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PERÚ

Ministerio de Salud

Hospital Nacional Docente Madre-Niño "San Bartolomé"

N° 126 - 2021 -DG-HONADOMANI-SB



Resolución Directoral

Lima, 21 de Junio de 2021



VISTO:

El Expediente N° 07652-21;

CONSIDERANDO:

Que, los artículos I y II del Título Preliminar de la Ley N° 26842 - Ley General de Salud dispone que la salud es condición indispensable del desarrollo humano y medio fundamental para alcanzar el bienestar individual y colectivo, y que la protección de la salud es de interés público. Por tanto, es responsabilidad del Estado regularla vigilarla y promoverla;

Que, el segundo párrafo del artículo 5° del Decreto Supremo N° 013-2006-SA, Reglamento de Establecimientos de Salud y Servicios Médicos de Apoyo, señala que *"los establecimientos de salud y servicios médicos de apoyo deben contar, en cada área, unidad o servicio, con manuales de procedimientos, guías de práctica clínica referidos a la atención de los pacientes, personal, suministros, mantenimiento, seguridad y otros que sean necesarios, según sea el caso"*;

Que, asimismo el inciso s) del artículo 37° del Decreto Supremo antes indicado, establece como funciones del Director Médico, disponer la elaboración del reglamento interno, de las guías de práctica clínica y de los manuales de procedimientos referidos a la atención de los pacientes, personal, suministro, mantenimiento, seguridad y otros que sean necesarios;

Que, mediante Resolución Ministerial N° 302-2015/MINSA, se aprobó la Norma Técnica N° 117-MINSA/DGSP-V.01 "Norma Técnica para la elaboración y uso de Guías de Práctica Clínica del Ministerio de Salud la misma que tiene como finalidad *"Contribuir a la calidad y seguridad de las atenciones de salud, respaldadas por Guías de Práctica Clínica, basadas en evidencias científicas, ofreciendo el máximo beneficio y el mínimo riesgo para los usuarios de las prestaciones en salud, así como la optimización y racionalización del uso de los recursos"*;

Que, con Memorando N° 0011.2021.OFSEG.HONADOMANI.SB de fecha 12 de enero de 2021, el Jefe de la Oficina de Seguros se dirige a la Jefa del Departamento de Pediatría solicitándole la GUIA DE PRACTICA O PROTOCOLO DE ATENCIÓN toda vez que dicho documento es requerido por el Seguro Integral de Salud para la gestión financiera del medicamento "COLECALCIFEROL 600000 UI SOL 10ML", adjuntando el Informe Técnico N° 02-2021-NEFROLOGÍA-SUBESPECIALIDADES PEDIATRICAS-HONADOMANI-SB, suscrita por la Dra. Jenny Patricia Ponce Gambini;

Que, con Informe N° 038-J-OGC-2021-HONADOMANI-SB, de fecha 26 de abril de 2021, el Jefe de la Oficina de Gestión de la Calidad remite a la Jefa del Departamento de Pediatría concluye otorgando su opinión favorable manifestando que *"La Guía de Práctica Clínica: Clinical Practice Global Consensus Recommendations on Prevention and Management of Nutritional Rickets, cumple con cuatro criterios de evaluación planteados por la norma técnica..."*;

Que, con Nota Informativa N° 21-21-NEFRO/SEP-DP-HONADOMANI-SB, de fecha 08 de junio de 2021, la Dra. Jenny Patricia Ponce Gambini, remite el Informe Técnico y la Guía traducida, para que continúen los trámites correspondientes de aprobación de tecnología sanitaria para el uso de colecalfierol (vitamina D3) en pacientes con deficiencia de vitamina D y/o raquitismo, el mismo

MINISTERIO DE SALUD
INSTITUTO DE GESTIÓN DE SERVICIOS DE SALUD
HOSPITAL NACIONAL DOCENTE MADRE NIÑO
SAN BARTOLOME
Documento Autenticado

LIC. WILLIAM A. FLORIAN PLASENCIA
FEDATARIO
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MINISTERIO DE SALUD
HOSPITAL NACIONAL DOCTOR MIGUEL ALVARO SAN BARTOLOMÉ

[Signature]

MIGUEL JULIO CANO GARDENAS
DIRECTOR GENERAL
CNP. 121000101. 4374

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Recomendaciones de Consenso Global en la Prevención y Manejo de Raquitismo Nutricional

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Introducción: La deficiencia de vitamina D y calcio son patologías comunes a nivel mundial, causando raquitismo nutricional y osteomalacia, lo cual tiene un gran impacto en la salud, crecimiento y desarrollo de los lactantes, niños y adolescentes; las consecuencias pueden ser letales o pueden durar hasta la adultez. Los objetivos de este consenso basado en evidencias son proveer a los profesionales de salud una guía para la prevención, diagnóstico y manejo del raquitismo nutricional y proporcionar a los responsables de la formulación de políticas un marco para trabajar en su erradicación.

Evidencia: Se llevó a cabo una búsqueda de literatura sistemática que examina la definición, el diagnóstico, el tratamiento y la prevención de los raquitismos nutricionales en los niños. Se desarrollaron recomendaciones basadas en la evidencia utilizando el sistema GRADE (Grading of Recommendations, Assessment, Development and Evaluation) que describe la fuerza de la recomendación y la calidad de la evidencia de respaldo.

Proceso: Treinta y tres expertos nominados en endocrinología pediátrica, pediatría, nutrición, epidemiología, salud pública y economía de la salud evaluaron la evidencia sobre preguntas específicas dentro de cinco grupos de trabajo. El grupo de consenso, que representa a 11 organizaciones científicas internacionales, participó en una conferencia de varios días en mayo de 2014 para alcanzar un consenso global basado en evidencia.

Resultados: Este documento de consenso define el raquitismo nutricional y sus criterios diagnósticos y describe el manejo clínico de raquitismo y osteomalacia. Se clasifican los factores de riesgo, particularmente en las madres y los bebés, y se ofrecen recomendaciones específicas de prevención que incluyen la fortificación y complementación alimentaria tanto para el contexto clínico como de salud pública.

Conclusión: El raquitismo, la osteomalacia y las deficiencias de vitamina D y calcio son problemas de salud pública mundial prevenibles en lactantes, niños y adolescentes. Se requiere con urgencia la implementación de programas internacionales de prevención del raquitismo, incluida la suplementación y el enriquecimiento de alimentos. (J Clin Endocrinol Metab 101: 394–415, 2016)

* Consulte el Apéndice A para conocer las afiliaciones de los autores.

Clasificación de la evidencia: 1=recomendación fuerte; y 2=recomendación débil. Calidad de la evidencia: ⊕⊕⊕, alta; ⊕⊕○, moderado; y ⊕○○, baja calidad. Abreviaturas: FA, fosfatasa alcalina; DXA, absorciometría dual de rayos X; RN, raquitismo nutricional; 25OHD, 25-hidroxivitamina D2 y/o D3 o 25-hidroxicolecalciferol D2 y/o D3; 1,25 (OH) 2D, 1,25-dihidroxivitamina D2 y/o D3 o 1,25-dihidroxicolecalciferol D2 y/o D3 (calcitriol); PTH, hormona paratiroidea; ECA, ensayo controlado aleatorio; UVB, ultravioleta B; Vitamina D2, ergocalciferol; Vitamina D3, colecalciferol.

Este artículo es publicado simultáneamente en *Hormone Research in Paediatrics* (DOI: 10.1195 / 000443136).





Sección 2: Prevención y tratamiento del raquitismo nutricional y la osteomalacia

2.1. Suplementación de vitamina D para la prevención del raquitismo y la osteomalacia

- 400 UI/d (10 µg) es adecuado para prevenir el raquitismo y se recomienda para todos los niños desde el nacimiento hasta los 12 meses de edad, independientemente de su modo de alimentación. (1⊕⊕⊕)
- Después de los 12 meses de edad, todos los niños y adultos deben cumplir con sus requerimientos nutricionales de vitamina D a través de la dieta y/o suplementos, al menos 600 UI/d (15 µg), según lo recomendado por el Instituto de Medicina (IOM). (1⊕⊕⊕)

2.2. Objetivo para la suplementación con vitamina D

- En niños sanos, no se recomienda la detección rutinaria de 25OHD y, en consecuencia, no se ha fijado un umbral específico de 25OHD para la suplementación con vitamina D en esta población. (1⊕⊕⊕)

2.3. Candidatos para la suplementación preventiva de vitamina D después de los 12 meses de edad

En ausencia de fortificación de alimentos, la suplementación de vitamina D debe administrarse a:

- Niños con antecedentes de deficiencia sintomática de vitamina D que requieran tratamiento. (1⊕⊕⊕)
- Niños y adultos con alto riesgo de deficiencia de vitamina D, con factores o condiciones que reducen la síntesis o la ingesta de vitamina D. (1⊕⊕⊕)
- Mujeres embarazadas (consulte la Sección 3.1).

2.4 Dosis de vitamina D y calcio para el tratamiento del raquitismo nutricional

- Para el tratamiento del raquitismo nutricional, la dosis mínima recomendada de vitamina D es de 2000 UI/d (50 g) durante un mínimo de 3 meses. (1⊕⊕⊕)
- Calcio oral, 500 mg/d, ya sea como ingesta dietética o suplemento se debería usar de manera rutinaria en combinación con vitamina D en el tratamiento, independientemente de la edad o el peso. (1⊕⊕⊕)



2.5. Apropriada vía de administración y duración del tratamiento

- Recomendamos tratamiento oral, lo cual restaura más rápidamente los niveles de 25OHD que el tratamiento IM. (1⊕⊕⊕)
- Para el tratamiento diario, tanto D2 como D3 son igualmente efectivos. (1⊕⊕⊕)
- Cuando se utilizan dosis únicas grandes, D3 parece ser preferible en comparación con D2 porque la primera tiene una vida media más larga. (1⊕⊕⊕)

- Se recomienda el tratamiento con vitamina D durante un mínimo de 12 semanas, reconociendo que algunos niños pueden requerir una duración de tratamiento más prolongada. (1⊕⊕⊕)

Sección 3: Prevención del raquitismo nutricional / osteomalacia: identificación de factores de riesgo

3.1. Prácticas dietéticas e ingesta de nutrientes en madres asociadas con raquitismo nutricional en los lactantes

- Debe evitarse la deficiencia materna de vitamina D asegurando que las mujeres en edad fértil alcancen las ingestas de 600 UI/d recomendadas por el IOM. (1⊕⊕⊕)
- Las mujeres embarazadas deben recibir 600 UI/d de vitamina D, preferiblemente como una preparación combinada con otros micronutrientes recomendados como hierro y ácido fólico. (2⊕⊕○)

3.2. Alimentación temprana, suplementación, alimentación complementaria e ingesta de nutrientes asociados con el raquitismo en los lactantes

- Además de la ingesta de 400 UI/d de vitamina D, los alimentos complementarios introducidos antes de las 26 semanas deben incluir fuentes ricas en calcio. (1⊕⊕⊕)
- Debe asegurarse una ingesta de al menos 500 mg/d de calcio elemental durante la infancia y la adolescencia. (1⊕⊕⊕)

3.3. Asociación de la exposición a la luz solar con el raquitismo nutricional

- Debido a que los rayos UVB desencadenan la síntesis epidérmica de la pro vitamina D3, la exposición restringida al sol incrementa el riesgo de deficiencia de vitamina D y raquitismo nutricional. (1⊕⊕⊕)
- Factores ambientales, como latitud, estación, hora del día, nubosidad y contaminación afectan la disponibilidad de UVB, mientras que los factores personales, como el tiempo que se pasa al aire libre, la pigmentación de la piel, la cobertura de la piel, la edad, la composición corporal y la genética afectan la dosis-respuesta de la exposición a los rayos UVB y la 25OHD circulante. (2⊕⊕○)
- Ningún umbral seguro de exposición a los rayos UV permite una síntesis suficiente de vitamina D en toda la población sin aumentar el riesgo de cáncer de piel. (2⊕⊕○)

Sección 4: Prevención de la osteomalacia durante el embarazo y la lactancia y raquitismo congénito

4.1. Relación entre la vitamina D durante el embarazo y el crecimiento infantil y la masa ósea



- Las mujeres embarazadas deben recibir suplementación de 600 UI/d de vitamina D. Esto garantizará una 25OHD materna adecuada, especialmente en mujeres con riesgo de deficiencia, para prevenir niveles elevados de fosfatasa alcalina (ALP) en sangre del cordón umbilical, aumento del tamaño de la fontanela, hipocalcemia neonatal y raquitismo congénito, y para mejorar la formación del esmalte dental. (2⊕○○)
- Hay poca evidencia de que la suplementación materna con vitamina D protegerá o mejorará la antropometría al nacimiento (2⊕⊕○) y no hay evidencia de que la suplementación con vitamina D proteja o mejore el crecimiento a corto o largo plazo o la acreción de masa ósea. (2⊕⊕○)

4.2. El efecto de la suplementación con calcio durante el embarazo sobre la masa ósea del lactante

- Las mujeres embarazadas no necesitan ingestas de calcio por encima de las ingestas recomendadas para no embarazadas para mejorar el hueso neonatal. (1⊕⊕⊕)

4.3. Influencia de la suplementación con calcio o vitamina D durante el embarazo o la lactancia en el calcio o vitamina D de la leche materna

- Las mujeres que amamantan deben asegurarse de cumplir con las recomendaciones dietéticas de vitamina D (600 UI/día) para sus propias necesidades, pero no para las necesidades de su bebé. (1⊕⊕⊕)
- Las mujeres que amamantan no deben tomar grandes cantidades de vitamina D como medio de complementar a su bebé. (2⊕⊕○)
- Las mujeres embarazadas y las que amamantan deben cumplir con la ingesta recomendada de calcio. La ingesta materna de calcio durante el embarazo o la lactancia no está asociada con las concentraciones de calcio en la leche materna. (1⊕⊕⊕)

