

Nutritional rickets in Turkish and refugee children aged 0-2: an increasing problem despite vitamin D prophylaxis

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ABSTRACT

Background. Nutritional rickets (NR) is still a major problem and is exacerbated by an increasing influx of immigrants. In this study, Turkish and immigrant cases followed with the diagnosis of NR in our pediatric endocrinology clinic were retrospectively evaluated.

Methods. Detailed data of cases diagnosed with NR between 2013 and 2020 and followed for at least six months were reviewed.

Results. In the study period, 77 cases of NR were identified. Turkish children constituted 76.6% (n=59) while 18 (23.4%) were immigrant children. The mean age at diagnosis was 8.1±7.8 months, 32.5% (n=25) were female, and 67.5% (n=52) were male. The 25-hydroxyvitamin D3 was below normal in all patients, with a mean value of 4.3±2.6 ng/mL. Parathyroid hormone (PTH) was above normal in all and the mean value was 301.7±139.3 pg/mL. While there were 3.9 cases of NR in 10,000 endocrine clinic patients in 2013, this rate increased more than four-fold to 15.7 patients in 2019.

Conclusions. Despite the vitamin D prophylaxis program in Türkiye, NR is seen significantly more frequently in recent years, which may be associated with an increasing number of refugees. High PTH levels indicate the severity of NR cases admitted to our clinic. However, clinically significant NR is only the tip of the iceberg and the true burden of subclinical rickets is unknown. Increasing compliance with the vitamin D supplementation program in refugee and Turkish children is important for the prevention of nutritional rickets.

Key words: children, immigrant, nutritional rickets, vitamin D deficiency.

Despite inexpensive and effective treatment options, nutritional rickets (NR) remains a global public health problem.¹ NR is a disease characterized by defective chondrocyte differentiation and insufficient mineralization of the growth plate and osteoid tissue, that develops before the closure of the epiphyseal plates, due either to vitamin D deficiency or insufficient calcium intake. However, the most common cause of rickets is vitamin D deficiency.^{1,2} In addition to various deformities in skeletal structure, serious findings such as tetany secondary to hypocalcemia, convulsions,

laryngospasm, muscle weakness, and cardiomyopathy can also be seen in NR.²

NR remains an important public health problem in both developed and developing nations, such as Türkiye, but its incidence differs between countries and regions. In Türkiye, the frequency of NR has previously been reported to be between 1.67%-19%.^{3,4} In recent years, the importance of vitamin D prophylaxis in preventing NR has been acknowledged and implemented in many countries.² For NR, a preventable disease, a five-year project (Prevention of Vitamin D Deficiency and Protection of Bone Health Project) was initiated in Türkiye in 2005, under the management of the Ministry of Health, General Directorate of Mother-Child Health and Family Planning.³ The main aim of this project was to reduce the

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frequency of NR by giving 400 IU of vitamin D daily to all children starting from birth. While the NR frequency before this project was 6% in a study conducted by Ozkan et al.⁵ in 1998 in Erzurum for children aged 0-3 years, another study by Ozkan et al.⁶ in 2008 showed that the NR frequency had decreased to 0.1%. This was evidence of the beneficial effect of the prophylaxis program.

However, and especially in recent years, NR cases have been encountered frequently in our clinic, and their medical histories revealed that prophylactic vitamin D was not used, or was only used sporadically, or for a very short time. This anecdotal evidence suggests a possible disruption (at least regionally) of the functioning of the prophylaxis program over time since the beginning of the project. Furthermore, immigrant children in Türkiye are at increased risk of NR due to poor living conditions, poor nutrition, and lack of access to health services.⁷⁻⁹ With the civil war that started in Syria in 2011, a migrant crisis has emerged in various countries, especially in Türkiye. According to the latest figures obtained from the Presidency of Migration Management,

there are 3.6 million Syrian refugees who have gained temporary protection status in Türkiye, and most of these people are not in the camps, but scattered throughout the country.¹⁰ The distribution of Syrians under temporary protection by years is shown in Figure 1. In our country, Syrian migrant children are secured within the scope of preventive medicine. Therefore, this study aimed to retrospectively evaluate patients followed up with a diagnosis of NR in our pediatric endocrinology outpatient clinic between 2013 and 2020, with their clinical, laboratory, and radiological findings.

