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Vitamin D–Deficient Rickets in Japan

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Abstract

Objectives: Our study aimed to clarify the trend of vitamin D deficiency and rickets diagnosed in the past 10 years. **Methods:** This observational study used health insurance claims data from 2005 to 2014. The number of beneficiaries for 2005 and 2014 were 91 617 and 365 800, respectively. We included children aged 0 to 15 years diagnosed with vitamin D deficiency or vitamin D–deficient rickets; those with congenital/secondary rickets and low-birth-weight infants were excluded. We analyzed the number of patients and the temporal trend of these diseases in Japan. **Results:** The annual number of patients from 2005 to 2008 was <5. The number of patients in 2009 and 2014 were 3.88 (95% confidence interval = 1.77-7.37) and 12.30/100 000 (95% confidence interval = 8.97-16.46), respectively. **Conclusions:** Diagnosed cases of vitamin D deficiency and vitamin D–deficient rickets have apparently increased in Japan. Further studies to identify the trend, cause, and prevention of vitamin D–deficient rickets are necessary.

Keywords

endocrinology, general pediatrics, vitamin D–deficient rickets, vitamin D deficiency, nutritional rickets, sunlight avoidance, atypical diet

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Introduction

Rickets is a serious disorder that may be congenital, genetic, or acquired secondary to vitamin D deficiency, with apparent physical features confirmed by radiological findings and blood tests. Vitamin D deficiency is caused by limited sunlight exposure and inadequate nutrition. Reports of vitamin D deficiency and vitamin D–deficient rickets have increased worldwide since around 2000, with these conditions considered important public health issues.[1-3]

In Japan, unique situations prevail. Parents are extremely protective of their children being exposed to sunlight, there are no recommendations of vitamin D supplementation for infants, vitamin D supplements for infants were not available until 2014, vitamin D–fortified food is extremely limited, and some children are on an atypical diet.[4] Earlier studies in Japan have shown the prevalence of vitamin D deficiency and vitamin D–deficient rickets based on hospital records or regional studies.[5,6] To date, however, population-based statistics of the prevalence of vitamin D deficiency and vitamin D–deficient rickets have been scarce in Japan. Accordingly, this study aimed to elucidate the number of pediatric patients diagnosed with vitamin D deficiency and vitamin D–deficient rickets, and the trend of these diseases using health insurance claims data in Japan in the past decade.

Materials and Methods

We obtained health insurance claims data from Japan Medical Data Center (JMDC). JMDC acquires medical data from the Japanese union-managed health insurance

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system (Health Insurance Association), which is composed of large private companies' associations/unions and contains medical data of the employees and their family members, representing approximately 1% of the total population of Japan.[7] The anonymous but individually traceable database includes patients' demographic characteristics, date of the medical service, diagnosis, procedures, prescription, and other health care services. JMDC codes the diagnosis of each claim according to the International Classification of Diseases Version 10 (ICD-10) 2003 version, and the standard disease codes issued by the Japanese government's medical insurance calculation code sets.[8] The numbers of beneficiaries obtained from the JMDC database were 91 617 and 365 800 in 2005 and 2014, respectively.

In the present study, we identified eligible subjects using the ICD-10 and standard disease codes. First, we enrolled patients aged 0 to 15 years from January 2005 to December 2014 with ICD-10 codes E55.0 (rickets, active) and E55.9 (vitamin D deficiency, unspecified) and the standard disease codes for vitamin D–deficient rickets and vitamin D deficiency (Appendix Table A.1). We excluded congenital/genetic cases and low-birth-weight infants using ICD-10 and the standard disease codes for the applicable diseases (Appendix Table A.2).

Codes for both vitamin D deficiency and vitamin D–deficient rickets were used because these disorders are the disease names commonly recalled by pediatricians when consulting patients, and the diagnosis is made according to the attending pediatrician's judgment. Thus, we included both vitamin D deficiency and vitamin D–deficient rickets in this study, because differentiation between the two may not have been clear among Japanese doctors before the relevant diagnosis guideline was announced in 2013. On the other hand, the standard disease codes for rickets and vitamin D-deficient rickets are different; the standard disease code for rickets was not used for extracting data to avoid the inclusion of congenital rickets (Appendix Tables A.1 and A.2). There was no change in the diagnostic criteria or treatment standards for rickets during the study period.