4.4. Causas y terapia del raquitismo congénito.

- La suplementación de las madres con 600 UI/d de vitamina D y el asegurarse de que reciban las ingestas recomendadas de calcio, o la terapia adecuada para las condiciones maternas que predisponen a la hipocalcemia o la deficiencia de vitamina D, previene el raquitismo congénito. (2⊕○○)

Sección 5: Evaluación del impacto del raquitismo nutricional y estrategias de salud pública para la prevención

5.1. Evaluación del impacto de la morbilidad

- La prevalencia de raquitismo se debe determinar mediante muestras basadas en la población, casos reportados de centros centinela o informes obligatorios. (1⊕⊕⊕)
- La detección del raquitismo nutricional debe basarse en las características clínicas, seguida de la confirmación radiográfica de los casos sospechosos. (1⊕⊕⊕)



- No está indicado el cribado poblacional con 25OHD sérico, fosfatasa alcalina sérica o radiografías. (1⊕⊕⊕)

5.2. Estrategias de salud pública para la prevención del raquitismo

- Complementar universalmente a todos los bebés con vitamina D desde el nacimiento hasta los 12 meses de edad, independientemente de su modo de alimentación. Más allá de los 12 meses, suplementar todos los grupos de riesgo y mujeres embarazadas. Los complementos de vitamina D deben incorporarse en los programas de atención primaria de salud infantil junto con otros micronutrientes e inmunizaciones esenciales (1⊕⊕⊕) y en los programas de atención prenatal junto con otros micronutrientes recomendados. (2⊕⊕O)
- Reconocer el raquitismo nutricional, la osteomalacia y las deficiencias de vitamina D y calcio como problemas de salud pública mundial prevenibles en lactantes, niños y adolescentes. (1⊕⊕⊕)
- Implementar programas de prevención de raquitismo en poblaciones con alta prevalencia de deficiencia de vitamina D e ingesta limitada de vitamina D y/o calcio, y en grupos de lactantes y niños en riesgo de raquitismo. (1⊕⊕⊕)
- Monitoree la adherencia a las recomendaciones de ingesta de vitamina D y calcio y implemente la vigilancia del raquitismo nutricional. (1⊕⊕⊕)
- Fortifique los alimentos básicos con vitamina D y calcio, según corresponda, basado en patrones dietéticos. La fortificación de los alimentos puede prevenir el raquitismo y mejorar el estado de vitamina D en lactantes, niños y adolescentes si se utilizan alimentos adecuados y se proporciona suficiente fortificación, si la fortificación está respaldada por la legislación pertinente y si el proceso se supervisa adecuadamente. Las fuentes alimentarias autóctonas de calcio deben promoverse o subvencionarse en los niños. (1⊕⊕⊕)
- Promover abordar el impacto en la salud pública de la deficiencia de vitamina D como un problema de salud pública y clínica. (1⊕⊕⊕)

5.3. Costo/beneficios económicos de los programas de prevención

- La rentabilidad de los programas de complementación y fortificación de alimentos necesita más estudios. (1⊕⊕⊕)



El raquitismo nutricional (RN), secundario a la deficiencia de vitamina D y/o de calcio en la dieta, sigue siendo un problema de salud pública global significativo a pesar de la disponibilidad de suplementos y numerosas guías publicadas para su prevención (1-8). Esto es preocupante porque el RN puede tener un gran impacto en la salud de los lactantes, niños y adolescentes, con repercusiones que persisten hasta la edad adulta. La morbilidad y la mortalidad asociadas con el RN pueden ser devastadoras, con consecuencias sustanciales, pero poco reconocidas para la sociedad y la economía de la salud. Las características del RN y osteomalacia incluyen: 1) convulsiones hipocalcémicas y espasmos tetánicos; 2) cardiomiopatía hipocalcémica potencialmente mortal; 3) dolor de huesos y debilidad muscular; 4) deformidades de las extremidades y la pelvis; 5) retraso del crecimiento; 6) retraso en el desarrollo; y 7) anomalías

dentalas (9,10). De manera alarmante, el RN también puede provocar la muerte por insuficiencia cardíaca causada por miocardiopatía hipocalcémica, incluso en los países desarrollados (11). Además, el estrechamiento de la salida pélvica después del RN de la niñez puede resultar en parto obstruido y muerte materna y fetal (12).

A pesar de un intenso enfoque en torno al papel del estado de la vitamina D en la salud y la enfermedad, ha habido un fracaso en todo el mundo en la implementación de las guías de salud pública y la erradicación de las manifestaciones más graves de la deficiencia de vitamina D y calcio en nuestra población más vulnerable - RN y osteomalacia de la infancia. Por lo tanto, el objetivo de este Consenso es brindar a los médicos con claridad y recomendaciones en el reconocimiento, el impacto social y el tratamiento del RN y osteomalacia, y permitir que los clínicos y los líderes de las políticas de salud establezcan intervenciones clínicas y de salud pública adecuadas para prevenir este problema de salud global debilitante, costoso y poco reconocido.

Métodos

En reconocimiento de la considerable variación en la definición, el diagnóstico y el tratamiento del RN en todo el mundo, la Sociedad Europea de Endocrinología Pediátrica decidió examinar las mejores prácticas actuales en RN y formular recomendaciones basadas en la evidencia. Se reunieron expertos de las siguientes sociedades: la Sociedad de Endocrinología Pediátrica (Pediatric Endocrine Society - PES), la Sociedad de Endocrinología Pediátrica del Pacífico asiático (Asia Pacific Pediatric Endocrine Society-APPES), la Sociedad de Endocrinología Pediátrica Japonesa (Japanese Society for Pediatric Endocrinology - JSPE), la Sociedad Latino-Americana de Endocrinología Pediátrica (SLEP), el Grupo Endocrino pediátrico Australiano (Australasian Pediatric Endocrine Group-APEG), la Sociedad India de Endocrinología Pediátrica y Adolescente (ISPAE), la Sociedad Africana de Endocrinología Pediátrica y Adolescente (ASPAE), la Sociedad China de Endocrinología y Metabolismo Pediátrico (CSPEM), la Sociedad Británica de Nutrición y la Sociedad Europea de Hepatología, Gastroenterología y Nutrición Pediátrica (ESPGHAN). Este documento de consenso incluye la evidencia acumulada hasta finales de 2014.

Los participantes incluyeron individuos de Europa, América del Norte (Estados Unidos y Canadá), América Latina, Asia, África y Australia, con un espectro equilibrado de experiencia y antigüedad profesional. Además, un experto en el desarrollo de guías basada en la evidencia sirvió en calidad de asesor. Los miembros del panel declararon cualquier posible conflicto de intereses en la reunión inicial del grupo. Se asignó a treinta y tres participantes a uno de los cinco grupos a los que se asignaron los temas 1 a 5, y se designó un presidente para cada grupo. Cada participante preparó un resumen basado en evidencia de la literatura relacionada con una pregunta en particular distribuida antes de la conferencia (que se llevó a cabo durante 3 días en mayo de 2014).

Cada grupo presentó los resúmenes revisados para su discusión en toda la conferencia. Este informe se basa en las preguntas abordadas. En otro lugar se ha publicado una descripción detallada de la clasificación GRADE (13). Las recomendaciones se basaron en hallazgos publicados y en la opinión de expertos cuando fue apropiado.



Se utilizó la mejor evidencia de investigación disponible para desarrollar recomendaciones. Se dio preferencia a los artículos escritos en inglés, identificados mediante búsquedas en PubMed con términos MeSH. Para cada punto, se describen las recomendaciones y la evidencia, con una modificación en la calificación de la evidencia de la siguiente manera: 1 = recomendación fuerte (se aplica a la mayoría de los pacientes en la mayoría de las circunstancias, los beneficios superan claramente el riesgo); y 2 = recomendación débil (opinión consensuada del grupo de trabajo o debería ser considerada; la mejor acción puede depender de las circunstancias o los valores del paciente, los beneficios y los riesgos estrechamente equilibrados o inciertos). La calidad de la evidencia se indica de la siguiente manera: ⊕⊕⊕, alta calidad (estudios de cohortes prospectivos o ensayos controlados aleatorios [ECA] con bajo riesgo de sesgo); ⊕⊕O, calidad moderada (estudios observacionales o ensayos con fallas metodológicas, evidencia inconsistente o indirecta); y ⊕OO, de baja calidad (series de casos u observaciones clínicas no sistemáticas) (13).

El público objetivo de esta guía incluye pediatras generales y especialistas, otros profesionales que brindan atención a pacientes con RN y formuladores de políticas de salud, particularmente en países con economías en desarrollo.

1.0 Definición del raquitismo nutricional y la interacción entre el estado de la vitamina D y la ingesta de calcio

1.1 Definición y diagnóstico del raquitismo nutricional

1.1.1 Recomendaciones

- El raquitismo nutricional, un trastorno de la diferenciación defectuosa de los condrocitos y de la mineralización de la placa de crecimiento y defectuosa mineralización osteoide, es causado por la deficiencia de vitamina D y/o la baja ingesta de calcio en los niños. (1⊕⊕⊕)
- El diagnóstico de raquitismo nutricional se realiza sobre la base de la historia, el examen físico y las pruebas bioquímicas y se confirma mediante radiografías. (1⊕⊕⊕)

1.1.2. Evidencia

La mineralización ósea requiere un suministro suficiente de iones minerales esenciales, calcio y fósforo y, la vitamina D optimiza su absorción en el intestino. Con una concentración insuficiente de calcio en suero causada por deficiencia de vitamina D o una ingesta insuficiente de calcio en la dieta, la PTH estimulará la resorción ósea osteoclástica para liberar los minerales óseos almacenados en el torrente sanguíneo y mantener el calcio sérico normal (14). La enfermedad ósea (raquitismo y osteomalacia) se desarrolla una vez que la PTH elevada ha dado lugar a niveles bajos de fósforo sérico, como resultado de una conservación alterada del fósforo renal (15).

El RN es un trastorno de la defectuosa apoptosis de los condrocitos de la placa de crecimiento y la mineralización de la matriz en los niños. La osteomalacia es una mineralización anormal de la matriz



en el hueso establecido y, aunque está presente en niños con raquitismo, se utiliza para describir defectos de mineralización ósea después de la finalización del crecimiento. Los niños con una enfermedad subyacente como malabsorción de grasas, enfermedad hepática, insuficiencia renal y enfermedades que requieren nutrición parenteral total también pueden desarrollar RN y se comentan brevemente en esta revisión. EL RN no incluye el raquitismo asociado con trastornos hereditarios del metabolismo de la vitamina D, incluida la deficiencia de 1-hidroxilasa y defectos del receptor de vitamina D, o raquitismo hipofosfatémico congénito o adquirido.

Las características clínicas y las consecuencias del RN son amplias y potencialmente graves (Tabla 1) (8). La mineralización defectuosa conduce al ensanchamiento radiográfico de la placa de crecimiento, así como al ahuecamiento y deshilachado metafisario, que confirman el diagnóstico de RN.

Las pruebas bioquímicas por sí solas no son suficientes para diagnosticar el RN y pueden no diferenciar si la causa principal del RN es la deficiencia de vitamina D o de calcio en la dieta, porque las deficiencias combinadas son comunes. Los datos de laboratorio típicos en RN son la disminución de la 25OHD, el fósforo sérico, el calcio sérico y el calcio urinario. Por el contrario, los niveles séricos de PTH, FA y fósforo urinario están invariablemente elevados (10, 16).

El estado de vitamina D se evalúa midiendo los niveles sanguíneos de 25OHD total. Se utiliza 25OHD total, asumiendo que 25OHD₂ y 25OHD₃ tienen el mismo valor biológico (16). Existe una variabilidad considerable entre los métodos de laboratorio para medir las concentraciones séricas de 25OHD (17). Los inmunoensayos son populares debido a su conveniencia y alto rendimiento de muestras; sin embargo, la reactividad cruzada entre los metabolitos de la vitamina D (25OHD₂, 25OHD₃ y 24,25(OH)₂D) y los altos niveles de sesgo estimado en varios ensayos automatizados ponen en duda su confiabilidad, particularmente a concentraciones altas y bajas de 25OHD (18). El Instituto Nacional de Estándares y Tecnología (NIST) (19) y la Universidad de Ghent (20) han establecido procedimientos de medición de referencia de orden superior para la 25OHD sérica basados en cromatografía líquida – espectrometría de masas en tándem por dilución isotópica.

En los últimos años, la precisión de los ensayos de 25OHD ha mejorado, incluso a través de actividades del Programa de Estandarización de Vitamina D (21), que tiene como objetivo estandarizar los resultados de diferentes técnicas de medición a los de los procedimientos de medición de referencia (22). Se observan reducciones significativas en la variación entre laboratorios de la 25OHD sérica utilizando cromatografía líquida-espectrometría de masas en tándem con la aplicación de materiales de referencia estándar del NIST (23). La deficiencia de calcio en la dieta se diagnostica al obtener un historial de ingesta de calcio. Debido a que las fuentes de calcio variarán según el país y la región, recomendamos que los médicos desarrollen un cuestionario de ingesta de calcio dietético específico para su país/región.