Material and Methods

Medical records of patients followed for NR in the Pediatric Endocrinology Clinic between October 2013 and July 2020, and the digital databank of the hospital were retrospectively reviewed. Patients with follow-up data for at least six months were included in the study. Age, sex, vitamin D prophylaxis status, symptoms at admission, anthropometric data, physical examination, laboratory evaluation, and imaging findings (wrist/knee X-rays) and treatments, and if any, length of stay in the

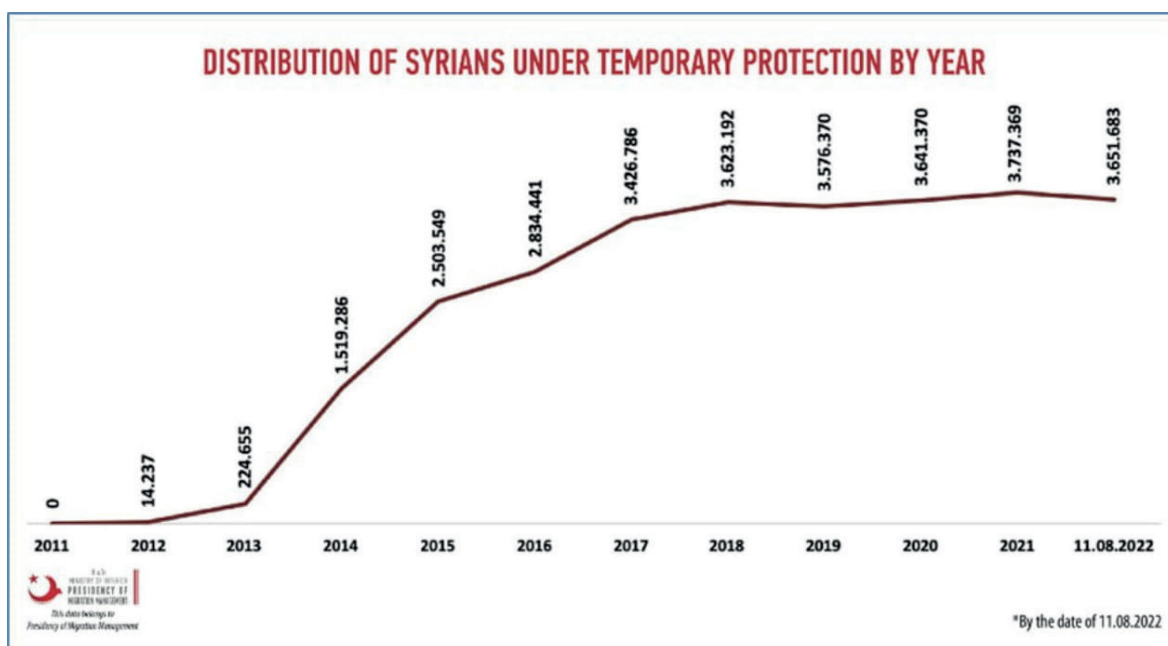


Fig. 1. Distribution of Syrians under temporary protection by year.¹⁰

hospital and recovery process information were recorded. Anthropometry included height, standard deviation score for height (height SDS), weight, weight SDS, body mass index (BMI), and BMI SDS. Laboratory results included serum calcium, phosphorus, alkaline phosphatase (ALP), parathyroid hormone (PTH), and 25-hydroxy vitamin D (25(OH)D) levels.

The diagnosis of NR was made clinically (skeletal deformities and/or hypocalcemia) and by laboratory findings (hypocalcemia or normocalcemia, high ALP and PTH, low 25(OH)D) and supported by direct X-ray imaging. Anthropometric evaluations were made using the CHILD METRICS program², the anthropometric calculation program of the Turkish Society of Pediatric Endocrinology and Diabetes, according to the data of healthy Turkish children created by Neyzi et al.^{11,12} The laboratory data of the patients were evaluated considering age-specific reference values of the laboratory. Reference ranges were 8.4-11 mg/dL for serum calcium, 134-350 mg/dL for ALP, and 14-72 pg/mL for PTH. The normal level of serum phosphorus in the first days of life is 4.8-8.2 mg/dL and then 3.8-6.5 mg/dL. A 25(OH)D level of <12 ng/mL was considered vitamin D deficiency, and a level of <5 ng/mL was considered severe vitamin D deficiency.² Defective mineralization appears radiographically as growth plate widening, as well as metaphyseal cupping and fraying, which confirm the diagnosis of NR.² Radiological evaluations were performed by a pediatric endocrinologist.

