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Oral Aspects in Children with Nephrotic Syndrome

Nefrotik Sendromlu Çocuklarda Ağız Bulguları

K. Görkem ULU GÜZEL,[a]
Dilek YILMAZ,[b]
Filiz ABACIGİL,[c]
Serhat PİRİNÇCİ[d]

Department of
[a]Pediatric Dentistry,
Aydın Adnan Menderes University
Faculty of Dentistry,
Departments of
[b]Pediatric Nephrology,
[c]Public Health,
Aydın Adnan Menderes University
Faculty of Medicine,
Aydın
[d]Urla Community Health Center,
İzmir

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Correspondence:
K. Görkem ULU GÜZEL
Aydın Adnan Menderes University,
Faculty of Dentistry,
Department of Pediatric Dentistry, Aydın,
TURKEY/TÜRKİYE
gorkemulu@yahoo.com

This study was presented as a poster at the 13th Congress of the European Academy of Pediatric Dentistry (EAPD) (2-5 June 2016, Sava Centar, Belgrade, Serbia).

ABSTRACT Objective: Nephrotic syndrome (NS) is caused by different disorders that damage the kidneys. This damage leads to the excessive release of protein into the urine. Due to alterations in mineral metabolism in young patients with nephrotic syndrome, dental development, periodontal tissues, and alveolar bone may be disturbed. The aim of this study was to assess the oral health status in children with nephrotic syndrome and compare the results with a control group. **Material and Methods:** The study was carried out at the University of Adnan Menderes Department of Pediatric Dentistry and Pediatric Nephrology. The study was approved by the Ethics Board Committee of the University Hospital. The study group consisted of 38 children with nephrotic syndrome and 52 healthy children were in the control group. Prepared forms to obtain descriptive information and dental examination findings were used for assessment. The statistical differences between the control and study groups were determined using chi-square and student's T test. **Results:** Enamel hypoplasia was present in one child in the study group. Mean dmft, DMFT, plaque, and gingival indices of the study group were 3.85, 3.17, 1.62±0.794 and 1.14±0.63 respectively. The control group's dmft, DMFT, plaque and gingival indices were 5.45, 3.73, 1.19±0.93 and 0.63±0.71. The means of dmfs, dmft, DMFS, DMFT indices were found to be lower in the study group compared to the control group. However, this difference was not statistically significant. Plaque index (PI) and gingival index (GI) values were determined to be higher in the study group than in the control group. While the difference between PI values was not statistically significant, the difference between GI values was found to be statistically significant. **Conclusion:** It was concluded that despite the poor oral hygiene in nephrotic syndrome patients, we found a low incidence of tooth decay. It assumed that immune suppressive drugs in this group of patients could have a negative impact on the oral health. However; the use of vitamin D and calcium may prevent the dental problems which arise from NS treatment.

Keywords: Nephrotic syndrome; dental caries; plaque index; chronic renal diseaes

ÖZET Amaç: Nefrotik sendrom (NS) çeşitli hastalıklar nedeniyle böbreklerin zarar görmesi sonucu gelişir. Bu hasara bağlı olarak idrarda çok fazla protein salınması ortaya çıkar. Nefrotik sendromlu genç hastalarda mineral metabolizmasındaki değişikliklere bağlı olarak diş gelişimi, periodontal dokular ve alveoler kemik de etkilenebilir. Bu çalışmanın amacı, nefrotik sendromu olan çocuklarda ağız-diş sağlığının değerlendirilmesi ve kontrol grubundaki çocuklar ile karşılaştırılmasıdır. **Gereç ve Yöntemler:** Bu araştırma, Adnan Menderes Üniversitesi (ADÜ) Diş Hekimliği Fakültesi Pedodonti Anabilim Dalı ve Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı'nda gerçekleştirilmiştir. Nefrotik sendromlu 38 çocuk çalışma grubu ve sistemik sağlıklı 52 çocuk kontrol grubu olarak oluşturulmuştur. Ağız içi muayene bulguları ve tanımlayıcı bilgileri elde etmek için hazırlanan formlar değerlendirme için kullanılmıştır. Kontrol ve çalışma grubu arasındaki istatistiksel farklılıklar ki-kare ve student's T testi ile değerlendirilmiştir. **Bulgular:** Çalışma grubundaki bir çocukta mine hipoplazisi gözlenmiştir. Çalışma grubunun dmft, DMFT, plak ve gingival indeks değerleri sırasıyla 3.85, 3.17, 1.62±0.79 ve 1.14±0.63; kontrol grubunun dmft, DMFT, plak ve gingival indeks değerleri sırasıyla. 5.45, 3.73, 1.19±0.93 and 0.63±0.71 olarak belirlenmiştir. Çalışma grubunda dmfs, dmft, DMFS, DMFT verileri kontrol grubuna göre daha düşük tespit edilmesine ragmen fark istatistiksel olarak anlamlı değildi. Plak indeksi (PI) ve Gingival indeks (GI) değerleri çalışma grubunda kontrol grubuna göre daha yüksek tespit edildi. PI değerleri arasındaki farklılık istatistiksel olarak anlamlılık göstermezken, GI değerlerindeki farklılık anlamlıydı. **Sonuç:** Nefrotik sendromlu hastalarda oral hijyen alışkanlıkları daha zayıf olmasına rağmen diş çürüğü insidansı daha düşük tespit edilmiştir. Bu hasta grubunda immun baskılayıcı ilaçların ağız sağlığını olumsuz yönde etkileyebileceği düşünülmekle birlikte, D vitamini ve kalsiyum kullanımının, NS tedavisinde gözlemlenebilecek dental problemleri engellediğini söyleyebiliriz.