Tabla 1. Características Clínicas Asociadas a Raquitismo Nutricional

Signos y síntomas óseos

- Hinchazón de muñecas y tobillos
- Cierre tardío de la fontanela (normalmente cerrado a los 2 años)
- Erupción dental tardía (sin incisivos a los 10 meses, sin molares a los 18 meses)
- Deformidad de la pierna (genu varo, genu valgo, deformidad angular)
- Rosario raquítrico (articulaciones costocondrales agrandadas: se palpa en la parte anterior, lateral a la línea del pezón)
- Abombamiento frontal
- Craneotabes (ablandamiento de los huesos del cráneo, generalmente evidente en la palpación de las suturas craneales en los primeros 3 meses)
- Dolor óseo, inquietud e irritabilidad

Características radiográficas

- Ensanchamiento de los extremos metafisiarios, deflecamiento de la línea metafisiaria, imagen en copa y patrón trabecular grueso de la metáfisis.
- Ensanchamiento de la placa de crecimiento
- Osteopenia
- Deformidades pélvicas que incluyen estrechamiento de la salida (riesgo de parto obstruido y muerte)
- Deformidades a largo plazo de acuerdo con las deformidades clínicas
- Fractura por traumatismo mínimo

Características no óseas

- Convulsiones hipocalcémicas y tetania
- Miocardiopatía dilatada hipocalcémica (insuficiencia cardíaca, arritmia, paro cardíaco, muerte)
- Falta de crecimiento y crecimiento lineal deficiente
- Retraso del desarrollo de la motricidad gruesa con debilidad muscular
- Aumento de la presión intracraneal

1.2. Estado de la vitamina D

1.2.1. Recomendación:

• El panel recomienda la siguiente clasificación del estado de vitamina D, basada en los niveles séricos de 25OHD: (1⊕⊕⊕)

- Suficiencia, > 50 nmol/L
- Insuficiencia, 30-50 nmol/L
- Deficiencia, < 30 nmol/L

1.2.2. Evidencia

Nuestra definición de deficiencia de vitamina D en el contexto de la mineralización esquelética y el metabolismo de los minerales para la prevención de RN se basa en pruebas sólidas (1, 2, 24-27) respaldadas por la mayor incidencia de RN con concentraciones de 25OHD < 30 nmol/L (1 ng/mL = 2,5 nmol/L). Nuestra definición es coherente con la del IOM (28). Los posibles efectos en la salud de mantener una concentración de suero > 50 nmol/L están más allá del alcance de esta revisión y se tratan en otra parte (29). Cabe señalar que el RN ha sido reportado en niños con concentraciones de 25OHD > 30 nmol/L (2,5,6,30) y que el RN puede no ocurrir con concentraciones muy bajas de



25OHD, pero es probable que ocurra con deficiencias sostenidas en el tiempo, es decir, deficiencia crónica. e integridad ósea (Figura 1).

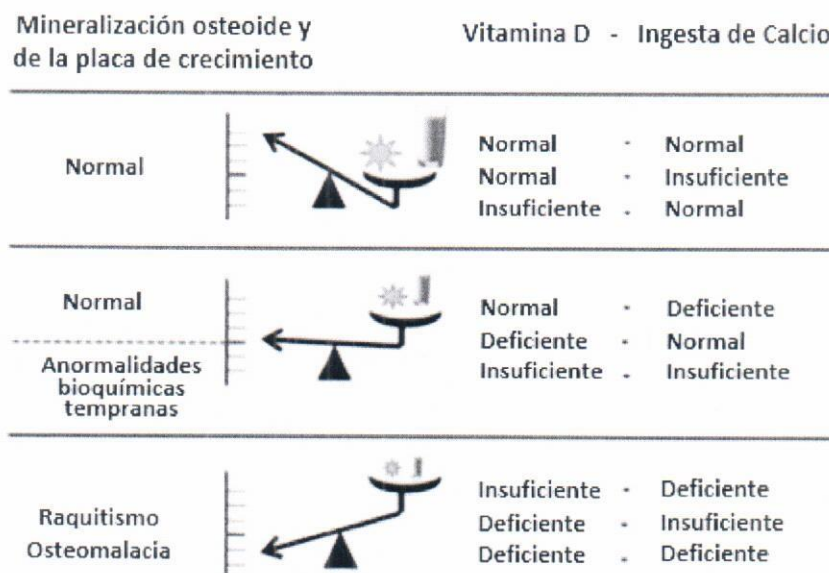


Figura 1: Alteraciones bioquímicas en la patogénesis del raquitismo según una clasificación en tres etapas del estado de la vitamina D (simbolizado por el sol) y la ingesta de calcio (simbolizado por un vaso de leche). [Modificado de Högl W. Complicaciones de la deficiencia de vitamina D desde el feto al infante: una causa, una prevención, pero ¿quién es responsable? Best Pract Res Clin Endocrinol Metab. 2015; 29 (3): 385–398. (246), con autorización. © 2015 Elsevier.]

Aunque el resultado funcional más significativo de la deficiencia de vitamina D es el desarrollo de osteomalacia y RN, asociaciones bioquímicas y de densidad ósea son además reportados. Las observaciones de laboratorio demuestran que la PTH aumenta cuando los niveles de 25OHD descienden por debajo de 34 nmol/L (7). Además, todos los pacientes con RN en ese estudio tenían niveles de 25OHD <34 nmol/L, y la PTH se elevó en todos menos en un paciente. En conjunto, las pruebas sugieren que un nivel de 25OHD en 30-34 nmol/L puede ser el límite crítico por debajo del cual es más probable que ocurra RN.

Las variaciones estacionales en la 25OHD de entre 13 y 24 nmol/L (31) enfatizan la importancia de mantener los niveles de 25OHD > 50 nmol/L (es decir, suficiente), para evitar períodos prolongados de niveles de 25OHD <30 nmol/L, con el riesgo de desarrollar RN.

1.3. Toxicidad por vitamina D

1.3.1. Recomendación

- La toxicidad se define como hipercalcemia y 25OHD sérico >250 nmol/L con hipercalciuria y PTH² suprimida. (1⊕⊕⊕)



1.3.2. Evidencia

La intoxicación se observa predominantemente en lactantes y niños pequeños después de la exposición a altas dosis de vitamina D (240 000 a 4 500 000 UI) (32–37). Las concentraciones altas de 25OHD pueden causar hipercalcemia, hipercalciuria y si es prolongada nefrocalcinosis e insuficiencia renal. Para permitir un margen de seguridad grande, el grupo de consenso sintió que era prudente utilizar la concentración de 250 nmol/L como límite superior recomendado de 25OHD sérico - incluso si la toxicidad sintomática de los ECAs solo ha sido reportado a niveles > 500 nmol/L (32). En lactantes sanos, la hipercalcemia y la hipercalciuria en ausencia de concentraciones elevadas de 25OHD ha sido reportado y podría estar relacionada con variaciones genéticas en el metabolismo de la vitamina D (38, 39).

1.4. Ingesta dietética de calcio para prevenir el raquitismo

1.4.1. Recomendaciones

- Para los bebés de 0 a 6 y de 6 a 12 meses de edad, la ingesta adecuada de calcio es de 200 y 260 mg/día, respectivamente. (1⊕⊕⊕)
- Para los niños mayores de 12 meses, la ingesta de calcio en la dieta < 300 mg/día aumenta el riesgo de raquitismo independientemente de los niveles séricos de 25OHD. (1⊕⊕)
- Para los niños mayores de 12 meses de edad, el panel recomienda la siguiente clasificación de ingesta dietética de calcio: (1⊕⊕)
- Suficiencia, >500 mg/d
- Insuficiencia, 300-500 mg/d
- Deficiencia, <300 mg / d

1.4.2. Evidencia

En los países en desarrollo donde la ingesta de calcio es característicamente muy baja, con pocos o ningún producto lácteo, la deficiencia de calcio en la dieta es la principal causa de RN entre los niños fuera del grupo de edad infantil.

En 2011, el IOM recomendó ingestas adecuadas de calcio para bebés, niños y adultos (16). La ingesta adecuada para los lactantes se basó en el contenido de calcio de la leche materna, que es de 200 mg/día y 260 mg/día para los bebés de 0 a 6 y de 6 a 12 meses de edad, respectivamente. Para los niños de 1 a 18 años de edad, el IOM estableció el requerimiento diario de calcio en 700-1300 mg/d, dependiendo de la edad (28). Sin embargo, no existe una definición verdadera de deficiencia de calcio en la dieta sin un biomarcador confiable del estado de ingesta de calcio, y hay pocos datos que indiquen cuál es el nivel más bajo de calcio para prevenir el RN. Informes de Nigeria, India y Bangladesh (6,30,40–43) destacaron el papel de la baja ingesta de calcio en la dieta en la patogenia del RN entre los niños. Aunque algunos de estos niños también tenían una 25OHD subóptima, otros tenían valores > 50 nmol/L, lo que apunta a la interacción entre el calcio y la vitamina D en la patogenia del RN (Figura 1). Estos estudios sugieren que en niños > 12 meses de edad, una ingesta



de calcio en la dieta < 300 mg/día aumenta significativamente el riesgo de RN independientemente de los niveles séricos de 25OHD, y que con una ingesta diaria >500 mg, no se observó RN.

1.5. Deficiencia de vitamina D y fracturas.

1.5.1. Recomendaciones

- Los niños con raquitismo radiográficamente confirmado tienen un mayor riesgo de fractura. (1⊕⊕○)
- Los niños con deficiencia simple de vitamina D no tienen mayor riesgo de fractura. (1⊕⊕○)

1.5.2. Evidencia

Según la evidencia de los estudios observacionales disponibles y los informes de casos, los niños con evidencia clínica, bioquímica y radiográfica de RN tienen un mayor riesgo de fractura. Un estudio retrospectivo encontró que las fracturas ocurrieron en siete de 45 (17.5%) bebés y niños pequeños con RN, con edades entre 2 y 14 meses (44). Sin embargo, las fracturas solo ocurrieron en aquellos que eran móviles y tenían evidencia radiográfica severa de raquitismo. Aunque ninguna de las fracturas se consideró característica de una lesión no accidental (maltrato infantil), dos bebés tenían fracturas costales laterales o anterolaterales. En una encuesta nacional en Canadá, 11 de 108 casos de RN (11%) habían sufrido fracturas, aunque no se proporcionaron detalles sobre los sitios óseos y el número de fracturas (1). También se han informado fracturas en casos o series de casos de RN en niños pequeños y adolescentes (45 a 50), pero no se dieron detalles sobre el número, el sitio y el tipo de fractura.

Se ha sugerido que las características radiográficas del raquitismo pueden confundirse con las características de una lesión no accidental (51, 52), pero faltaron los datos bioquímicos y radiográficos necesarios sobre los casos para la validación de las conclusiones de los autores. Además, los niveles séricos de 25OHD son similares en bebés con lesiones accidentales y no accidentales (53). Por tanto, la deficiencia simple de vitamina D, es decir, la deficiencia de vitamina D sin signos bioquímicos o radiológicos de raquitismo, no se ha asociado con un mayor riesgo de fracturas en lactantes y niños.



2.0. Prevención y tratamiento del raquitismo nutricional y la osteomalacia

2.1. Suplementos de vitamina D para la prevención del raquitismo y la osteomalacia

2.1.1. Recomendaciones

- 400 UI/d (10 g) es adecuado para prevenir el raquitismo y se recomienda para todos los bebés desde el nacimiento hasta los 12 meses de edad, independientemente de su modo de alimentación. (1⊕⊕⊕)

- Más allá de los 12 meses de edad, todos los niños y adultos deben cumplir con sus requisitos nutricionales de vitamina D a través de la dieta y/o suplementos, al menos 600 UI/día (15 g), según lo recomendado por el IOM. (1⊕⊕⊕)

2.1.2. Evidencia

Pocos estudios publicados han incluido la prevención de los signos clínicos o radiográficos del raquitismo como resultado. En consecuencia, también revisamos estudios que evaluaron el efecto de diferentes regímenes³ de suplementación con vitamina D sobre los niveles de 25OHD y otros parámetros óseos (como la densidad mineral ósea) con el objetivo de prevenir el RN manteniendo niveles por encima del rango raquítico, es decir, >30 nmol/L (54).

En lactantes y niños, 400 UI/d de vitamina D administradas como suplemento durante la infancia son suficientes para prevenir los signos radiográficos de raquitismo a corto plazo (hasta 12 meses) (54). Específicamente, un ECAs demostró que la suplementación de 400 UI/d de vitamina D era suficiente para prevenir los signos radiográficos del raquitismo a los 6 meses de edad, incluso entre los bebés nacidos con deficiencia de vitamina D (25). De manera similar, no se observaron casos de raquitismo confirmado radiográficamente después de la administración de 400 UI/d de vitamina D durante 12 meses, mientras que la incidencia fue del 3.8% en bebés y niños pequeños turcos que no recibieron suplementos (55). Además, no se informaron casos de raquitismo confirmado radiográficamente en un estudio de vigilancia de 2 años de lactantes canadienses que recibieron 400 UI/día de vitamina D (1). En todo el mundo, no ha habido informes de raquitismo confirmado radiográficamente en bebés o niños que reciben 400 UI de forma diaria y regular. Además, se ha demostrado en ECAs que esta dosis alcanza niveles de 25OHD con mayor frecuencia por encima del rango raquítico (deficiencia grave) en comparación con 100 o 200 UI/d (25).

También se revisó brevemente la prevención de la deficiencia de vitamina D en ausencia de RN. En un ECA, doble ciego, de lactantes sin deficiencia de vitamina D (25OHD > 50 nmol/L), se evaluó el impacto de 400, 800, 1200 y 1600 UI de vitamina D₃ por día (54). Las dosis de 400 UI/d mantuvieron los niveles de 25OHD >50 nmol/L en el 97% de los lactantes después de 12 meses; las dosis de 800 y 1200 UI/d no supusieron ningún beneficio adicional para los parámetros de densidad mineral ósea, y 1600 UI/d plantearon preocupaciones sobre la posible toxicidad. Un estudio en lactantes con deficiencia de vitamina D (25OHD < 25 nmol/L) encontró que una dosis única de 100.000 UI mantuvo los niveles de 25OHD por encima de 37,5 nmol/L durante 3 meses sin hipercalcemia, mientras que dosis más altas condujeron a niveles inaceptablemente altos de 25OHD (56).

Entre los bebés y niños pequeños con niveles de 25OHD < 50 nmol/L para quienes la suplementación diaria con vitamina D puede no ser ideal, las dosis en bolo intermitentes de 50 a 100 000 UI cada 3 meses son prometedoras, aunque se mantiene una comprensión integral de la seguridad y eficacia de este enfoque para ser estudiado.



