaU) was 12-70mg/dl (16). A study by Patil et al showed the mean SaU was 41.9375 mg/dl in controls (17). Arora et al found that the SaU levels were higher in patients with CRF compared to controls (18), which was in accordance with our results (Table 1).

Other conditions in which increased serum urea is seen include dehydration, gastrointestinal bleeding, heart failure without renal involvement, diets that include increased intake of proteins, severe infections, long-standing periods of starvation, prolonged corticosteroid therapy, etc (19).

Creatinine is a traditional biochemical marker for assessment of renal function and increased serum concentrations of creatinine may indicate a decreased kidney function.

Table 3. Gingival Enlargement Index Distribution and Comparison in the Controls and Subjects with Chronic Renal Disease and Juvenile Diabetes

Subjects	Gingival Enlargement Index Score			Chi-Square test	p Value; significance
	Score 0	Score1	Score 2		
Healthy Controls	15 (100%)	0 (0%)	0 (0%)		p < 0.001
CKD + Juvenile Diabetes	1 (6.75%)	9 (60%)	5 (33.3%)	Chi=26.250	highly significant difference

Table 4. Correlation of Salivary levels of Cystatin-C, Urea and Creatinine with the previously existing latest records of Serum levels of Cystatin-C, Urea and Creatinine in the Controls and Subjects with Chronic Kidney Disease and Juvenile Diabetes

Group	Comparison Group	Pearson Correlation 'r value'	p value; significance
Salivary Urea	Serum Urea	r = 0.961	p < 0.001**
Salivary Creatinine	Serum Creatinine	r = 0.594	p = 0.019*
Salivary Cystatin C	Serum Cystatin C	r = 0.476	p = 0.043*

Unfortunately, any measurable increase in creatinine occurs when there is damage to >50% of active nephrons (GFR<40 mL/min/1.73 m2). Additionally, the serum creatinine concentration also depends on several factors including tubular resorption, total muscle mass, nutritional status, age, and gender (20).

Recently, cystatin-C has been identified as a marker of renal impairment in the early stages. Filler et al in their review study of the role of cystatin-C as a marker of GFR also found that serum creatinine levels depend on the muscle mass, which is usually low in young children (21).

The kidneys play a major role in the metabolism of cystatin-C whose levels do not depend on the body mass; thus, it has proved to be a superior marker for early detection of renal impairment compared to creatinine.

Creatinine is a large molecule with low lipid solubility, and thus in it unable to easily pass through the membranes or tight intercellular

junctions of the cells into the saliva. Hence, salivary concentrations of creatinine are not usually altered unless there is increased diffusion due to altered mechanisms, as seen in advanced renal impairment patients (22-25). A slight increase in salivary creatinine values were seen in our study (Table 1).

Our study showed that changes in salivary urea levels were more significant in the subjects compared to the creatinine levels. This observation was similar to a report by Zuniga et al (25) who found that compared to salivary creatinine, salivary urea was a more sensitive marker of CKD, particularly in earlier stages.

Cystatin-C is a 13kDa molecule that is filtered from the glomerulus and is catabolized in the proximal renal tube. The cystatin-C levels increase when the GFR reduces. The serum levels of cystatin-C are not affected by age, gender, race, or muscle mass, as is seen with creatinine, and thus it is established as a superior biomarker to estimate renal function loss (23). According to studies done by Keevil BG et al (24) (1998) and HorioM et al (25) (2011), serum cystatin-C is better as a screening test for decreased GFR while serum creatinine is better for monitoring changes in established renal disease. The increased serum concentrations of these biomarkers are also reflected in the saliva. This finding is consistent with the results of our studies, where the levels of salivary cystatin-C are increased, (Table 1) whereas the level of creatinine remained constant and low, suggesting that salivary cystatin-C could be used as an early marker for renal impairment.

Demirtas et al. found a significant correlation between high serum cystatin-C levels and cardiovascular risk factors in primary hypertensive patients (26).

Increased cystatin-C levels have also been associated with cancer, smoking, thyroid dysfunction, and prolonged glucocorticoid therapy.

Peterson S et al (1985) (27) attributed the relative paucity of caries in these patients to the increased plaque pH by metabolic end products of urea buffering metabolism. A relative low caries prevalence was seen in the subjects of our study (Table 2) compared to the controls, which was in accordance with other studies by Al-Nowaiser A (28) et al (2003) Davidovich E (29) (2005), and Skorecki et al (30) (2005).

Periodontal disease, increased levels of plaque, calculus, gingival inflammation and increased prevalence and severity of destructive periodontal diseases can be seen in patients with CKD. Calcium channel blockers and calcineurin inhibitors, which are routinely used for treatment of renal diseases, can lead to gingival hyperplasia in CKD patients. Gingival bleeding, and petechia and ecchymosis resulting from platelet dysfunction are also observed in these patients. Furthermore, anticoagulants that are prescribed in CKD patients can also result in gingival bleeding in these patients. This manifestation of an increased bleeding tendency can be attributed to an abnormal thrombocyte function and a decrease in the platelet factor III. Periodontal problems with attachment loss, gingival recession and formation of deep pockets are also reported (4). Gingival hyperplasia, which is a relatively common periodontal complication in renal transplantation patients, has been attributed to cyclosporin dosage and the presence of dental plaque, which is a factor that contributes to gingival inflammation (31), involving the interdental papilla, marginal and attached gingiva. The mean gingival index was 1.4±0.73 in the cases and 0.0 in the controls was with a p value of < 0.001 (highly significant difference) (Table 2).