The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee (document number: E-23536505-000-3592, date:14.03.2022, Malatya Training and Research Hospital).

Informed consent was not obtained because of the retrospective nature of the study.

Statistical analysis

The Statistical Package for Social Sciences (SPSS), version 21.0, was used for statistical

analysis (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the chi-square test. Normal distribution of data was evaluated with the Kolmogorov-Smirnov test. Student t-test and Mann-Whitney U test were used to compare the groups for numerical data, as appropriate to distribution. Descriptive statistics for the data are given as median (minimum-maximum) for skewed parameters and mean±SD for normally-distributed parameters. A p-value of <0.05 was considered significant.

Results

The records of a total of 83 patients were accessed but six of the cases were excluded due to insufficient data. Finally, 77 patients with NR, aged 0-2 years, were included in the study. While 59 (76.6%) of the 77 cases were Turkish children, 18 (23.4%) were immigrants. All of the immigrants were of Syrian origin. The distribution of all patients admitted to the pediatric endocrinology outpatient clinic and patients with NR according to the years of diagnosis is shown in Figure 2. In addition, the number of patients with NR among the 10,000 pediatric endocrinology clinic patients per year is shown in Figure 2. While the number of NR patients per 10,000 pediatric endocrinology clinic patients was 3.8 in 2013, this rate increased more than four-fold to 15.7 in 2019 (Fig. 2). When distributed according to diagnosis months, March and January were the most common, and September and October were the least common (Fig. 3). All patients were under the age of two, and the mean age at diagnosis was 8.1±7.8 months (Median 5.9 months). In terms of sex, 32.5% (n=25) were female, and 67.5% (n=52) were male. Of the 77 cases whose birth weight and week were recorded, 11 were preterm. In nine patients, there was a history of small for gestational age (SGA). Anthropometric measurements by vitamin D level and ethnicity are shown in Table I.

Turkish and immigrant children were compared in terms of some clinical and laboratory findings,

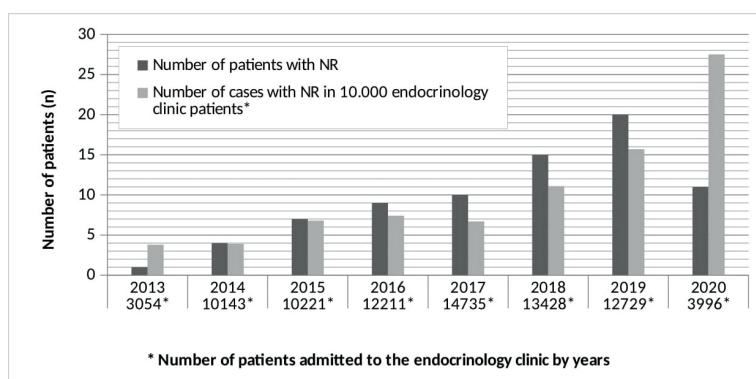


Fig. 2. Distribution of all patients admitted to the pediatric endocrinology outpatient clinic and patients with NR according to the years of diagnosis. In addition, the number of patients with NR per 10,000 pediatric endocrinology clinic patients per year (3 months in 2013 and 7 months in 2020).

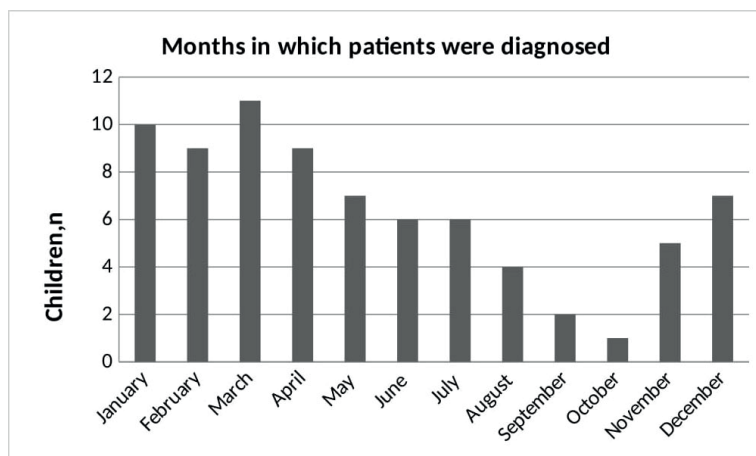


Fig. 3. Months in which patients were diagnosed.