2.2. Objetivo para la suplementación con vitamina D

2.2.1. Recomendación

- En niños sanos, no se recomienda la detección sistemática de 25OHD y, en consecuencia, no se ha fijado un umbral específico de 25OHD para la administración de suplementos de vitamina D en esta población. (1⊕⊕⊕)

2.2.2. Evidencia

Ningún estudio ha examinado específicamente el mejor enfoque de seguimiento una vez que se han administrado suplementos para prevenir el raquitismo por deficiencia de vitamina D. 25OHD es un parámetro de monitorización razonable para asegurar niveles > 30 a 34 nmol/L para la prevención de RN. Bioquímicamente, una caída en la concentración de 25OHD < 34 nmol/L se asocia con niveles crecientes de PTH, pero este punto de intersección depende de la ingesta de calcio predominante (7). La frecuente coexistencia de deficiencia de calcio en la dieta y de vitamina D altera el umbral para el desarrollo del raquitismo (57). De manera similar, monitorear las concentraciones de 25OHD como una política de salud pública para todas las personas no es práctico; afortunadamente, los grupos de alto riesgo se pueden identificar fácilmente en función del perfil clínico (Tabla 2).

2.3. Candidatos para la suplementación preventiva de vitamina D después de los 12 meses de edad

2.3.1. Recomendaciones

En ausencia de la fortificación de los alimentos, se deben administrar suplementos de vitamina D a:

- Niños con antecedentes de deficiencia sintomática de vitamina D que requieren tratamiento. (1⊕⊕⊕)
- Niños y adultos con alto riesgo de deficiencia de vitamina D con factores o condiciones que reducen la síntesis o la ingesta de vitamina D. (1⊕⊕⊕)
- Mujeres embarazadas (consulte la Sección 3.1).

2.3.2. Evidencia

La suplementación es una forma viable y aceptable de asegurar una ingesta adecuada de vitamina D independientemente de la nutrición (58). Las pautas de consenso para la suplementación con vitamina D se han elaborado a partir de una variedad de grupos pediátricos/endocrinos (16, 59-62). Aunque existen numerosos estudios sobre la deficiencia de vitamina D en poblaciones pediátricas y evaluaciones primarias de la eficacia de varios programas de suplementación de mujeres embarazadas, madres que amamantan, lactantes, niños y adolescentes, hay más opinión que evidencia sobre muchos aspectos de este tema. Sin embargo, existe evidencia sólida y de alta calidad de que la suplementación con vitamina D debe proporcionarse a los grupos de riesgo. Todos los grupos en riesgo (Tabla 2) son específicamente vulnerables y, en ausencia de fortificación de alimentos, requieren suplementación. La fortificación de la fórmula infantil con vitamina D está bien



establecida y recomendada por todos los países europeos, Australia, Nueva Zelanda y la Academia Estadounidense de Pediatría (60). La fortificación con vitamina D de las leches es obligatoria en Canadá, y la “leche enriquecida” se fortifica voluntariamente en los Estados Unidos (63). Los niños con enfermedades crónicas y afecciones que afectan la síntesis/absorción/metabolismo de la vitamina D también pueden beneficiarse de la suplementación y pueden requerir dosis más altas (58), pero no están dentro del ámbito de este consenso sobre RN.

Tabla 2. Factores de Riesgo para Raquitismo Nutricional y Osteomalacia y su prevención

Factores maternos

- Deficiencia de vitamina D
 - Pigmentación de piel oscura
 - Cobertura de todo el cuerpo con ropa
 - Latitud alta durante la temporada de invierno/primavera
 - Otras causas de exposición restringida al sol (UVB), por ejemplo, vida predominante en interiores, discapacidad, contaminación, nubosidad
 - Dieta baja en vitamina D
- Dieta baja en calcio
 - Pobreza, desnutrición, dietas especiales

Factores de lactancia/niñez

- Deficiencia neonatal de vitamina D secundaria a deficiencia materna/deficiencia de vitamina D
 - Falta de suplementación infantil con vitamina D
 - Lactancia materna prolongada sin alimentación complementaria adecuada a partir de los 6 meses
 - Latitud alta durante la temporada de invierno/primavera
 - Pigmentación oscura de la piel y/o exposición restringida al sol (UVB), por ejemplo, vida predominante en interiores, discapacidad, contaminación, nubosidad
 - Dieta baja en vitamina D
- Dieta baja en calcio
 - Pobreza, desnutrición, dietas especiales

Los factores de riesgo se previenen mediante:

- Exposición al sol (el contenido de UVB de la luz solar depende de la latitud y la estación)
 - Suplementos de vitamina D
 - Fortalecimiento estratégico del suministro habitual de alimentos
 - Ingesta normal de calcio
-

2.4. Dosis de vitamina D y calcio para el tratamiento del raquitismo nutricional

2.4.1. Recomendaciones

- Para el tratamiento del raquitismo nutricional, la dosis mínima recomendada de vitamina D es de 2000 UI/d (50 g) durante un mínimo de 3 meses. (1⊕⊕⊕)



- El calcio oral, 500 mg/d, ya sea como ingesta dietética o como suplementos, debe usarse de forma rutinaria junto con la vitamina D en el tratamiento, independientemente de la edad o el peso. (1⊕⊕⊕)

2.4.2. Evidencia

La mayoría de los estudios afirman que las diferentes dosis comúnmente empleadas para tratar la deficiencia de vitamina D son seguras, observándose hipercalcemia y/o hipercalciuria como efecto secundario solo en unos pocos individuos y generalmente se observa en el rango de 300 000 a 600 000 UI (64). En un pequeño estudio de niños con RN (n = 17), dosis de 1700 a 4000 UI de vitamina D2 aumentaron rápidamente las concentraciones de 25OHD en 1 semana y normalizaron los niveles de calcio, fosfato y FA a las 10 semanas (65). Los niños de 2 a 36 meses con RN (n = 19), 5000 a 10 000 UI de vitamina D3 oral y calcio de 0,5 a 1,0 g diarios normalizaron PTH, calcio y fosfato séricos en 3 semanas, aunque los niveles de FA permanecieron elevados (66).

La administración simultánea de calcio con vitamina D parece ser adecuada y recomendada por varios estudios (67,68). En 123 niños nigerianos con RN debido a deficiencia de calcio, el objetivo combinado de nivel de FA < 350 U/L y evidencia radiográfica de curación casi completa del raquitismo se observó en un porcentaje más alto de pacientes que recibieron una combinación de calcio y vitamina D (58%) o calcio solo (61%) que en aquellos que recibieron vitamina D sola (19%) (5). De manera similar, en 67 niños indios con RN debido a una deficiencia combinada de calcio y vitamina D, se observó una curación completa a las 12 semanas en un porcentaje más alto con la terapia combinada (50%) que con vitamina D (15,7%) o calcio solo (11,7%). (30). El tratamiento combinado se justifica porque los estudios han demostrado que la dieta de los niños y adolescentes con RN es generalmente baja tanto en vitamina D como en calcio (5,6,30,69).

2.5. Vía apropiada de administración y duración del tratamiento.

2.5.1. Recomendaciones

- Recomendamos el tratamiento oral, el cual restaura los niveles de 25OHD más rápidamente que el tratamiento IM. (1⊕⊕⊕)
- Para el tratamiento diario, tanto D2 como D3 son igualmente efectivos. (1⊕⊕⊕)
- Cuando se utilizan dosis grandes únicas, D3 parece ser preferible en comparación con D2 porque el primero tiene una vida media más larga. (1⊕⊕⊕)
- Se recomienda el tratamiento con vitamina D durante un mínimo de 12 semanas, reconociendo que algunos niños pueden requerir una duración de tratamiento más prolongada. (1⊕⊕⊕)

2.5.2. Evidencia

Algunos estudios compararon la administración intramuscular y oral de vitamina D, pero la mayoría de estudios fueron realizados en adultos y, por lo tanto, pueden no ser del todo relevantes para los niños con RN. Se administró vitamina D oral o IM a 24 voluntarios normales (de 50 a 78 años de



edad) en una dosis de 600 000 UI de D2 o D3 (70). Se observaron niveles máximos de 25OHD a los 30 y 120 días en los que recibieron tratamiento oral e intramuscular, respectivamente. Otro estudio en 92 adultos con 25OHD < 75 nmol/L comparó 300 000 UI de vitamina D3 IM con 50 000 UI de D3 administradas por vía oral en seis ocasiones durante 3 meses (71). Una mayor proporción de sujetos que recibieron tratamiento oral tuvieron 25OHD > 75 nmol/L a los 3 y 6 meses que los sujetos que recibieron IM.

Un ECA en 61 niños con RN comparó una dosis única IM de 600 000 UI de vitamina D3 con una dosis oral semanal de 60 000 UI D3 durante 10 semanas (72). No hubo diferencias a la 1, 4 y 12 semanas entre los grupos en lo referente a perfil óseo, concentraciones de 25OHD o efectos secundarios. Un metaanálisis de estudios que compararon la administración de vitamina D2 y D3 concluyó que, cuando se administraba en forma de bolo, la vitamina D3 era más eficaz para aumentar las concentraciones de 25OHD, pero no se observaron diferencias significativas con las dosis diarias (73).

No hay ECAs sobre la duración del tratamiento para niños con RN, y la mayor parte de la literatura consiste en artículos de revisión. La revisión encargada por el SPE recomienda que el tratamiento oral diario se administre durante 8 a 12 semanas (74). En revisiones del Reino Unido se recomiendan duraciones similares de entre 8 y 12 semanas de tratamiento diario (75, 76). En la declaración de consenso de Australia y Nueva Zelanda se recomienda una duración de 3 meses (77). Dada la evidencia limitada, se recomienda una duración mínima del tratamiento de 12 semanas para lograr una curación integral y la normalización de la FA, reconociendo que algunos niños pueden requerir un tratamiento más prolongado.

Varios estudios exploraron el concepto de "terapia stoss", es decir, la administración de una gran dosis dada en una sola dosis o en dosis divididas durante varios días. Se ha recomendado este enfoque para facilitar el uso y el cumplimiento de la terapia. Tres dosis orales únicas diferentes (150 000, 300 000 o 600 000 UI) en 56 niños turcos de 3 a 36 meses con RN no afectaron la tasa de mejora del raquitismo a los 30 días (64).

Sin embargo, ocho sujetos (dos en el grupo de 300 000 UI, seis en el grupo de 600 000 UI) desarrollaron hipercalcemia. Un estudio reciente en la India comparó dosis orales únicas de 300 000 frente a 600 000 UI de vitamina D3 en 76 niños con raquitismo de 6 meses a 5 años (78). A las 12 semanas, todos los niños demostraron curación radiográfica con disminuciones comparables en FA y PTH. Sin embargo, se produjo hipercalcemia en cinco niños (6,5%) - dos recibieron 300 000 UI y tres recibieron 600 000 UI. Varios artículos de revisión abogan por diferentes recomendaciones con la "terapia de stoss" que no están respaldadas por evidencia (75-77). Los pocos estudios que compararon el tratamiento diario con la "terapia de stoss" incluyeron grupos con diferentes características de los sujetos. Aunque recomendamos el tratamiento diario como primera línea de tratamiento, reconocemos que, en algunas situaciones, la terapia de stoss puede ser más práctica. Por lo tanto, proporcionamos recomendaciones de dosis de vitamina D para ambas opciones de tratamiento (Tabla 3). Cualquier tratamiento debe ir seguido de un suplemento (consulte las secciones 2.1 y 2.3).



Tabla 3: Dosis de tratamiento de vitamina D para el raquitismo nutricional

Edad	Dosis diaria por 90 días, IU	Dosis única, IU	Dosis diaria de mantenimiento, IU
< 3 meses	2000	N/A	400
3 – 12 meses	2000	50 000	400
>12 meses a 12 años	3000 – 6000	150 000	600
>12 años	6000	300 000	600

Abreviatura: N/A, no disponible. Reevalúe la respuesta al tratamiento después de 3 meses ya que puede ser necesario un tratamiento adicional. Asegúrese de una ingesta diaria de calcio de al menos 500 mg. Para la conversión de UI a µg, dividir entre 40.

3.0. Prevención del raquitismo nutricional/osteomalacia: identificación de factores de riesgo

3.1. Prácticas dietéticas e ingesta de nutrientes en las madres asociadas con el raquitismo nutricional en los lactantes

3.1.1. Recomendaciones

- Debe evitarse la deficiencia materna de vitamina D asegurándose de que las mujeres en edad fértil alcancen la ingesta de 600 UI/d recomendada por el IOM. (1⊕⊕⊕)
- Las mujeres embarazadas deben recibir 600 UI/d de vitamina D, preferiblemente como preparación combinada con otros micronutrientes recomendados como hierro y ácido fólico. (2⊕⊕⊕)

3.1.2. Evidencia

La dieta materna y la ingesta de nutrientes como predictor del raquitismo infantil no se han abordado en la literatura como una hipótesis a priori. Sin embargo, los datos disponibles se han recopilado durante estudios de intervención con vitamina D, estudios de casos o series de casos en mujeres durante el embarazo.

Muchos casos de RN incluyeron datos sobre la 25OHD materna y, en algunos casos, información dietética (79–81). La deficiencia neonatal de vitamina D siempre es causada por la deficiencia materna y puede tener consecuencias potencialmente mortales, como convulsiones hipocalcémicas y miocardiopatía dilatada en bebés no suplementados (11). La hipocalcemia (ver Sección 4.1.2) u otros signos bioquímicos tempranos de raquitismo (como FA y PTH elevados) están presentes antes de que aparezcan los signos radiográficos de RN en recién nacidos y lactantes no suplementados (82, 83). Un alto porcentaje de madres de lactantes con deficiencia sintomática de vitamina D pertenecen a grupos de alto riesgo deficientes de vitamina D y que amamantan exclusivamente (11, 24, 83-85).



En una serie de casos canadiense, seis bebés de las Primeras Naciones presentaron convulsiones hipocalcémicas en los primeros 30 días de vida, con deficiencia de vitamina D materna presunta o confirmada y falta de suplementación durante el embarazo (86). Todos fueron alimentados con fórmula, lo que sugiere que, aunque su ingesta de vitamina D habría sido suficiente en circunstancias normales, en estos bebés el suministro oral de vitamina D a través de la leche de fórmula fue insuficiente para tratar su deficiencia neonatal grave preexistente.