This is in contrast to studies conducted by Lucas et al (32) and Al Nowaiser et al (28), in which relatively lower rates of periodontal disease or gingival inflammation were observed in children with CRF. This reduced gingival inflammatory response to dental plaque, which subjects suffering from CRF seem to present with, can be attributed to a modified tissue response as a result of systemic involvement.

Gingival bleeding occurs in patients with abnormalities of primary hemostasis, in particular, platelet dysfunction and impaired platelet-vessel wall interaction (33). The subjects showed a higher gingival bleeding index as compared to the controls (Table 2). Gingival bleeding is also commonly associated with other conditions such as leukemia, scorbutic gingivitis or vitamin C deficiency, acute herpetic gingivostomatitis, acute necrotizing ulcerative gingivitis, and mononucleosis (34).

Another manifestation of CKD is gingival enlargement that is secondary to drug therapy or

transplantation as observed by Al Nowaiser et al (28), Chabria et al (35) and Lucas et al (32).

Proctor (36) found that gingival enlargement could be induced by cyclosporin and/or calcium channel blockers. It primarily affects the labial interdental papillae although it can become extensive, involving the gingival margins, labial interdental papillae, and lingual and palatal surfaces. The subjects in our study showed a higher mean gingival enlargement index compared to the controls (Table 3).

The other most prevalent types of gingival overgrowth in children are drug-induced gingival overgrowth, hereditary gingival fibromatosis (HGF), and neurofibromatosis I (von Recklinghausen disease) (37).

Conclusion

Renal diseases represent a major proportion of medical, social and economic problems worldwide, which makes the screening and early diagnosis a very important global challenge. Dentists should be aware of distinctive oral characteristics related to CKD. Findings from the present study may improve the understanding of clinicians and, therefore, can help with early identification of oral manifestations in individuals with CKD.

By tapping into the hidden biomarker library being saliva within our mouths, frequent withdrawing of blood for diagnostic purposes in CKD may be prevented. Research shows that salivary biomarkers of renal functions can be distinguished in the whole unstimulated saliva. Thus, saliva has the potential of being a non-invasive, simple, and rapid adjunctive tool for diagnosing, monitoring, and staging CKD cases, making this biomarker a convenient medium for assessing the progression of the condition.

However, further studies need to be carried out to assess the specificity of the saliva as a biomarker.

Conflict of Interest

There are no conflicts of interest.

Acknowledgement

The authors wish to acknowledge S. K Medical Centre and Ruby Hall Clinic for their cooperation and for allowing the investigators to collaborate with them for the purpose of their research work.

References

1. Greenberg MS, Glick M, Ship JA. Burkets Oral Medicine Diagnosis and treatment, BC Decker Inc Hamilton, 11th ed;2008.
2. Picken M. Atlas of renal pathology. Arch Pathol Lab Med 2000;124:927.
3. Hovind P, Tarnow L, Rossing K, Rossing P, Eising S, Larsen N, Binder C, Parving HH. Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes. Diabetes Care 2003;26:1258–1264
4. Kuravatti S, David MP, Indira A.P. Oral manifestations of chronic kidney disease-an overview. International Journal of Contemporary Medical Research 2016;3(4):1149-1152.
5. Johnson AC, Leway AS, Coresh J, Levin A, Lau J, Eknoyan G: Clinical practical guidelines for Chronic Kidney Disease in adults: Part I. Definition, Disease stages, Evaluation, Treatment, and Risk factors. American Family Physician 2004;70:869-876.
6. Floege J, Johnson R J, Feehally J. Comprehensive Clinical Nephrology 4th ed Elsevier Inc; 2010.
7. Gupta M, Gupta M, Abhishek. Oral conditions in renal disorders and treatment considerations – A review for pediatric dentist. The Saudi Dental Journal;2015: 27: 113–119
8. Mani MK. Prevention of chronic renal failure at the community level. Kidney Int.2003;83(63):S86–S89
9. Agarwal SK, Dash SC, Irsha DM. Prevalence of Chronic Renal Failure in adults in Delhi, India. Nephrol Dial Transplant.
10. Onopiuk A, Tokarzewicz A, Gorodkiewicz E. Cystatin C: A Kidney Function Biomarker Advances in Clinical Chemistry.2015; 68:57-69.
11. Rahime R. Can salivary creatinine and urea levels be used to diagnose chronic kidney disease in children as accurately as serum creatinine and urea levels? A case–control
12. Löe H, Silness J. Periodontal disease in pregnancy. Acta Odontologica Scandinavica, 1963;21:533-551, ISSN 0001-6357.
13. Ainamo J, Bay I. Problems and proposals for recording gingivitis and plaque. International Dental Journal.1975;25(4):229-235, ISSN 1875-595X.
14. Ingles E, Rossmann JA, Caffesse RG, Dr Odont. New clinical index for drug-induced gingival overgrowth. Quintessence international;1997;30(7).
15. Patil S, Khandelwal S, Doni B, Rahman F, Kaswan S. Oral Manifestations in Chronic Kidney Disease Patients Attending Two Hospitals in North Karnataka, India; OHDM; 2009; 11:3: 100-106.
16. Nandan RK, Sivapathasundaram B, Sivakumar G. Oral manifestations and analysis of salivary and blood Urea levels of patients undergoing hemodialysis and kidney transplant. Indian J Dent Res 2005;16(3):77-82.
17. Patil S, Puranik S, Mallikarjun J, Vohra R, Shivhare P, Gujar P. Assessment of Salivary Urea in Different stages of Chronic Renal Failure Patients. Int J Oral Care Res. 2016;4(1):21-24