Table I. Anthropometric measurements according to vitamin D level and ethnicity at the time of diagnosis (n=77).

	Full cohort n (%)	Turkish children (n=59)	Immigrant children (n=18)	<i>p</i>	25(OH)D ≤ 5 (n=47)	25(OH)D >5 (n=30)	<i>p</i>
Mean age, months	8.1±7.8	7.9±7.5	8.7±8.1	0.702	7.1±7.8	9.6±7.7	0.162
Sex (female/ male)	25/52 (32.5/67.5)	18/41 (30.5/69.5)	7/11 (38.9/61.1)	0.570	13/34 (27.2/73.2)	12/18 (40/60)	0.321
Birth weight (g)	3149±440	3115±63	3292±64	0.195	3077±48	3258±75	0.096
Height (cm)	67.6±11.2	66.7±11.0	70.3±2.8	0.230	64.4±11.2	72.6±9.2	0.001
Height SDS	-0.59±1.09	-0.58±1.0	-0.60	0.970	-0.60±1.2	-0.57±9.2	0.915
Body weight (kg)	7.6±3.0	7.5±3.1	8.1±2.8	0.442	6.7±3.0	9.1±2.3	<0.001
Body weight SDS	-0.46±1.1	-0.35±1.2	-0.8±0.8	0.148	-0.47±1.1	-0.43±1.1	0.876
BMI SDS	-0.01±1.1	0.04±1.2	-2.1±0.8	0.391	-0.10±1.1	0.12±1.1	0.001

SDS: standard deviation score, BMI: body mass index, 25(OH)D: 25-hydroxyvitamin D3 (ng/mL)

but no statistically significant difference was found. At presentation, short stature (height SDS <-2 SD) was found in 8 (13.5%) Turkish children, while this number was 2 (11.1%) in immigrant children ($p=0.573$). There were 2 (3.3%) Turkish and 1 (5.5%) immigrant child with BMI SDS <-2 SD ($p=0.556$). In our study, the number of children with 25(OH)D value <5 was 47 (61%) and 36 (61%) of them were Turkish and 11 (61%) were immigrants ($p=0.610$). Of the 55 children admitted with hypocalcemia ($\text{Ca}<8.4$ mg/dL), 44 (74.5%) were Turkish and 11 (61%) were immigrants ($p=0.164$). The number of Turkish children admitted with clinical findings only was 35 (59.3%) and the number of immigrant children was 11 (61%) ($p=0.344$). A total of 52 mothers had vitamin D levels (immigrant: 14). The number of Turkish mothers with 25(OH)D level <5 was 24 (63.1%) and the number of immigrant mothers was 9 (64.2%) ($p=0.603$).

The most common reasons for referral to the pediatric endocrinology outpatient clinic were incidentally-detected low calcium/vitamin D levels, bowed legs, and convulsions. Complaints

at the time of diagnosis according to vitamin D level and ethnicity are shown in Table II. The most common findings on physical examination were rachitic rosary, enlarged wrists, and genu varum, in descending frequency. In cases of severe vitamin D deficiency; convulsions, rachitic rosary, and wrist enlargement were found to be significantly more common. When the laboratory data were evaluated, hypocalcemia was found in 68.8% (53/77) of the cases, hypophosphatemia was found in 61.0% (47/77), while ALP levels were high in 94.8% (73/77), and PTH levels were invariably high in all 77 cases examined. The 25(OH)D level was below normal in all cases. The mean vitamin D level was 4.3 ± 2.6 ng/mL, and severe deficiency was found in 61.0% (47/77) of the patients. The level of vitamin D in the cases and the biochemical parameters according to ethnicity are shown in Table III.

Information about vitamin D prophylaxis was recorded in the records of 77 patients. It was noted that 55 (71.4%) patients never received vitamin D prophylaxis, whereas 22 patients

Table II. Complaints at the time of diagnosis according to vitamin D level and ethnicity (n=77).