La prevención de la deficiencia materna es fundamental, y todas las madres deben cumplir con su requerimiento nutricional de vitamina D, que actualmente se establece en 600 UI/d, aunque este valor no se basa en evidencia directa de ECA sobre suplementación con vitamina D en mujeres embarazadas (28). Es posible que se requiera una mayor ingesta de vitamina D para prevenir la deficiencia tanto materna como neonatal (87). La prevención de la deficiencia congénita de vitamina D se describe en la Sección 4.4.

3.2. Alimentación temprana, suplementación, alimentación complementaria e ingesta de nutrientes asociados con RN en lactantes

3.2.1. Recomendaciones

- Además de una ingesta de 400 UI/d de vitamina D, los alimentos complementarios introducidos antes de las 26 semanas deben incluir fuentes ricas en calcio. (1⊕⊕⊕)
- Debe asegurarse una ingesta de al menos 500 mg/d de calcio elemental durante la infancia y la adolescencia. (1⊕⊕⊕)

3.2.2. Evidencia

Existe evidencia abundante, aunque de baja calidad, de múltiples informes de casos, series de casos (11, 48, 49, 88) y estudios observacionales (1, 2, 45, 50, 85, 89-99) que indican que la lactancia materna exclusiva sin la suplementación con vitamina D es un factor de riesgo importante de RN en los bebés. Además, la lactancia materna prolongada con la introducción tardía de la alimentación complementaria se asocia con RN en los lactantes que no reciben suplementos de vitamina D (26,100-105). Numerosos datos de observación (55,106-111) y un ECA (25) sugieren que los lactantes que reciben suplementos de vitamina D durante el primer año de vida no tienen riesgo de desarrollar RN. La evidencia para proporcionar 400 UI/d de vitamina D a los lactantes se presenta en la Sección 2.1.

La evidencia principalmente de países en desarrollo demuestra que la dieta tradicional baja en calcio causa RN (30, 43, 69, 93, 112-114). Por lo tanto, las dietas especiales durante la infancia, como las que evitan la leche y los productos lácteos, las que usan leche de soja o de arroz que no están diseñadas específicamente para bebés y/o las dietas veganas y macrobióticas, pueden predisponer a los bebés a RN (115-120). Las recomendaciones sobre la ingesta suficiente de calcio se presentan en la Sección 1.4.



3.3. Asociación de la exposición a la luz solar con el raquitismo nutricional

3.3.1. Recomendaciones

- Debido a que los rayos UVB desencadenan la síntesis epidérmica de pro vitamina D3, la exposición restringida al sol aumenta el riesgo de deficiencia de vitamina D y raquitismo nutricional (1⊕⊕⊕)
- Los factores ambientales como la latitud, la estación, la hora del día, la nubosidad y la contaminación afectan la disponibilidad de UVB, mientras que factores personales como el tiempo al aire libre, la pigmentación de la piel, la cobertura de la piel, la edad, la composición corporal y la genética afectan la dosis-respuesta a la exposición a los rayos UVB y a la 25OHD circulante. (2⊕⊕O)
- Ningún umbral seguro de exposición a los rayos UV permite una síntesis suficiente de vitamina D en la población sin aumentar el riesgo de cáncer de piel. (2⊕⊕O)

3.3.2. Evidencia

La radiación solar (banda UVB de 290 a 315 nm) estimula la síntesis de pro vitamina D a partir del 7-deshidrocolesterol epidérmico, que se isomeriza a colecalciferol y posteriormente se metaboliza a 25OHD. La exposición al sol aumenta la 25OHD circulante (121-123). Suponiendo la disponibilidad de UVB, la capacidad de un individuo para sintetizar vitamina D aumenta con una exposición epidérmica más prolongada. Sin embargo, la exposición puede verse afectada por factores ambientales como la latitud, la altitud, la estación, la hora del día, la nubosidad y la calidad del aire (123-129), así como por factores personales como la ocupación, el estilo de vida, la cultura como la vestimenta y las preferencias, lo que puede modificar el tiempo que se pasa al aire libre y/o la superficie de la piel expuesta a la luz solar (130-133). Finalmente, la dosis-respuesta de la 25OHD circulante a la exposición cutánea a los rayos UVB depende de la pigmentación de la piel, la edad, la composición corporal, los factores genéticos y los niveles basales de 25OHD, entre otros (121, 131, 134-138).

Numerosos datos de observación global informan de una asociación entre la exposición epidérmica restringida y el RN como consecuencia de la deficiencia de vitamina D (85, 139-143). La radiación ultravioleta causa cáncer de piel y la exposición a la radiación ultravioleta de la luz solar y fuentes artificiales en una etapa temprana de la vida eleva el riesgo de desarrollar cáncer de piel (144). Sin pruebas firmes que expliquen las variaciones de edad, color de la piel, latitud, hora del día y época del año, actualmente no es práctico proporcionar consejos prescriptivos sobre la exposición solar segura a la población en general. Todos los factores de riesgo se resumen en la Tabla 2.

4.0. Prevención de la Osteomalacia durante el embarazo y la lactancia y Raquitismo Congénito

4.1. La relación entre la vitamina D durante el embarazo y el crecimiento infantil y la masa ósea

4.1.1. Recomendaciones



- Las mujeres embarazadas deben recibir 600 UI/d de vitamina D suplementaria. Esto asegurará la suficiencia de la 25OHD materna, especialmente en mujeres con riesgo de deficiencia, para prevenir la FA elevada en sangre del cordón umbilical, aumento del tamaño de la fontanela, hipocalcemia neonatal y raquitismo congénito, y mejorar la formación del esmalte dental. (2⊕⊕○)
- Hay poca evidencia de que la suplementación materna con vitamina D protegerá o mejorará la antropometría del nacimiento (2⊕○○), y no hay evidencia de que la suplementación con vitamina D proteja o mejore el crecimiento a corto o largo plazo o la acumulación de masa ósea. (2⊕⊕○)

4.1.2. Evidencia

Existe evidencia moderada de que el nivel bajo de vitamina D materna durante el embarazo se asocia con FA elevada en sangre del cordón y un tamaño de fontanela más grande al nacer (145, 146). Evidencia moderada a fuerte de dos ECAs (145,147), dos ensayos controlados (148, 149) y un estudio observacional (150) indicaron que el estado bajo de vitamina D materna durante el embarazo aumenta el riesgo de hipocalcemia neonatal; sin embargo, un ECA más pequeño y un ensayo controlado no respaldaron estos hallazgos (146,151). Un único ensayo controlado grande sugiere que la suplementación con vitamina D durante el embarazo mejora la formación del esmalte dental en la descendencia (148).

Hay datos contradictorios sobre la asociación entre el estado de vitamina D de la madre durante el embarazo y la antropometría del nacimiento. Tres ECA de calidad moderada a alta con dosis diarias o regímenes de dosis alta única no encontraron una asociación (151-153), mientras que dos ensayos controlados de evidencia de grado moderado encontraron una asociación positiva (146,147).

Tres ECA de calidad baja a alta no encontraron ninguna diferencia en la antropometría del nacimiento en la descendencia de madres suplementadas con 400, 2000 o 4000 UI/d; ninguno de los estudios tuvo un grupo placebo (87, 154, 155).

Hay datos inconsistentes sobre la asociación entre los niveles de 25OHD en suero materno y el crecimiento lineal durante el primer año de vida (152, 157, 162) y evidencia insuficiente o débil para una asociación entre los niveles de 25OHD en suero materno y la masa o densidad ósea al nacer (150, 158-161) o en la niñez tardía (162-164).

4.2. El efecto de la suplementación con calcio durante el embarazo sobre la masa ósea infantil

4.2.1. Recomendación

- Las mujeres embarazadas no necesitan ingestas de calcio, por encima de las recomendadas para no embarazadas, para mejorar el hueso neonatal. (1⊕⊕⊕)



4.2.2. Evidencia

Los estudios de suplementación con calcio durante el embarazo no han tenido como resultado objetivo el raquitismo congénito o neonatal, pero tres ECAs de suplementación con calcio materno durante el embarazo midieron el hueso neonatal (165-167). Estos ECAs se realizaron en África occidental, donde la ingesta típica de calcio en la dieta es de 250 a 300 mg/d (165), en los Estados Unidos con una ingesta promedio de aproximadamente 2000 mg/d (166) y en un estudio multicéntrico de la Organización Mundial de la Salud en poblaciones con una ingesta dietética de calcio de aproximadamente 600 mg/día (Argentina, Perú, India, Egipto, Vietnam, Sudáfrica) (167). La suplementación con calcio materno no tuvo ningún efecto sobre la evaluación mineral ósea neonatal medido por absorciometría de rayos X de energía dual en los estudios de Gambia y EE. UU., excepto en el último estudio en la descendencia de mujeres en el quintil más bajo de ingesta de calcio en la dieta (<600 mg/d). No hubo ningún efecto de la suplementación con calcio materno en la antropometría neonatal o infantil, un hallazgo consistente con los estudios observacionales.

4.3. Influencia de la suplementación con calcio o vitamina D durante el embarazo o la lactancia sobre el calcio o vitamina D de la leche materna

4.3.1. Recomendaciones

- Las mujeres que amamantan deben asegurarse de cumplir con las recomendaciones dietéticas de vitamina D (600 UI/día) para sus propias necesidades, pero no para las necesidades de su bebé (1⊕⊕⊕).
- Las mujeres que amamantan no deben tomar grandes cantidades de vitamina D como un medio para complementar a su bebé. (2⊕⊕⊕)
- Las mujeres embarazadas y que amamantan deben cumplir con la ingesta recomendada de calcio. La ingesta materna de calcio durante el embarazo o la lactancia no está asociada con las concentraciones de calcio en la leche materna. (1⊕⊕⊕)

4.3.2. Evidencia

La ingesta materna de vitamina D durante la lactancia se correlaciona con la actividad de la vitamina D de la leche. Varios ECAs doble ciego encontraron que las ingestas maternas elevadas de vitamina D (2000, 4000 y 6400 UI/d) se asociaron con una mayor concentración de vitamina D en la leche materna (Figura 2) (168-171).

Se ha sugerido complementar a las madres con altas cantidades de vitamina D como un medio para aumentar las concentraciones séricas de 25OHD tanto en la madre (Figura 3) como en el bebé (172-175). Es probable que la ingesta materna de vitamina D de hasta 4000 UI/d sea segura durante el embarazo y la lactancia (16). Sin embargo, el hallazgo de que los bebés de madres suplementadas con 2000 UI/d o más tienen concentraciones séricas de 25OHD similares a las de los bebés que reciben 400 UI/d (Figura 4), así como preocupaciones de seguridad, y nuestra propia recomendación de que todos los bebés reciban 400 UI de vitamina D por día nos lleva a recomendar que las madres deben tomar las cantidades recomendadas (600 UI/d) en lugar de dosis más altas de vitamina D.



La ingesta materna de calcio durante el embarazo o la lactancia no influye en las concentraciones de calcio de la leche materna. Solo un estudio observacional encontró una asociación débil entre la ingesta materna de calcio durante el embarazo y el nivel de calcio de la leche materna en el día 40 (leche madura) (176). Numerosos estudios, incluidos dos ECAs (177, 178) y dos estudios observacionales (179, 180) no han encontrado una relación entre la ingesta materna de calcio y las concentraciones de calcio en la leche materna. Ningún estudio ha investigado el efecto de la ingesta materna de vitamina D durante el embarazo sobre las concentraciones de calcio de la leche o de vitamina D. Dos ECAs doble ciego encontraron que la concentración de 25OHD en suero materno o la ingesta materna de vitamina D (hasta 4000 UI / día) durante la lactancia fue no asociado con las concentraciones de calcio en la leche (181, 182).

4.4. Causas y terapia del raquitismo congénito.

4.4.1. Recomendación

- Suplementar a las madres con 600 UI/d de vitamina D y asegurarse de que reciban la ingesta recomendada de calcio, o la terapia adecuada de las afecciones maternas que predisponen a la hipocalcemia o la deficiencia de vitamina D, previene el raquitismo congénito. (2⊕00)

4.4.2. Evidencia

Aproximadamente 80 casos de raquitismo congénito, definido como bebés que se presentan dentro de las primeras 4 semanas de vida con signos bioquímicos y radiográficos de raquitismo, se han descrito en la literatura médica. Por lo general, las madres de bebés con raquitismo congénito tienen osteomalacia con deficiencia grave de vitamina D, bajo consumo de calcio e hipocalcemia en el momento del parto y no habían tomado suplementos de vitamina D durante el embarazo (83, 183-197). En casos raros, el raquitismo congénito puede ocurrir cuando las madres han tenido hipocalcemia prolongada grave no causada principalmente por deficiencia de vitamina D, como hipoparatiroidismo mal tratado (198-201), insuficiencia renal (202-206), recibieron enemas que contienen fosfato (207), o hipermagnesemia iatrogénica (208).

Los mecanismos para el desarrollo del raquitismo congénito siguen siendo poco conocidos, especialmente cómo el disminuido suministro de calcio materno, como la anomalía materna primaria común en todos los casos, afecta la mineralización fetal. Claramente, el raquitismo congénito solo ocurre en situaciones metabólicas extremas. Es justo afirmar que todos los casos notificados de raquitismo congénito podrían haberse evitado mediante la suplementación de vitamina D, la ingesta normal de calcio durante el embarazo y la terapia adecuada de las afecciones maternas asociadas con hipocalcemia prolongada o deficiencia de vitamina D. La evidencia es muy limitada sobre la terapia para el raquitismo congénito, pero el raquitismo generalmente responde a la vitamina D con o sin suplementos de calcio.