Anahtar Kelimeler: Nefrotik sendrom; diş çürüğü; plak indeksi; kronik böbrek hastalıkları

Nephrotic syndrome (NS), a common kidney disease, in children is characterized by massive proteinuria, hypoalbuminemia, edema, and usually concomitant hyperlipidemia. While frequent relapses are observed in 60% of cases, corticosteroids (CS) used in the treatment have an important role in providing remission of the disease.[1] High dose CS is used for about 30 days for complete remission, then the dose is reduced, and the treatment is completed in about 4-12 months. Additionally, the re-use of CS is required during each relapse.[2]

In nephrotic syndrome; T cell dysfunction involved in the etiopathogenesis of the disease, decreased immunoglobulin G (Ig G) levels and concomitant use of CS and other immunosuppressive drugs such as cyclosporine-cyclophosphamide-mycophenolate mofetil for therapy, contribute to immunodeficiency. Accordingly, oral plaque-associated gingivitis and fungal infections have been reported frequently in children with NS.[3]

Vitamin D plays an important role in absorption of calcium and phosphorus. Absorption of calcium and phosphorus help to improve healthy bone and teeth development.[4]

In children with nephrotic syndrome, loss of 25-hydroxycholecalciferol (25-OH D) and vitamin D binding protein (VDBP) in the urine, alterations in calcium and phosphorus balance due to CS treatment, and inflammation in the pathogenesis lead to metabolic bone disease.[5] The storage in the bone mass that starts in fetal life and continues throughout childhood becomes stabilized in adulthood. While CS in doses higher than 5 mg/day is considered a risk factor for osteoporosis in adults, CS at a dose of 60 mg/m^2/d is given to children with NS for one month at relapses and is used for a long time.[2] While normal physiological doses of CS are required for normal osteoblast differentiation, high doses of CS have been shown to decrease the number of osteoblasts by increasing apoptosis and to decrease bone formation by increasing the number of osteoclasts.[1,2] In addition, corticosteroids have been reported to lead to negative calcium balance and secondary hyperparathyroidism by increasing calcium loss in the kidneys and intestine.

Renal disease involves multiple organs including the soft and hard tissues of the oral cavity. Oral manifestations in children with renal diseases include ammonia-like odor, dysgeusia (impaired taste), stomatitis, xerostomia, parotitis, decreased salivary flow, and gingival enlargement secondary to drug therapy. Enamel opacities may be seen due to disturbed calcium and phosphate metabolism. Oral findings frequently include increased plaque accumulation, gingivitis, gingival overgrowth, and enamel hypoplasia. The prevalence of dental caries is low in these children.[6] However, no study involving the oral features of NS patients specifically was found. Only a single previous study showed that Candida spp, might intensify plaque-related gingivitis in NS patients. Children and teenagers with NS undergoing immunosuppressive treatment are predisposed to gingivitis.[3] Since the oral health status is an important component of systemic health, the oral findings of NS patients should be evaluated.

The objective of this study is to evaluate oral and dental health in children with nephrotic syndrome. In this context, we aimed to investigate the effects of NS, evaluate oral findings, determine the treatment needs, and to refer these cases to the necessary treatments.