	Full cohort n (%)	Turkish children	Immigrant children	<i>p</i>	25(OH)D ≤ 5 (n:47)	25(OH)D > 5 (n:30)	<i>p</i>
Low Ca/25(OH)D in incidental examination	29 (37.7)	23 (39.0)	6 (37.7)	0.784	14 (29.8)	15 (50.0)	0.062
Bowed legs	29 (37.7)	19 (32.2)	10 (55.6)	0.067	16 (34)	13 (43.3)	0.280
Convulsions	21 (27.3)	13 (22.0)	8 (44.4)	0.062	20 (42.6)	1 (3.3)	<0.001
Hand cramps, tremors	13 (16.9)	11 (18.6)	2 (11.1)	0.455	10 (21.3)	3 (23.1)	0.198
Anterior fontanelle width	9 (11.7)	7 (11.9)	2 (11.1)	0.931	6 (12.8)	3 (10.0)	0.507
Delay/problem in walking	5 (6.5)	3 (5.1)	2 (11.1)	0.332	2 (4.3)	3 (10.0)	0.072

ALP: alkaline phosphatase, Ca: calcium, 25(OH)D: 25-hydroxyvitamin D3 (ng/mL)

Table III. The level of vitamin D in the cases and the biochemical parameters according to ethnicity (n=77).

	Full cohort n (%)	Turkish children	Immigrant children	<i>p</i>	25(OH)D ≤ 5	25(OH)D > 5	<i>p</i>
Corrected serum calcium (mg/dL)	7.4 ± 1.2	7.4 ± 1.2	7.1 ± 1.2	0.279	6.8 ± 1.0	8.2 ± 0.9	<0.001
Phosphorus (mg/dL)	3.4 ± 0.7	3.4 ± 0.7	3.4 ± 0.7	0.788	3.2 ± 0.6	3.6 ± 0.8	0.042
ALP (IU/L)	914 ± 401	905 ± 644	943 ± 489	0.903	1002 ± 305	777 ± 492	0.016
PTH (pg/mL)	301.7 ± 139.3	302 ± 146	298 ± 114	0.922	146 ± 21	116 ± 21	0.028
25(OH)D (ng/mL)	4.3 ± 2.6	4.0 ± 2.5	5.3 ± 2.8	0.097	2.6 ± 1.3	6.9 ± 1.7	<0.001

ALP: alkaline phosphatase, PTH: parathormone, 25(OH)D: 25-hydroxyvitamin D3 (ng/mL)

used it irregularly. Vitamin D levels of 52 mothers were measured, and the mean 25(OH) D level was 4.6 (range: 3-12) ng/mL.

There were no direct radiographic images available in 22 cases, whereas the imaging was suboptimal in five cases. In the 50 available records, the most common findings in the direct radiographs were cupping (84.0%; 42/50) and enlargement and fraying (76.0%; 38/50) in the wrist and/or knee metaphyses. In the patient with the most severe skeletal findings, a greenstick fracture and extensive osteopenia were detected in the bilateral radius diaphysis, except for metaphyseal findings. Stoss therapy with vitamin D (150,000 or 300,000 IU oral or IM) was administered in 16 cases (20.8%) of NR, long-term high-dose vitamin D (2,000 or 5,000 IU/day for six weeks) in fifty-five (71.4%), and 60,000 IU stoss + 5,000 IU/day in six cases (7.8%). Fifteen of the 22 (68.2%) patients who received stoss treatment were children of immigrants. Additional calcium was also added to the treatment in the form of intravenous and/or oral elemental calcium.

Discussion

This article draws attention to the problem of vitamin D deficiency and nutritional rickets in the light of the latest information in the literature and data in our country. Despite the vitamin D support programs, NR continues to be a significant and preventable public health problem worldwide. Vitamin D prophylaxis is recommended at 400 IU/day in the first year of life.^{2,13} In studies conducted in Türkiye, the regular use of 400 IU/day of vitamin D was effective in preventing rickets.^{14,15} NR cannot be completely eliminated in developed countries due to immigration from underdeveloped regions, and it has been reported that its frequency has increased recently.^{7-9,16} The primary cause of NR is vitamin D deficiency worldwide. However, the inadequate calcium intake in underdeveloped regions is also seen as an important cause.^{2,16} In Türkiye, the most common reason for NR has been shown to be

vitamin D deficiency.^{6,14,15,17} However, vitamin D supplementation was never used in more than 70% (n=55) of these patients who developed NR, and it was used irregularly by the remaining 22 cases. Inadequate and irregular use of vitamin D by our patients suggested that they did not know the importance of vitamin D and had problems in compliance with drug use.