All eligible cases included in the insurance claims database over the study period were de-duplicated before analysis using anonymous but individually traceable coding. We defined the patients as cases when there was at least one claim with the relevant disease code each year, and also analyzed the number of newly diagnosed patients during the 10-year period.

The number of patients with vitamin D deficiency or vitamin D–deficient rickets for each year was estimated using the Poisson exact method. Blood test parameters and prescriptions commonly prescribed for vitamin D deficiency and vitamin D–deficient rickets and the percentage of patients who received treatment were analyzed. We used Stata version 13.1 (StataCorp, College Station, TX) for the statistical analysis.

This study was approved by the Ethics Committee of The University of Tokyo, No. 10773-(2), and was conducted in accordance with the World Medical Association Declaration of Helsinki. Obtaining informed consent was waived by the ethics committee due to the retrospective/observational design of the study.

Results

From 2005 to 2008, the annual number of patients diagnosed as having vitamin D deficiency or vitamin D–deficient rickets in the data set was <5, whereas 9 and 45 patients were diagnosed in 2009 and 2014, respectively. The number of patients per 100 000 persons was estimated as 3.88 in 2009 (95% confidence interval = 1.77-7.37) and increased to 12.30 (95% confidence interval = 8.97-16.46) in 2014 (Table 1). Due to the low number of patients identified from 2005 to 2008, those data were considered statistically unreliable; therefore, we used data from 2009 to 2014 for the subsequent analyses.[9]

Blood tests for alkaline phosphatase and calcium, phosphorous, parathyroid hormone, and $1,25(OH)_2D$ were conducted in 75%, 71%, 30%, and 21% of patients, respectively. A total of 60% of patients underwent radiography, and there was no increase in radiological examinations over time. The patients tended to be male more frequently than female, but the difference was not statistically significant (Table 1). The mean treatment period during which vitamin D deficiency or vitamin D–deficient rickets was diagnosed was 17.6 months. Alfacalcidol, the only medicine that can be prescribed for vitamin D deficiency in Japan, was prescribed in 72% of patients.

Discussion

Our study showed an apparent increase of vitamin D deficiency and vitamin D–deficient rickets diagnosed in Japan over the past decade. This result coincides with the trends reported in other countries. Between 2007 and 2011, the prevalence of patients aged <15 years hospitalized for rickets in England was 3.16/100 000 patients.[10] In the United States, a study using diagnostic codes for nutritional rickets in Minnesota reported a prevalence of 24.1/100 000 persons aged <3 years from 2000 to 2010.[11] Furthermore, in Quebec, Canada, the incidence of rickets was

Table 1. Number of Vitamin D–Deficient Rickets Patients, Aged 0 to 15 Years, in Japan, Obtained From the JMDC Database (2009-2014)[a,b].

Year	No. of Vitamin D–Deficient Patients	No. of Boys	No. of Girls	Sample Size in the JMDC Database	Patients per 100 000 Population	95% Confidence Interval[c]
2009	9	4	5	231 874	3.88	1.77-7.37
2010	21	9	12	347 331	6.05	3.74-9.24
2011	35	19	16	436 662	8.02	5.58-11.15
2012	40	23	17	442 439	9.04	6.46-12.31
2013	49	28	21	426 782	11.48	8.49-15.18
2014	45	28	17	365 800	12.30	8.97-16.46

Abbreviation: JMDC, Japan Medical Data Center.
[a]JMDC is a private company in Tokyo, Japan, that specializes in providing medical data to stakeholders in the medical field such as pharmaceutical companies, medical device companies, and research institutes.
[b]Data from 2005 to 2008 are not shown because the annual number of vitamin D–deficient patients included in the database was less than 6, per the rule-based use of suppression and aggregation (Reference: "Guidelines for Working with Small Numbers," Washington State Department of Health, Revised October 2010, Appendix 1).
[c]Analyzed with the Poisson exact method.

reported as 23.9/100 000 persons; a program aimed to provide infants with free vitamin D supplement was implemented, but the adherence was found to be low.[12]