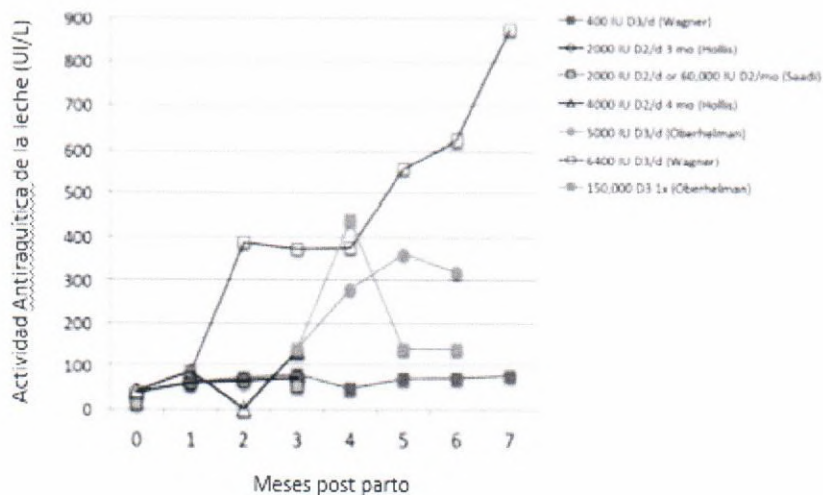


Figura 2. Los RCTs doble ciego han demostrado que la ingesta materna de 1000 a 6400 UI/día de vitamina D se asocia con un aumento de las concentraciones de vitamina D en la leche materna (156, 168, 169, 171). Las líneas de color similar representan el mismo estudio, y la leyenda proporciona la dosis de suplemento de vitamina D (UI/d, a menos que se indique lo contrario). Oberhelman y col. (171) informaron concentraciones de colecalciferol en la leche solamente.

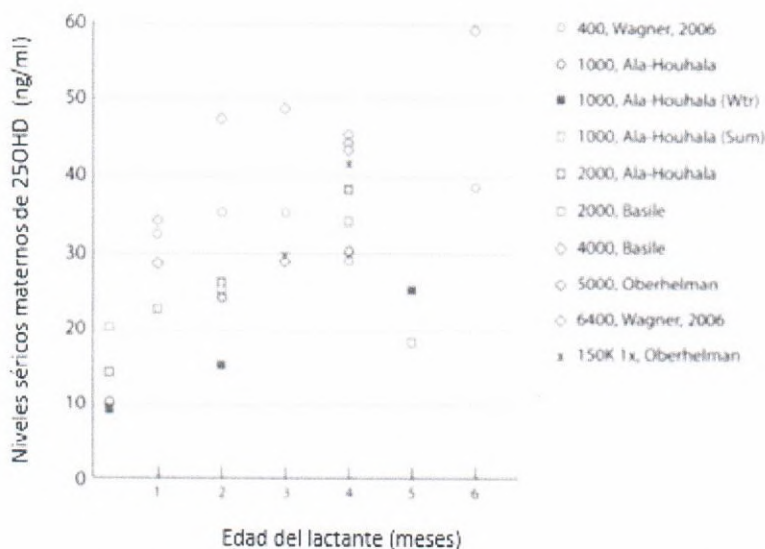


Figura 3. Los RCTs doble ciego han demostrado que las concentraciones de 25OHD en suero materno aumentan con la suplementación con vitamina D (169, 171, 174, 182). La mayoría de los ensayos comenzaron la suplementación poco después del nacimiento. Los marcadores de color similar representan el mismo estudio, y la leyenda proporciona la dosis de suplemento de vitamina D en UI/d, a menos que se indique lo contrario. 1 ng/ml $\approx$ 2.5 nmol/L. Wtr, invierno; Sum, verano.



5.0. Evaluación del impacto del raquitismo nutricional y estrategias de salud pública para su prevención

5.1. Evaluación del impacto en la morbilidad

5.1.1. Recomendaciones

- La prevalencia del raquitismo debe determinarse mediante muestras basadas en la población, informes de casos de centros centinela o informes obligatorios. (1⊕⊕⊕)
- El cribado del raquitismo nutricional debe basarse en las características clínicas, seguido de la confirmación radiográfica de los casos sospechosos. (1⊕⊕⊕)
- No está indicado el cribado poblacional con 25OHD sérico, FA sérica o radiografías. (1⊕⊕⊕)

5.1.2. Evidencia

El RN se ha reportado cada vez más en países de ingresos altos y bajos (55, 209-213). Utilizando una metodología diferente, la incidencia de RN ha sido reportado como 2.9, 4.9, 7.5 y 24 por 100 000 en Canadá (1), Australia (2), el Reino Unido (3) y los Estados Unidos (99), respectivamente. Muchos estudios se basan en hospitales, pero brindan información adicional sobre el impacto del RN. Los bebés con RN pueden presentar convulsiones hipocalcémicas. Se desconoce la incidencia de la miocardiopatía dilatada asociada con RN e hipocalcemia, pero es potencialmente la complicación más mortal y económicamente más costosa del RN (11). Los métodos utilizados para el diagnóstico de RN en reporte de casos (102) y series de casos pequeñas a grandes (104, 214-217) son muy variables y muchos carecen de confirmación radiográfica (209). Las encuestas realizadas por médicos pueden estimar el impacto de la enfermedad, pero se han realizado pocas (1, 2). Los estudios basados en la población proporcionan la evaluación más precisa de la importancia de esta enfermedad (3, 99, 211, 218-221). A pesar de las diferentes metodologías, los informes publicados indican que el mayor impacto del RN se encuentra en África, Asia y Oriente Medio debido a la evitación del sol o la insuficiencia de calcio en la dieta (209, 213).

Incluso los países de ingresos altos han observado un resurgimiento del RN, principalmente entre inmigrantes de origen africano, asiático o del Medio Oriente. Este aumento general de la incidencia del RN en los países de ingresos altos corresponde a un aumento en el número de individuos de minorías étnicas, inmigrantes y grupos de refugiados (1-4, 99, 222). La incidencia entre las poblaciones caucásicas establecidas es estable o está disminuyendo. En regiones con una prevalencia baja de RN, la inclusión de RN como una enfermedad notificable es potencialmente el medio más rentable de identificación y vigilancia de casos (1, 2, 4, 99, 222).

La medición de la 25OHD sérica es útil para el diagnóstico de deficiencia de vitamina D en RN, pero no para el cribado poblacional (223,224). La FA sérica elevada se ha utilizado como herramienta de detección de RN (225). Sin embargo, la enfermedad aguda, los fármacos, la enfermedad hepática, los brotes de crecimiento y la hiperfosfatemia transitoria de la infancia y la niñez pueden elevar los valores de FA. Debido a la invasividad de la venopunción, el alto costo y los bajos valores predictivos positivos, la FA y la 25OHD sérica no pueden recomendarse para el cribado poblacional. Aunque las radiografías de muñecas y rodillas confirman definitivamente el raquitismo activo (226), la exposición a la radiación impide recomendar radiografías de detección en niños asintomáticos.



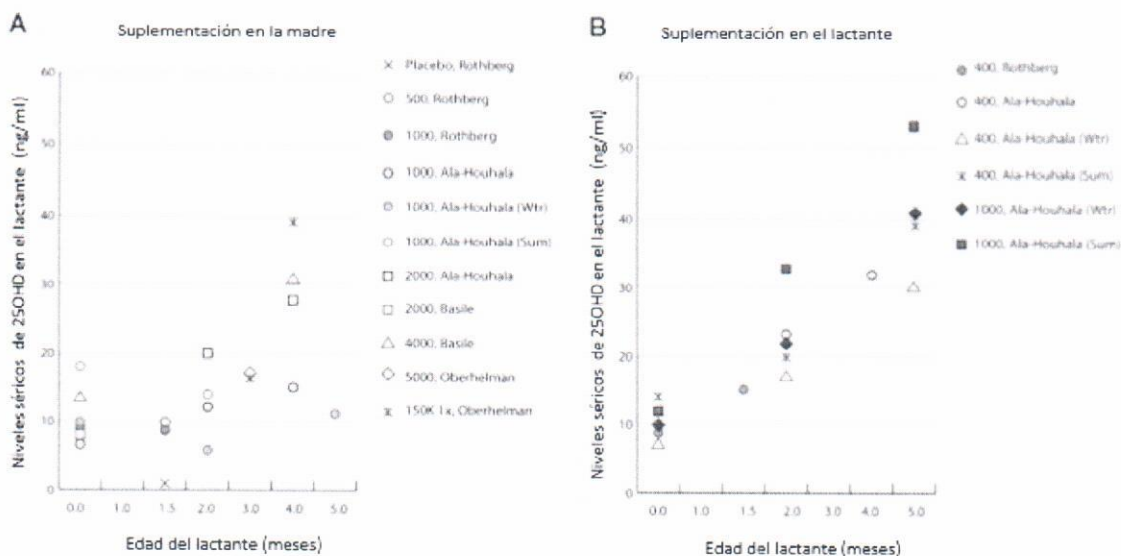


Figura 4. Concentraciones de 25OHD en suero infantil por edad en RCT en los que la madre recibió un suplemento de vitamina D (A) o el lactante (B) (171,173-175-182). Los marcadores de color similar representan el mismo estudio, y la leyenda proporciona la dosis de suplemento de vitamina D en UI/d, a menos que se indique lo contrario. 1 ng/ml $\approx$ 2.5 nmol/L. Wtr, invierno; Sum, verano.

5.2. Estrategias de salud pública para la prevención del raquitismo

5.2.1. Recomendación

- Complementar universalmente a todos los bebés con vitamina D desde el nacimiento hasta los 12 meses de edad, independientemente de su modo de alimentación. Más allá de los 12 meses, complementar todos los grupos de riesgo y mujeres embarazadas. Los suplementos de vitamina D deben incorporarse en los programas de atención primaria de salud infantil junto con otros micronutrientes e inmunizaciones esenciales (1⊕⊕⊕), y en los programas de atención prenatal junto con otros micronutrientes recomendados. (2⊕⊕⊕)
- Reconocer el raquitismo nutricional, la osteomalacia y las deficiencias de vitamina D y calcio como problemas de salud pública mundial prevenibles en bebés, niños y adolescentes. (1⊕⊕⊕)
- Implementar programas de prevención del raquitismo en poblaciones con alta prevalencia de deficiencia de vitamina D o ingesta limitada de vitamina D y/o calcio y en grupos de lactantes y niños con riesgo de raquitismo. (1⊕⊕⊕)
- Monitorear el cumplimiento de las ingestas recomendadas de vitamina D y calcio e implementar la vigilancia del raquitismo nutricional. (1⊕⊕⊕)
- Fortificar los alimentos básicos con vitamina D y calcio, según corresponda, según los patrones dietéticos. El enriquecimiento de los alimentos puede prevenir el raquitismo y mejorar el estado de vitamina D en lactantes, niños y adolescentes si se utilizan los alimentos adecuados y se proporciona el enriquecimiento suficiente, si el enriquecimiento está respaldado por la legislación pertinente y si el proceso se supervisa adecuadamente. Las fuentes alimentarias autóctonas de calcio deben promoverse o subvencionarse en los niños. (1⊕⊕⊕)



- Promover abordar el impacto en la salud pública de la deficiencia de vitamina D como un problema tanto clínico como de salud pública. (1⊕⊕⊕)

5.2.2. Evidencia

Suplementos de vitamina D

Los lactantes de 0 a 12 meses y los adolescentes tienen un mayor riesgo de RN y osteomalacia por deficiencia de vitamina D debido al rápido crecimiento. La vitamina D se encuentra en una cantidad limitada de alimentos y la ingesta dietética, aparte de los alimentos fortificados, tiene poco impacto en el estado general de vitamina D. Los programas que ofrecen suplementos de micronutrientes proporcionan la mejora más rápida en el estado de los micronutrientes de las personas o las poblaciones objetivo (227,228).

Fortificación de alimentos con vitamina D

La fortificación alimentaria de los alimentos básicos de consumo habitual proporciona de forma segura una ingesta adecuada para prevenir la deficiencia a un costo mínimo. La fortificación obligatoria de los alimentos básicos con vitamina D y calcio garantiza la adecuación nutricional (229). Después de la fortificación con vitamina D de la leche en América del Norte y de la leche, la margarina y los cereales en el Reino Unido, la prevalencia de RN disminuyó drásticamente, tanto que se consideró casi erradicada (16, 63, 228).

Los estudios en adultos y niños destacan la necesidad de que los alimentos apropiados (230) estén adecuadamente fortificados y sean consumidos por los segmentos de la población en riesgo (231) para que la ingesta de vitamina D de la mayoría de los miembros de una población se acerque a las recomendaciones dietéticas (232, 233). Debido a que la fortificación de alimentos ricos en calcio con vitamina D es óptima para la salud ósea, los productos lácteos comúnmente se fortifican. En los países donde los productos lácteos no se consumen ampliamente, la harina, la margarina, el aceite de cocina o los alimentos a base de soja pueden enriquecerse con vitamina D.

Aunque varios estudios han evaluado la eficacia de la fortificación de alimentos con vitamina D para aumentar las concentraciones de 25OHD en diferentes grupos de edad y comunidades, relativamente pocos estudios de fortificación se han dirigido a niños. Una revisión sistemática y un metaanálisis concluyeron a partir de ECAs basados en alimentos que los alimentos enriquecidos con vitamina D aumentan la 25OHD sérica y reducen la prevalencia de la deficiencia (<30 nmol/L) en adultos, siempre que se elijan los vehículos apropiados en función del análisis de la dieta habitual (234). La fortificación de la harina del pan chupatty* (6000 UI/kg) elevó la 25OHD de aproximadamente 12,5 nmol/L a aproximadamente 48 nmol/L en niños durante un período de 6 meses (235). Se estimó que la fortificación de la leche líquida y la margarina aumentaba la ingesta de vitamina D en niños de 4 años de 176 a 360 UI/d (4,4 a 9 g/d) y concentraciones de 25OHD de 55 a 65 nmol/L (236). La fortificación de la leche también ha sido una estrategia exitosa para mejorar el estado de vitamina D de los escolares en la India (237). Los requisitos de fortificación y suplementación pueden variar con la exposición de la población a la luz solar (consulte la Sección 3) (238).