Rickets due to vitamin D deficiency is most common in children under two years of age, with the highest incidence occurring between 3-18 months.^{1,18} In children aged 0-3 years, NR is more common in boys.¹⁹ In our study, the mean age at diagnosis was 8.1±7.8 months, and the male:female ratio was 2.08:1. While clinical findings in NR may include convulsions, tetany, respiratory problems, and heart failure due to hypocalcemia, skeletal findings, such as craniotabes, rachitic rosary, Harrison's groove, bowed legs, and enlargement of the joints can be seen due to insufficient mineralization in the fast-growing bones.^{2,20} The most common causes of hospital admission in our patients in decreasing order were incidentally-detected low Ca or vitamin D, bowed legs, convulsions, and contraction and trembling in the hands, whereas the most common examination findings were rachitic rosary, enlargement of the wrists, and genu varum (bowlegs). In the study of Ward et al.²¹, the most common reason for admission under one year of age was hypocalcemic convulsions, while skeletal deformities were observed in older children. NR may present with life-threatening findings and may also lead to permanent skeletal deformities.^{2,21} However, no permanent skeletal deformity was detected in any of our patients.

Nutritional status, including vitamin D status, affects not only growth but also skeletal maturity in childhood.^{1,20} Cesur et al.¹⁷ found short stature in 34.4% of patients with NR between 0 and 2 years of age. NR has been associated with stunted growth, which is commonly observed in Afghan children (a country with one of the highest rates of malnutrition in the world).²² In our study, short stature was found in 13% of the cases. Severe vitamin D deficiency was

associated with shorter height, lower weight and lower BMI SDS. In addition, the frequency of convulsions increased and metabolic parameters [lower calcium and phosphorus, higher ALP and PTH] were more impaired in severe vitamin D deficiency.

To maintain bone health in children, vitamin D levels must be sufficient. "Adequate vitamin D level" is defined as a serum 25(OH)D level >20 ng/mL. To maintain this level, the American Institute of Medicine (IOM) and the American Academy of Pediatrics (AAP) recommend 400 U/day of vitamin D be given to infants for the first 12 months.^{23,24} Vitamin D levels were ≤ 11.9 ng/mL in all our patients and severe vitamin D deficiency was found in 61% of the cases.

Vitamin D supplementation for infants, adding vitamin D to various foods, and increasing sunlight exposure have been studied, and some protection strategies have been developed to prevent NR worldwide.^{25,26} Additionally, sufficient calcium intake is advocated in underdeveloped countries.²⁷

Considering the period of study starting in 2013, cases have increased over time, especially in 2019 and 2020 (Fig. 2). The dramatic increase in 2020 can be explained by the decrease in total hospital admissions due to the COVID-19 pandemic. This raises the question of whether there is a problem with the functioning of the prophylaxis program. In their incidence study in Canada, Ward et al.²¹ detected 104 NR cases aged between 2 weeks and 6.3 years in a two-year period, and none of the patients had received prophylactic vitamin D supplementation. The authors argued that vitamin D prophylaxis is recommended in the current guidelines, but it is not applied consistently. We wish to highlight that refugee children are a much more vulnerable subpopulation than settled children and adults. For this reason, all countries should develop a public health policy that provides vitamin D supplementation and adequate calcium needs to protect refugee children, whose numbers have been increasing across the globe in recent years, as well as protecting indigenous children living in any high risk environment.

Although rickets prevention projects exist through prophylaxis programs and food-infused vitamin supplements in developed countries, the frequency of rickets is still increasing due to immigration. In Europe and America, most rickets cases are due to vitamin D deficiency and are frequently seen in children with dark skin coming from Asia, the Middle East, and Africa.^{16,20} Asylum seekers are disadvantaged concerning preventive health services. This may be due to poor living conditions, nutritional problems, language barriers, financial difficulties, and lack of access to health services.^{7,20} Türkiye received significant immigration from Syria in recent years (Fig. 1). Of the 77 cases identified in our study, 18 (23.4%) were immigrant children, suggesting a major contribution of immigration to NR frequencies. Thus, the implementation and maintenance of prophylaxis for immigrant babies will reduce the incidence of NR in Türkiye.