18. Arora R, Sarvaiya B. Estimation of salivary Urea levels and its relation with dental caries in children with chronic renal failure. J Oral Health Res. 2010; 1(2):72-74.
19. Higgins C. Urea and the clinical value measuring blood urea concentration. www.acutecaretesting.org July 2016.
20. Sans L, Radosevic A, Quintian C, Montañés R, Gràcia S, Vilaplana C, et al. Cystatin C estimated glomerular filtration rate to assess renal function in early stages of autosomal dominant polycystic kidney disease. PLoS ONE. 2017;12(3): e0174583
21. Filler G, Bokenkamp A, Hofmann W, Bricon T, Martinez-Bru C, Grubb A. Cystatin C as a marker of GFR- history, indications, and future research. Clinical Biochemistry; 2005;38:1-98.
22. Venkatapathy R, Govindarajan V, Oza N, Parames waran S, Pennagaram B Dhanasekaran, Prashad KV, Salivary creatinine estimation as an alternative to serum creatinine in chronic kidney disease patients, Int. J. Nephrol. 2014:742724.
23. Ferguson TW, Komenda P, Tangri N. Cystatin C as a biomarker for estimating glomerular filtration rate. Curr Opin Nephrol Hypertens. 2015; 24:295–300
24. Keevil BG, Kilpatrick ES, Nichols SP, et al. Biological variation of cystatin C: Implications for the assessment of glomerular filtration rate. Clin Chem 1998;44:1535–1539.
25. Horio M, Imai E, Yasuda Y, et al. Performance of serum cystatin C versus serum creatinine as a marker of glomerular filtration rate as measured by inulin renal clearance. Clin Exp Nephrol 2011;15:868–876.
26. Demirtaş S, Akan O, Can M, Elmali E, Akan H. Cystatin C can be affected by nonrenal factors: a preliminary study on leukemia. Clin. Biochem. 2006; 39 (2): 115–118.
27. Peterson S, Woodhead J, Cram J. Caries Resistance in Children with Chronic Kidney Disease: Plaque pH, Salivary pH, and Salivary Composition. Pediatric Research;1985:19:8:796-799.
28. Al-Nowaiser A, Roberts GJ, Trompeter RS, Wilson M, Lucas VS (2003) Oral health in children with chronic renal failure. Pediatr Nephrol 18:39–45
29. Davidovich E, Schwarz Z, Davidovitch M ,Eidelman E, Bimstein E. Oral findings and periodontal status in children, adolescents and young adults suffering from renal failure. J Clin Periodontol. 2005;32:1076–1082
30. Skorecki K, Green J, Brenner BM. Chronic renal failure. 2005: In: Kasper, D.L., Braunwald, E., Fauci, A.S., Hauser, S.L., Longo, D.L., Jameson, J.L. (Eds.), Harrison´ s Principles of Internal Medicine. McGraw-Hill, New York. 1653–1663
31. Ellis JS, Seymour RA, Taylor JJ, Thomason JM: Prevalence of gingival overgrowth in transplant patients immunosuppressed with tacrolimus. J Clin Periodontol.2004; 31: 126–131.
32. Lucas VS, Roberts GJ. Oro-dental health in children with chronic renal failure and after renal transplantation: a clinical review. Pediatr Nephrol.2005: 20:1388–1394.
33. Boccardo P, Remuzzi G, Galbusera M. Platelet Dysfunction in Renal Failure. Seminars in Thrombosis And Hemostasis. 2004;30(5): 579-589.
34. Pari A, Ilango P, Subbareddy V, Katamreddy V, Parthasarthy H. Gingival Diseases in Childhood – A Review. J Clin Diagn Res. 2014; 8(10): ZE01–ZE04
35. Chabria D, Weintraub RG, Kilpatrik NM. Mechanisms and management of gingival overgrowth in pediatric transplant recipients:a review. Int. J. Pediatr. Dent.2003; 13:220–229.
36. Proctor R, Kumar N, Stein A, Moles D, Porter S. Oral and Dental Aspects of Chronic Renal Failure.J Dent Res. 2005;84(3):199-208.
37. Doufexi A, Mina M, Ioannidou E. Gingival overgrowth in children: epidemiology, pathogenesis, and complications. A literature review. J Periodontol. 2005;76(1):3-10.