In Japan, past reports have been conducted in limited regions or institutions. One study in Hokkaido (the second largest island within the Japanese archipelago, situated north), performed using a hospital survey for rickets during 1999 and 2004, reported an incidence of 9/100 000 persons in children aged <4 years.[5] A study in Kyoto of 1120 otherwise normal newborns found craniotabes in 22% of the cohort, and a low serum 25(OH) D level in 37.3%.[6]

Vitamin D–deficient rickets and vitamin D deficiency are diseases that physicians typically diagnose only when those diseases are strongly suggested, indicating the accuracy and credibility of using health insurance claims data to identify patients.[13,14]

The reasons for the increase in diagnosed vitamin D deficiency and vitamin D–deficient rickets in our study over time are multiple. Specifically, we suspect increased sunlight avoidance and limited nutrition as the main causes. Japanese women strictly apply sun protection to their children, and children's time outdoors is decreasing because of lifestyle changes. Moreover, some mothers limit foods for fear of allergy.[15] Especially, some avoid animal protein and/or dairy products,[4] and fortified foods are not readily available. Oily fish is the best natural dietary source of vitamin D, but the consumption of meat has surpassed that of fish by the Japanese population since 2006.[16] In addition, some mothers give breast milk exclusively, which has low vitamin D content,[17] without appropriate weaning.

There are a number of limitations of the present study. First, the most important limitation of our study is the small sample size, especially before 2008. As of 2014, JMDC database of those aged 0 to 15 includes approximately 2% of the total Japanese population in that age range.[7] However, as there was no national database of insurance claims before 2011, this set of data is still valuable for determining a longitudinal trend. Second, the risk of miscoding cannot be completely eliminated, and another important limitation is hence the risk of misdiagnosis. Third, as the JMDC database is a database of employees of large private companies, the result may be skewed to higher income families. Fourth, information of ethnicity is not included in the claims data. Nonetheless, non-Japanese people living in Japan only account for 1.7% of the population, and most are from China and Korea.[18] Fifth, the results of any medical tests/assays are not included in the claims data. It is likely that some patients in our database had low calcium levels due to not consuming dairy products, and rice/soy milk are generally not fortified with calcium in Japan. Finally, no record of breastfeeding is included in the claims.

On the other hand, a major strength of this study was the scale of our data. To our knowledge, there have been no previous population-based studies, and no large-scale database existed before 2011 in Japan; therefore, using JMDC data is of value to assess the longitudinal trend of vitamin D-deficient rickets.

In conclusion, this study showed that diagnosed cases of vitamin D deficiency and vitamin D–deficient rickets are increasing in Japan. Public health investigations are necessary through population-based studies to identify the trends, causes, and appropriate prevention strategies of these diseases.

Appendix A

Table A.1. Diseases Included in the Data Set.

ICD-10 Code	Standard Disease Code	Standard Disease Name
E55.0	8845186	Vitamin D–deficient rickets
E55.9	2689005	Vitamin D deficiency

Table A.2. Diseases Excluded From Our Data Set.

ICD-10 Code	Standard Disease Code	Standard Disease Name
E55.0	8845185	Vitamin D–dependent rickets
E55.0	8847927	Hepatic rickets
E55.0	8845189	Rickets of prematurity
E83.3	8833309	Primary hypophosphatemic rickets
E83.3	2689003	Vitamin D dependency
E83.3	2689012	Vitamin D dependency type II
E83.3	2689011	Vitamin D dependency type I
E83.3	8839503	Vitamin D–resistant rickets
E83.3	8837885	Hypophosphatasia
N25.0	8835613	Renal rickets
P07.0	7650008	Ultra-low birth weight infants
P07.0	7650009	Ultra-low birth weight infants
P07.1	7650005	Extremely low birth weight infants
P07.1	7650007	Extremely low birth weight infants
P07.1	7650003	Low birth weight infants
P071	7650004	Low birth weight infants
P07.2	8838571	Babies born before 28 weeks of gestation
P07.3	7651002	Preterm babies
P07.3	8838570	Babies born between 28 and 37 weeks of gestation

Author Contributions

MI: Contributed to conception and design; contributed to acquisition; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
JT: Contributed to conception and design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
ST: Contributed to conception and design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
MT: Contributed to conception; contributed to interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
TI: Contributed to conception; contributed to interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
SK: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
YK: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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