Immigrant health centers (IHCs) affiliated with community health centers have been established in areas with a high concentration of migrants in order to provide preventive health services and primary health care services more effectively and efficiently for Syrians in Türkiye and to increase access to health services. The costs related to the expansion and operation of IHCs are covered by the SIHHAT Project funded by the European Union.²⁸ These centers implement the same vaccination program for migrants as for Turkish citizens. All children receive 400 units/day of vitamin D supplementation until the age of one year. However, rickets can be seen not only in migrants or refugees but also in resident children. Therefore, all countries should consider vitamin D supplementation and adequate calcium intake as a public health policy to protect children from this preventable disease.

Our study found vitamin D deficiency in all 52 mothers whose vitamin D levels were checked. Severe vitamin D deficiency is common in pregnant women and newborns in low socioeconomic provinces of Türkiye.²⁹ Vitamin D deficiency in pregnant women can cause

congenital rickets in babies who do not receive adequate vitamin D support. When Paterson et al.³⁰ analyzed 24 cases diagnosed with rickets due to neonatal vitamin D deficiency, 11 of the 12 mothers with known serum vitamin D levels had a vitamin D measurement below 10 ng/mL, and symptomatic osteomalacia was found in 16 of the mothers. The risk factors for maternal vitamin D deficiency are low socioeconomic status, covered clothing for religious/cultural reasons, and low educational level, which are frequently observed in Türkiye.³¹ In addition to these, language problems, inability to access preventive healthcare services and inability to continue follow-ups due to address changes increase the risk in migrant Syrian mothers.⁷ The Vitamin D prophylaxis program for pregnant women, initiated by the Ministry of Health in 2011 is still ongoing.³² This program should be followed and supported as well.

In the treatment of NR, oral vitamin D can be given as a single daily dose for three months or in high doses for patients >3 months in 1-3 divided doses. In addition, adequate calcium intake (500 mg/day) or oral calcium supplementation for 10-15 days is recommended.² Most (71.4%) of our patients were treated with a daily dose, while 20.8% received a single high dose and 7.8% received both a high dose and a daily dose. Compliance with treatment can be expected to be low among immigrants struggling with difficulties such as obtaining adequate food, shelter and the experience of leaving their homes. For these reasons, we believed that stoss treatment would be more appropriate, as we predicted that compliance with daily vitamin D use would be low in refugee families. NR patients with findings of severe hypocalcemia, such as convulsions, tetany, and respiratory distress, must be hospitalized. Hospitalization and intravenous calcium support were required in 32 of our patients (41.5%).

Some limitations of the study should be noted. The study was a retrospective file-based study

and in some patients the symptoms may not have been systematically evaluated or tested. Secondly, there are two pediatric endocrinology centers in Malatya, and cases treated with NR in the other pediatric endocrinology center were not included. Therefore, our study does not provide incidence data for Malatya province. Thirdly, since we aimed to investigate issues related to the functioning of the prophylaxis program by revealing the frequency of cases seen in our center, the study did not include a control group. Fourthly, the very high PTH level in all our cases suggests that only the most severe cases of NR were seen during the study period. Therefore, the actual disease burden in Türkiye is likely to be much heavier and the true incidence of subclinical rickets is unknown. Finally, feeding pattern, time of sun exposure and other risk factors for NR were not assessed.

Despite the vitamin D prophylaxis available in Türkiye, there has been a trend towards an increasing incidence of NR in recent years. Since NR is completely preventable, universal vitamin D supplementation and adequate calcium should be provided, not only for the resident population but also for refugee and migrant children. Mothers should be encouraged to use vitamin D during breastfeeding. To reduce the frequency of NR it will be important to continue the vitamin D prophylaxis program for infants, which was initiated to prevent NR and was shown to be successful, and to carry out an ongoing clinical audit of the program to identify any problems and thus improve its effectiveness.

Ethical approval

The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee (document number: E-23536505-000-3592, date:14.03.2022). Informed consent was not obtained because of the retrospective nature of the study.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: İD; data collection: İD, MAB; analysis and interpretation of results: İD; draft manuscript preparation: İD, MAB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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