MATERIAL AND METHODS

This research was carried out in 80 patients: 38 with NS and 52 generally healthy, no chronic disease or drug therapy (control group) at the age of 3-18 years followed-up by the Departments of Pediatric Nephrology and Pediatric Dentistry between June 2015 and August 2015. The study was approved by the Ethics Board Committee of the University Hospital (Non-Interventional Clinical Trials, Ethics committee approval no: 2015/564-28). And prior to the start of the study, the informed consent of parents were obtained.

Detailed history was taken from the patient's care givers and their socioeconomic status, teeth-brushing habits, and frequency of going to dentist were noted on the forms.

The oral dental health examinations of all patients were done by a pediatric dentist. The examinations were performed in a fully equipped dental clinic using a mirror and probe after the teeth had been dried.

Dental examinations were done in NS children during the remission period (4 weeks after the completion of the treatment). All NS patients who participated in the study were taking calcium and vitamin D while receiving corticosteroids (CS) according to the recommendations of Recommended Daily Intake (RDI).

All primary and permanent teeth were evaluated according to the dmft/ dmfs (d: decay, m: missing, f: filling/ t: teeth, s: surface) and DMFT/ DMFS (D: decay, M: missing, F: filling/ T: teeth, S: surface) indices. The plaque index (PI) score was based on the Silness and Löe and gingival index (GI) was based on Löe and Silness.[7,8] Probing depth was recorded as the distance from the free gingiva to the bottom of the gingival sulcus using a Williams probe. Gingival growth was recorded as positive if the distance between the cement-enamel junction and the free gingival margin was greater than 2 mm on the buccal surfaces of all teeth present in the mouth. Likewise, gingival recession was recorded as positive or negative by looking at the distance between the enamel-cement junction and the free gingival margin. Plaque index, gingival index, number of sites with bleeding on probing, and probing depth were measured for the buccal and lingual surfaces of the mandibular right permanent first molar or second primary molar, left permanent or primary central incisor, right first pre-molar or first primary molar, maxillary left permanent first molar or second primary molar, right permanent or primary central incisor, left first pre-molar or first primary molar teeth of all patients.

The presence and degree of enamel hypoplasia in all teeth present in the mouth were scored as modified Developmental Defects of Enamel (DDE) index according to the following criteria.[9] 1. No hypoplasia; 2. Horizontal white discoloration, no missing enamel; 3. Horizontal yellow-brown discoloration, no missing enamel; 4. Fuzzy appearance; 5. Horizontal grooves; 6. Stained appearance of all enamel; 7. Hypoplasia of all enamel; 8. Morphological anomaly.

SPSS 17.0 for Windows™ software was used for statistical analysis. Descriptive statistics were presented as mean ± standard deviation, median and minimum-maximum levels. Categorical variables were presented as frequencies (%). The differences were evaluated using the chi square and the student's T test for the statistical analysis of the clinical parameters (dmft, dmfs DMFT, DMFS, PI, GI, bleeding on probing, probing depth, gingival recession, gingival growth) between the NS group and the control group. Type 1 error was accepted as 0.05.

RESULTS

Sixteen female (42%), and 22 male (58%) patients with nephrotic syndrome at the age of 3-18 years (mean age 11.5±4.8 years) were examined in the Pediatric Nephrology Clinic. Fifty-two patients (mean age 11.6±4.6 years), of which 24 were female (46%) and 28 (54%) male, who were examined in pediatric dental clinic and agreed to participate in the study and had no systemic disorder were included in the study as a control group.

In the study, 42% of the NS patients revealed that a kidney biopsy had been performed. Other cases were diagnosed based on the age of diagnosis of disease, pure NS clinic symptoms, laboratory tests (normal C3-C4, negative Anti-ds DNA, negative direct coombs, normal kidney function tests), the absence of symptoms and response to systemic steroids. At the time of study, all patients were in remission. In the present study given the drug usage, of 38 patients with NS, 38 were taking CS, 7 cyclosporine, 12 cyclophosphamide, 3 mycophenolate mofetil, 38 calcium, and 38 vitamin D.

The mean dmfs, dmft, DMFS, DMFT indices were found to be lower in the study group compared to the control group. However, this difference was not statistically significant ($p>0.05$) (Table 1). Plaque index and GI values were determined to be higher in the study group compared to the control group. While the difference between PI values

TABLE 1: Comparison of dmft, dmfs, DMFT, DMFS values of the nephrotic syndrome group and the control group.