*chupatty: pan sin levadura de Nepal, Bangladesh, India y Pakistán (sur de Asia)



Fortificación de alimentos con calcio

La ingesta inadecuada de calcio en la dieta es un factor de riesgo de RN en niños mayores de 12 meses con una ingesta baja de productos lácteos, una situación común en los países de bajos ingresos. El IOM recomienda una ingesta de calcio de 500 mg/d en niños de 1 a 3 años cuando los niños tienen mayor riesgo de RN, basados en la retención de calcio en los estudios de absorción (16). En poblaciones con bajo consumo de lácteos, como en África y partes de Asia, las fuentes alimentarias autóctonas de calcio o la fortificación de alimentos básicos con calcio pueden proporcionar una ingesta adecuada de calcio en los niños (213,239). Las sales de calcio se pueden usar para fortalecer las fórmulas infantiles, los alimentos complementarios y los alimentos básicos en áreas donde la ingesta de lácteos es baja. El carbonato de calcio para la fortificación de alimentos está disponible a muy bajo costo (227).

La fortificación de alimentos aumentó de manera efectiva la ingesta de calcio en la dieta mediante el uso de laddoos* fortificados con calcio en la dieta de niños pequeños indios desfavorecidos (240) y mediante la fortificación de cereales con calcio para niños de 7 a 12 años (241). Más de 1100 alimentos están fortificados con calcio en los Estados Unidos, sin embargo, los productos lácteos representan más del 65% de la ingesta de calcio de los adolescentes (242). En el Reino Unido, la fortificación de la harina con calcio es una fuente importante de ingesta de calcio (16% del total) para las adolescentes jóvenes (243). Hay datos limitados de estudios sobre la fortificación con calcio o la aceptabilidad de la diversificación de la dieta para incluir localmente disponible y asequible alimentos ricos en calcio en los países en desarrollo. El monitoreo periódico de RN es importante para determinar la efectividad de los programas de fortificación y/o suplementación en la prevención de RN.

*laddoos: es un dulce en forma de esfera que se origina en el subcontinente indio

Promoción de la salud

La educación de los proveedores y las organizaciones médicas, las aseguradoras de salud, los responsables de la formulación de políticas, los gobiernos, los funcionarios de salud pública y el público en general es vital para abordar el problema de salud pública del RN y la deficiencia de vitamina D. Se les debe proporcionar pautas sobre la importancia de una ingesta adecuada de vitamina D y calcio en niños, adolescentes y mujeres embarazadas y lactantes (244). Las estrategias nacionales y mundiales de promoción de la salud pública son esenciales para aumentar la conciencia de los profesionales y la comunidad, y es imperativa la acción mundial para proteger a todos los niños de la deficiencia de vitamina D y calcio.



5.3. Costo/beneficios económicos de los programas de prevención

5.3.1. Recomendación

- La rentabilidad de los programas de suplementación y enriquecimiento de alimentos necesita un estudio más a fondo. (1⊕⊕O)

5.3.2. Evidencia

Evidencia muy débil respalda una política de proporcionar suplementos de vitamina D a los niños asiáticos en el Reino Unido durante los primeros 2 años de vida (245). Sin embargo, este informe tiene limitaciones metodológicas que excluyen cualquier conclusión. Se requieren investigaciones urgentes para modelar la rentabilidad de las estrategias alternativas de suplementación con vitamina D y los programas de fortificación de alimentos. Los modelos económicos futuros deberían incluir:

- Recursos asociados a diferentes estrategias de suplementación.
- Costos indirectos de tratamiento y complicaciones.
- Uso de recursos de la práctica actual
- Efectividad de diferentes enfoques
- Adherencia esperada
- Resultados como la calidad de vida asociada con los niveles de 25OHD y
- Costos de atención médica por enfermedades causadas por efectos tanto esqueléticos como extraesqueléticos de la deficiencia de vitamina D.

Los costos de los programas de suplementación y/o fortificación de vitamina D variarán según el nivel de 25OHD objetivo y las características de la población. Se deben realizar análisis de subgrupos dirigidos a grupos de alto riesgo, como personas con piel de pigmentación oscura, exposición limitada al sol e ingesta baja de calcio.

Conclusión

La deficiencia de vitamina D debe considerarse una de las principales prioridades de salud pública mundial. El RN puede tener consecuencias graves, incluida la muerte por miocardiopatía o trabajo de parto obstruido, miopatía, convulsiones, neumonía, deformidad y discapacidad de por vida, deterioro del crecimiento y dolor. El RN es la "punta del iceberg" y su resurgimiento indica una deficiencia generalizada de vitamina D con importantes implicaciones para la salud pública. El RN y la osteomalacia son trastornos totalmente prevenibles que van en aumento en todo el mundo y deben considerarse una epidemia mundial. Abogamos por la erradicación del RN y la osteomalacia a través de la suplementación con vitamina D de todos los bebés, mujeres embarazadas y personas de grupos de alto riesgo y la implementación de programas internacionales de fortificación de alimentos para asegurar la suficiencia nutricional de vitamina D y calcio para toda la población. Este documento de consenso proporciona a los responsables de la formulación de políticas un marco de referencia para trabajar en la erradicación mundial del raquitismo.



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Expresiones de gratitud

Sally Farrand proporcionó apoyo editorial. Esta guía fue elaborada por ESPE, PES, SLEP, ASPAE, ISPAE, CSPPEM, JSPE, APEG, APPES, ESPGHAN y otros participantes expertos. El consenso fue apoyado económicamente por las sociedades mencionadas y una beca educativa (no participativa) de Danone Nutricia.

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Resumen de los conflictos de intereses: M.Z.M. ha recibido honorarios y honorarios por conferencias de Nutricia y Alexion. T.D.T. es consultor de Biomedical Systems. W.H. ha recibido

honorarios y honorarios por conferencias de Internis y Alexion. Ningún otro autor tiene nada que revelar.

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Global Consensus Recommendations on Prevention and Management of Nutritional Rickets

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Background: Vitamin D and calcium deficiencies are common worldwide, causing nutritional rickets and osteomalacia, which have a major impact on health, growth, and development of infants, children, and adolescents; the consequences can be lethal or can last into adulthood. The goals of this evidence-based consensus document are to provide health care professionals with guidance for prevention, diagnosis, and management of nutritional rickets and to provide policy makers with a framework to work toward its eradication.

Evidence: A systematic literature search examining the definition, diagnosis, treatment, and prevention of nutritional rickets in children was conducted. Evidence-based recommendations were developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system that describe the strength of the recommendation and the quality of supporting evidence.

Process: Thirty-three nominated experts in pediatric endocrinology, pediatrics, nutrition, epidemiology, public health, and health economics evaluated the evidence on specific questions within five working groups. The consensus group, representing 11 international scientific organizations, participated in a multiday conference in May 2014 to reach a global evidence-based consensus.

Results: This consensus document defines nutritional rickets and its diagnostic criteria and describes the clinical management of rickets and osteomalacia. Risk factors, particularly in mothers and infants, are ranked, and specific prevention recommendations including food fortification and supplementation are offered for both the clinical and public health contexts.

Conclusion: Rickets, osteomalacia, and vitamin D and calcium deficiencies are preventable global public health problems in infants, children, and adolescents. Implementation of international rickets prevention programs, including supplementation and food fortification, is urgently required. (*J Clin Endocrinol Metab* 101: 394–415, 2016)

Summary of Consensus Recommendations¹

Section 1: Defining nutritional rickets and the interplay between vitamin D status and calcium intake

1.1. Definition and diagnosis of nutritional rickets

- Nutritional rickets, a disorder of defective chondrocyte differentiation and mineralization of the growth plate

and defective osteoid mineralization, is caused by vitamin D deficiency and/or low calcium intake in children. (1⊕⊕⊕)

- The diagnosis of nutritional rickets is made on the basis of history, physical examination, and biochemical testing, and is confirmed by radiographs. (1⊕⊕⊕)

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Grading of evidence: 1 = strong recommendation; and 2 = weak recommendation. Quality of evidence: ⊕⊕⊕, high; ⊕⊕○, moderate; and ⊕○○, low quality.

Abbreviations: ALP, alkaline phosphatase; DXA, dual-energy x-ray absorptiometry; NR, nutritional rickets; 25OHD, 25-hydroxyvitamin D₂ and/or D₃ or 25-hydroxycholecalciferol D₂ and/or D₃; 1,25(OH)₂D, 1,25-dihydroxyvitamin D₂ and/or D₃ or 1,25-dihydroxycholecalciferol D₂ and/or D₃ (calcitriol); PTH, parathyroid hormone; RCT, randomized controlled trial; UVB, ultraviolet B; Vitamin D₂, ergocalciferol; Vitamin D₃, cholecalciferol.

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1.2. Vitamin D status

- The panel recommends the following classification of vitamin D status, based on serum 25-hydroxyvitamin D (25OHD) levels. (1⊕⊕⊕)

- Sufficiency, >50 nmol/L
- Insufficiency, 30–50 nmol/L
- Deficiency, <30 nmol/L

1.3. Vitamin D toxicity

- Toxicity is defined as hypercalcemia and serum 25OHD > 250 nmol/L, with hypercalciuria and suppressed PTH. (1⊕⊕⊕)

1.4. Dietary calcium intake to prevent rickets

- For infants 0–6 and 6–12 months of age, the adequate calcium intake is 200 and 260 mg/d, respectively. (1⊕⊕⊕)
- For children over 12 months of age, dietary calcium intake of <300 mg/d increases the risk of rickets independent of serum 25OHD levels. (1⊕⊕⊕)
- For children over 12 months of age, the panel recommends the following classification of dietary calcium intake. (1⊕⊕⊕)
- Sufficiency, >500 mg/d
- Insufficiency, 300–500 mg/d
- Deficiency, <300 mg/d

1.5. Vitamin D deficiency and fractures

- Children with radiographically confirmed rickets have an increased risk of fracture. (1⊕⊕⊕)
- Children with simple vitamin D deficiency are not at increased risk of fracture. (1⊕⊕⊕)

Section 2: Prevention and treatment of nutritional rickets and osteomalacia

2.1. Vitamin D supplementation for the prevention of rickets and osteomalacia

- 400 IU/d (10 μg) is adequate to prevent rickets and is recommended for all infants from birth to 12 months of age, independent of their mode of feeding. (1⊕⊕⊕)
- Beyond 12 months of age, all children and adults need to meet their nutritional requirement for vitamin D through diet and/or supplementation, which is at least 600 IU/d (15 μg), as recommended by the Institute of Medicine (IOM). (1⊕⊕⊕)

2.2. Target for vitamin D supplementation

- In healthy children, routine 25OHD screening is not recommended, and consequently, no specific 25OHD threshold for vitamin D supplementation is targeted in this population. (1⊕⊕⊕)

2.3. Candidates for preventative vitamin D supplementation beyond 12 months of age

In the absence of food fortification, vitamin D supplementation should be given to:

- Children with a history of symptomatic vitamin D deficiency requiring treatment. (1⊕⊕⊕)
- Children and adults at high risk of vitamin D deficiency, with factors or conditions that reduce synthesis or intake of vitamin D. (1⊕⊕⊕)
- Pregnant women (see Section 3.1).

2.4. Dose of vitamin D and calcium for the treatment of nutritional rickets

- For treatment of nutritional rickets, the minimal recommended dose of vitamin D is 2000 IU/d (50 μg) for a minimum of 3 months. (1⊕⊕⊕)
- Oral calcium, 500 mg/d, either as dietary intake or supplement should be routinely used in conjunction with vitamin D in the treatment regardless of age or weight. (1⊕⊕⊕)

2.5. Appropriate route of administration and duration of therapy

- We recommend oral treatment, which more rapidly restores 25OHD levels than IM treatment. (1⊕⊕⊕)
- For daily treatment, both D₂ and D₃ are equally effective. (1⊕⊕⊕)
- When single large doses are used, D₃ appears to be preferable compared to D₂ because the former has a longer half-life. (1⊕⊕⊕)
- Vitamin D treatment is recommended for a minimum of 12 weeks, recognizing that some children may require longer treatment duration. (1⊕⊕⊕)

Section 3: Prevention of nutritional rickets/osteomalacia: identification of risk factors

3.1. Dietary practices and nutrient intakes among mothers associated with nutritional rickets in infants

- Maternal vitamin D deficiency should be avoided by ensuring that women of childbearing age meet intakes of 600 IU/d recommended by the IOM. (1⊕⊕⊕)
- Pregnant women should receive 600 IU/d of vitamin D, preferably as a combined preparation with other recommended micronutrients such as iron and folic acid. (2⊕⊕⊕)

3.2. Early feeding, supplementation, complementary feeding, and nutrient intake associated with rickets in infants

- In addition to an intake of 400 IU/d of vitamin D, complementary foods introduced no later than 26 weeks should include sources rich in calcium. (1⊕⊕⊕)

- An intake of at least 500 mg/d of elemental calcium must be ensured during childhood and adolescence. (1⊕⊕⊕)

3.3. Association of sunlight exposure to nutritional rickets

- Because UVB rays trigger epidermal synthesis of pre-vitamin D₃, restricted exposure to sun increases the risk of vitamin D deficiency and nutritional rickets. (1⊕⊕⊕)
- Environmental factors, such as latitude, season, time of day, cloud cover, and pollution affect availability of UVB, whereas personal factors, such as time spent outdoors, skin pigmentation, skin coverage, age, body composition, and genetics affect the dose-response of UVB exposure and circulating 25OHD. (2⊕⊕○)
- No safe threshold of UV exposure allows for sufficient vitamin D synthesis across the population without increasing skin cancer risk. (2⊕⊕○)

Section 4: Prevention of osteomalacia during pregnancy and lactation and congenital rickets