		NS group	Control group	p
dmft	N	12	24	0.21
	Mean	3.85	5.45	
	Median	4.00	5.00	
	Minimum	0	0	
	Maximum	8	15	
dmfs	N	12	24	0.12
	Mean	5.25	11.54	
	Median	4.00	8.00	
	Minimum	0	0	
	Maximum	14	49	
DMFT	N	30	38	0.71
	Mean	3.17	3.73	
	Median	3.00	3.00	
	Minimum	0	0	
	Maximum	9	14	
DMFS	N	30	38	0.72
	Mean	5.56	5.78	
	Median	3.5	4.5	
	Minimum	0	0	
	Maximum	31	28	

d: decay; **m:** missing; **f:** filling / **t:** teeth; **s:** surface and **D:** decay; **M:** missing; **F:** filling/**T:** teeth; S: surface.

was not statistically significant (p>0.05), the difference between GI values was found to be statistically significant (p<0.05). Although the difference between bleeding on probing, probing depth and gingival over growth values was lower, the difference between gingival recessions was higher in the study group compared to the control group. Also the difference was not statistically significant (p>0.05) (Table 2).

When the values related to enamel hypoplasia were examined, three scores of enamel hypoplasia were detected only in 1 of 38 patients with NS.

The education level of the parents was compared and in the control group, 21.2% of the mothers had graduated university while in the NS group 13.2% as was identified and the difference was statistically significant (p=0.005).

However, in the control group 26.9% of the fathers had graduated from university, while in the NS group they were 10.5%. However, this result was not statistically significant (p=0.07).

In both groups the age of brushing the teeth and socioeconomic status of families had no significant differences (p=0.112 and p=0.419 respectively).

DISCUSSION

In our study, dmfs, dmft, DMFS, DMFT values were observed to be lower in nephrotic syndrome

TABLE 2: Comparison of plaque index, gingival index, bleeding on probing, probing depth, gingival recession, gingival growth comparisons of the nephrotic syndrome group and the control group.

	NS group	Control group	p
Plaque index	1.62±0.79	1.19±0.93	0.35
Gingival index	1.14±0.63	0.63±0.71	0.03
Bleeding on probing	0.10±0.31	0.173±0.38	0.06
Probing depth	0.02±0.16	0.05±0.23	0.15
Gingival recession	0.02±0.16	0	0.18
Gingival over growth	0.05±0.22	0.05±0.23	0.83
Hypoplasia	0.07±0.35	0	0.01

patients compared to the control group. Similar to our study, the results of studies in chronic kidney disease (CKD) patients also show that the prevalence of tooth decay is low, despite the poor oral care.[10-13] The low prevalence of decay in patients with CKD was explained by the increase in saliva pH in parallel with the increase of urea in saliva and neutralization of bacterial metabolic products by the resulting alkaline environment.[11,14,15]

Enamel hypoplasia has been reported as a common condition in people with renal disease.[11,13,16-18] Koch *et al*. stated that renal diseases may affect the enamel formation of primary teeth in early post-natal life and may also be responsible for various lesions in the permanent teeth dentition.[18] Nunn *et al*. also found an elevated prevalence of enamel anomalies and suggested that this may be related to the onset of the disease and the cause may be due to impaired calcium and phosphate metabolism.[11] They reported that diffuse opacities at the highest rate were observed, followed by specific opacities and hypoplasia. Ertugrul *et al*.[19] reported that 47.7% of patients had an enamel hypoplasia and suggested that this may be related to abnormal calcium and phosphate metabolism. They also argued that there was a correlation between the location of hypoplasia on the tooth and the age at which the renal failure began. Gülhan and Seymen[20] observed enamel hypoplasia in the study of 15 patients with CKD, especially in the region of the incisor teeth and in the region of permanent molars including mainly the 6-year-old teeth. They reported the presence of hypoplasia of incisal edges of front teeth and chewing faces of the molar teeth of all patients. In our study, score "3: yellow-brown discoloration" was found to be on the maxillary right central incisor in only one of 38 NS patients. This patient had diagnosed at 10 years old with NS. Based on diagnosing NS after tooth eruption and since it was a local hypoplasia, NS could not have affected the enamel formation and it might be due to other factors. In the control group, none of the individuals have hypoplasia.

Children with NS demonstrate decreased 25-hydroxyvitamin D levels in response to urinary excretion of vitamin D–binding protein. Suboptimal vitamin D stores may lead to decreased 1,25-dihydroxyvitamin D levels or even secondary hyperparathyroidism and metabolic bone disease. Vitamin D supplementation for children with NS has been recommended by some groups.[21] Previous studies on the role of vitamin D intake suggest it could prevent progression of dental caries and periodontal diseases.[4,22,23] In this study all NS patients were using calcium and vitamin D in while receiving corticosteroids. Although NS patients had poor oral hygiene, they showed lower dmft/DMFT values compared with the control group, which might be related to the usage of Vitamin D supplementation.

Long-term corticosteroid therapy has been used in some diseases where different results with a bone mineral density have been reported.[24,25] The different results in the studies were related to primary disease, use of CS in the dose of a difference, depending on the time of construction of the bone. However, there are a few publications related to dental effects of oral CS in children with nephrotic syndrome. A previous study suggested that children with NS undergoing immunosuppressive treatment are predisposed to gingivitis but it did not evaluate the changes in alveolar bone.[3]

In some of the studies investigating the possible interaction between oral health and CKD, the PI values of patients with renal disease were reported to be higher than those of healthy individuals and to be similar in some cases.[20] It was claimed that the increase in PI is related to neglect of oral care procedures resulting from the impact of negative changes in the general health status of patients with renal disease.[15] Lutfioglu *et al*.[26] observed statistically significant higher PI and GI scores in the CKD patients compared to the control group. In our study, PI and GI values were higher in the NS group compared to the control group, and probing depth values, bleeding on probing, and gingival recession values were found to be lower. This might be related to poor oral hygiene and usage of calcium and Vitamin D supplementation to prevent problems in alveolar bone.

Immune deregulation in children with renal disorders is apparent by some degree of immunosuppression invariably seen in them. Moreover, corticosteroids form the first line of drugs in the treatment of nephrotic syndrome. These children are at a high risk of infection and are susceptible to bacteremia.[6] Davidovich *et al.*[27] presented that the gingival overgrowth seen in renal disease is believed to be related to an alteration of the fibroblast metabolism by cyclosporine and/or its metabolites, increasing protein synthesis, collagen, antihypertensive medication, and extracellular matrix formation. In an earlier study, presence of gingival hyperplasia in children with renal disease did not show any relationship with the use of immunosuppressant therapy.[11] They detected a mild gingival over growth in CKD patients, but they were at aesthetically acceptable levels, and were generally at levels that would not prevent the eruption of the incisors. However, no significant correlation was found between the use of cyclosporine or nifedipine and the prevalence of gingival growth. They attributed the cause of hyperplasia seen in patients who do not use any medication which was reported to cause gingival hyperplasia to lack of oral hygiene and bacterial plaque accumulation, as well as hyperplasia-like changes that can be seen in the contours of the gingiva in children who are in permanent eruption.[10] In the present study gingival over growth was detected in 2 children with nephrotic syndrome and it was found that one of these children used cyclosporine for more than one year, and the other did not. Oral hygiene habits were found to be insufficient in both children and the development of gingival over growth was thought to have resulted from long term cyclosporine use and the inadequate oral hygiene habits.

This study has limitations because of the small number of cases, not being able determine vitamin D levels and saliva pH and buffering capacity.

CONCLUSION

In our study, we found that a low incidence of decay although oral hygiene was poor in NS patients. In addition to this, in NS patients the predisposition to periodontal problems has not been identified. Only a single patient who was diagnosed NS at the age of 10, showed local enamel hypoplasia. For this single patient it is suggested that NS could not have affected the enamel formation. It is thought that the usage of vitamin D and calcium in the treatment process prevents the dental problems which arising from NS.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *K. Görkem Ulu Güzel, Dilek Yılmaz, Filiz Abacıgil;* ***Design:*** *K. Görkem Ulu Güzel, Dilek Yılmaz, Filiz Abacıgil;* ***Control/Supervision:*** *K. Görkem Ulu Güzel, Dilek Yılmaz, Filiz Abacıgil;* ***Data Collection and/or Processing:*** *K. Görkem Ulu Güzel, Dilek Yılmaz;* ***Analysis and/or Interpretation:*** *K. Görkem Ulu Güzel, Dilek Yılmaz, Filiz Abacıgil, Serhat Pirinçci;* ***Literature Review:*** *K. Görkem Ulu Güzel, Dilek Yılmaz;* ***Writing the Article:*** *K. Görkem Ulu Güzel;* ***Critical Review:*** *Dilek Yılmaz;* ***References and Fundings:*** *K. Görkem Ulu Güzel, Dilek Yılmaz;* ***Materials:*** *K. Görkem Ulu Güzel, Dilek Yılmaz.*

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