4.1. The relationship between vitamin D during pregnancy and infant growth and bone mass

- Pregnant women should receive 600 IU/d of supplemental vitamin D. This will ensure adequacy of maternal 25OHD, especially in women at risk of deficiency, to prevent elevated cord blood alkaline phosphatase (ALP), increased fontanelle size, neonatal hypocalcemia and congenital rickets, and to improve dental enamel formation. (2⊕⊕○)
- There is little evidence that maternal supplementation with vitamin D will protect or improve birth anthropometry (2⊕○○) and no evidence that supplementation with vitamin D will protect or improve short- or long-term growth or bone mass accretion. (2⊕⊕○)

4.2. The effect of calcium supplementation during pregnancy on infant bone mass

- Pregnant women do not need calcium intakes above recommended non-pregnant intakes to improve neonatal bone. (1⊕⊕⊕)

4.3. Influence of calcium or vitamin D supplementation in pregnancy or lactation on breast milk calcium or vitamin D

- Lactating women should ensure they meet the dietary recommendations for vitamin D (600 IU/d) for their own needs, but not for the needs of their infant. (1⊕⊕⊕)
- Lactating women should not take high amounts of vitamin D as a means of supplementing their infant. (2⊕⊕○)
- Pregnant and lactating women should meet the recommended intakes of calcium. Maternal calcium intake

during pregnancy or lactation is not associated with breast milk calcium concentrations. (1⊕⊕⊕)

4.4. Causes and therapy of congenital rickets

- Supplementing mothers with 600 IU/d of vitamin D and ensuring they receive recommended calcium intakes, or appropriate therapy of maternal conditions predisposing to hypocalcemia or vitamin D deficiency, prevents congenital rickets. (2⊕○○)

Section 5: Assessing the burden of nutritional rickets and public health strategies for prevention

5.1. Assessment of disease burden

- The prevalence of rickets should be determined by population-based samples, by case reports from sentinel centers, or by mandatory reporting. (1⊕⊕⊕)
- Screening for nutritional rickets should be based on clinical features, followed by radiographic confirmation of suspected cases. (1⊕⊕⊕)
- Population-based screening with serum 25OHD, serum ALP, or radiographs is not indicated. (1⊕⊕⊕)

5.2. Public health strategies for rickets prevention

- Universally supplement all infants with vitamin D from birth to 12 months of age, independent of their mode of feeding. Beyond 12 months, supplement all groups at risk and pregnant women. Vitamin D supplements should be incorporated into childhood primary health care programs along with other essential micronutrients and immunizations (1⊕⊕⊕), and into antenatal care programs along with other recommended micronutrients. (2⊕⊕○)
- Recognize nutritional rickets, osteomalacia, and vitamin D and calcium deficiencies as preventable global public health problems in infants, children, and adolescents. (1⊕⊕⊕)
- Implement rickets prevention programs in populations with a high prevalence of vitamin D deficiency and limited vitamin D and/or calcium intakes, and in groups of infants and children at risk of rickets. (1⊕⊕⊕)
- Monitor adherence to recommended vitamin D and calcium intakes and implement surveillance for nutritional rickets. (1⊕⊕⊕)
- Fortify staple foods with vitamin D and calcium, as appropriate, based on dietary patterns. Food fortification can prevent rickets and improve vitamin D status of infants, children, and adolescents if appropriate foods are used and sufficient fortification is provided, if fortification is supported by relevant legislation, and if the process is adequately monitored. Indigenous food sources of calcium should be promoted or subsidized in children. (1⊕⊕⊕)

- Promote addressing the public health impact of vitamin D deficiency as both a clinical and a public health issue. (1⊕⊕⊕)

5.3. Economic cost/benefits of prevention programs

- The cost-effectiveness of supplementation and food fortification programs needs further study. (1⊕⊕⊕)

Nutritional rickets (NR), secondary to vitamin D deficiency and/or dietary calcium deficiency, remains a significant global, public health problem despite the availability of supplementation and numerous published guidelines for its prevention (1–8). This is concerning because NR can have a major impact on the health of infants, children, and adolescents, with ramifications that persist into adulthood. The morbidity and mortality associated with NR can be devastating, with substantial but poorly recognized consequences for society and health economics. Features of NR and osteomalacia include: 1) hypocalcemic seizures and tetanic spasms; 2) life-threatening hypocalcemic cardiomyopathy; 3) bone pain and muscle weakness; 4) limb and pelvic deformities; 5) failure to thrive; 6) developmental delay; and 7) dental anomalies (9, 10). Alarming, NR can also lead to death from heart failure caused by hypocalcemic cardiomyopathy, even in developed countries (11). In addition, narrowing of the pelvic outlet after NR in childhood can result in obstructed labor and maternal and fetal death (12).

Despite intense focus around the role of vitamin D status in health and disease, there has been a worldwide failure to implement public health guidance and eradicate the most severe manifestations of vitamin D and calcium deficiency in our most vulnerable population—NR and osteomalacia of childhood. Therefore, the goal of this Consensus Statement is to provide clinicians with clarity and recommendations on the recognition, societal burden, and treatment of NR and osteomalacia, and to enable clinicians and health policy leaders to establish appropriate clinical and public health interventions to prevent this debilitating, costly, and under-recognized global health problem.

Methods

In recognition of the considerable variation in the definition, diagnosis, and management of NR worldwide, the European Society for Pediatric Endocrinology decided to examine current best practice in NR and to formulate evidence-based recommendations. Experts were assembled from the following societies: the Pediatric Endocrine Society (PES), the Asia Pacific Pediatric Endocrine Society (APPES), the Japanese Society for Pediatric Endocrinology (JSPE), the Sociedad Latino-Americana de Endocrinología Pediátrica (SLEP), the Australasian Pediatric Endocrine Group (APEG), the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE), the African Society for Pe-

diatric and Adolescent Endocrinology (ASPAE), the Chinese Society of Pediatric Endocrinology and Metabolism (CSPEM), the British Nutrition Society, and the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN). This consensus paper includes the cumulative evidence up to the end of 2014.

Participants included individuals from Europe, North America (United States and Canada), Latin America, Asia, Africa, and Australia, with a balanced spectrum of professional seniority and expertise. In addition, an expert on the development of evidence-based guidelines served in an advisory capacity. Panel members declared any potential conflict of interest at the initial meeting of the group. Thirty-three participants were assigned to one of five groups to which topics 1–5 were allocated, and a chairperson was designated for each group. Each participant prepared an evidence-based summary of the literature relating to a particular question distributed before the conference (which was held over 3 days in May 2014).

Each group presented the revised summaries for discussion to the full conference. This report is based on the questions addressed. A detailed description of the GRADE classification has been published elsewhere (13). Recommendations were based on published findings and on expert opinion when appropriate.

The best available research evidence was used to develop recommendations. Preference was given to articles written in English, identified by PubMed searches with MeSH terms. For each point, recommendations and evidence are described, with a modification in the grading evidence as follows: 1 = strong recommendation (applies to most patients in most circumstances, benefits clearly outweigh the risk); and 2 = weak recommendation (consensus opinion of working group or should be considered; the best action may depend on circumstances or patient values, benefits, and risks closely balanced or uncertain). Quality of evidence is indicated as follows: ⊕⊕⊕, high quality (prospective cohort studies or randomized controlled trials [RCTs] at low risk of bias); ⊕⊕, moderate quality (observational studies or trials with methodological flaws, inconsistent or indirect evidence); and ⊕, low quality (case series or nonsystematic clinical observations) (13).

The target audience for these guidelines includes general and specialist pediatricians, other professionals providing care for patients with NR, and health policy makers, particularly in countries with developing economies.

1.0. Defining Nutritional Rickets and the Interplay between Vitamin D Status and Calcium Intake

1.1. Definition and diagnosis of nutritional rickets

1.1.1. Recommendations

- Nutritional rickets, a disorder of defective chondrocyte differentiation and mineralization of the growth plate and defective osteoid mineralization, is caused by vitamin D deficiency and/or low calcium intake in children. (1⊕⊕⊕)
- The diagnosis of nutritional rickets is made on the basis of history, physical examination, and biochemical testing and is confirmed by radiographs. (1⊕⊕⊕)

1.1.2. Evidence

Bone mineralization requires sufficient supply of the essential mineral ions, calcium and phosphate, with vitamin D optimizing their absorption from the gut. With insufficient serum calcium concentration caused by either vitamin D deficiency or inadequate dietary calcium intake, PTH will stimulate osteoclastic bone resorption to release stored bone minerals into the bloodstream and maintain normal serum calcium (14). Bone disease (rickets and osteomalacia) develops once elevated PTH has led to low serum phosphate levels, as a result of impaired renal phosphate conservation (15).

NR is a disorder of defective growth plate chondrocyte apoptosis and matrix mineralization in children. Osteomalacia is abnormal matrix mineralization in established bone, and although present in children with rickets, it is used to describe bone mineralization defects after completion of growth. Children with an underlying disease such as fat malabsorption, liver disease, renal insufficiency, and illnesses necessitating total parenteral nutrition can also develop NR and are briefly discussed in this review. NR does not include rickets associated with heritable disorders of vitamin D metabolism, including 1- α -hydroxylase deficiency and vitamin D receptor defects, or congenital or acquired hypophosphatemic rickets.

The clinical features and consequences of NR are broad and potentially severe (Table 1) (8). Defective mineralization leads to radiographic growth plate widening as well as metaphyseal cupping and fraying, which confirm the diagnosis of NR.

Biochemical testing alone is not sufficient to diagnose NR and may not differentiate whether the primary cause of NR is vitamin D or dietary calcium deficiency because combined deficiencies are common. Typical laboratory findings in NR are decreases in 25OHD, serum phosphorus, serum calcium, and urinary calcium. Conversely, serum PTH, ALP, and urinary phosphorus levels are invariably elevated (10, 16).

Vitamin D status is assessed by measuring blood levels of total 25OHD. Total 25OHD is used, assuming that 25OHD₂ and 25OHD₃ are of equal biological value (16). There is considerable variability between laboratory methods for measuring serum 25OHD concentrations (17). Immunoassays are popular due to their convenience and high sample throughput; however, cross-reactivity between vitamin D metabolites (25OHD₂, 25OHD₃, and 24,25(OH)₂D) and high levels of estimated bias in several automated assays cast doubt on their reliability, particularly at high and low concentrations of 25OHD (18). Higher-order reference measurement procedures for serum 25OHD have been established by the National Institute of Standards and Technology (NIST) (19) and Ghent University (20) based on isotope di-

Table 1. Clinical Features Associated With Nutritional Rickets

Osseous signs and symptoms
Swelling wrists and ankles
Delayed fontanelle closure (normally closed by age 2 y)
Delayed tooth eruption (no incisors by age 10 mo, no molars by age 18 mo)
Leg deformity (genu varum, genu valgum, windswept deformity)
Rachitic rosary (enlarged costochondral joints—felt anteriorly, lateral to the nipple line)
Frontal bossing
Craniotabes (softening of skull bones, usually evident on palpation of cranial sutures in first 3 mo)
Bone pain, restlessness, and irritability
Radiographic features
Splaying, fraying, cupping, and coarse trabecular pattern of metaphyses
Widening of the growth plate
Osteopenia
Pelvic deformities including outlet narrowing (risk of obstructed labor and death)
Long-term deformities in keeping with clinical deformities
Minimal trauma fracture
Non-osseous features
Hypocalcemic seizure and tetany
Hypocalcemic dilated cardiomyopathy (heart failure, arrhythmia, cardiac arrest, death)
Failure to thrive and poor linear growth
Delayed gross motor development with muscle weakness
Raised intracranial pressure

lution liquid chromatography-tandem mass spectrometry. In recent years, the accuracy of 25OHD assays has improved, including through activities of the Vitamin D Standardization Program (21), which aims to standardize the results of different measurement techniques to those of the reference measurement procedures (22). Significant reductions in interlaboratory variation in serum 25OHD are observed using liquid chromatography-tandem mass spectrometry with the application of NIST standard reference materials (23).

Dietary calcium deficiency is diagnosed by obtaining a calcium intake history. Because the sources of calcium will vary by country and region, we recommend that clinicians develop a dietary calcium intake questionnaire specific to their country/region.

1.2. Vitamin D status

1.2.1. Recommendation:

- The panel recommends the following classification of vitamin D status, based on serum 25OHD levels: (1⊕⊕⊕)
 - Sufficiency, >50 nmol/L
 - Insufficiency, 30–50 nmol/L
 - Deficiency, <30 nmol/L

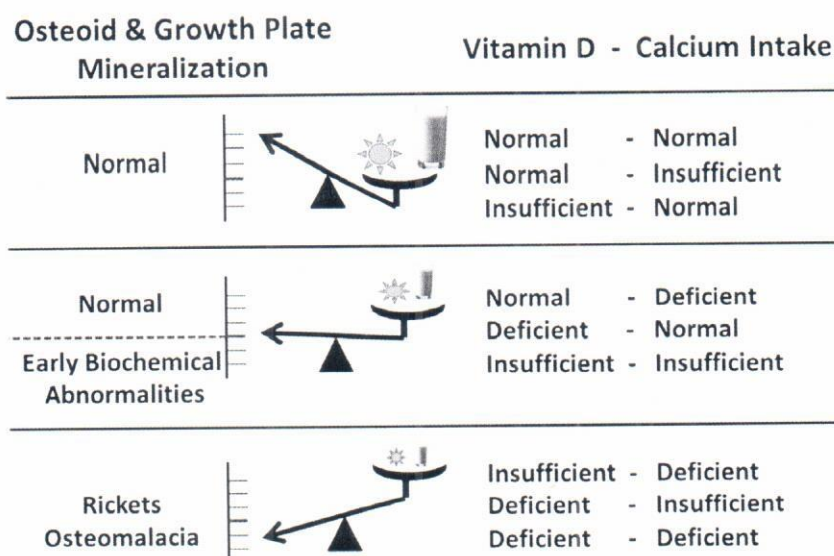


Figure 1. Biochemical disturbances in rickets pathogenesis based on a three-stage classification of vitamin D status (symbolized by the sun) and calcium intake (symbolized by a glass of milk). [Modified from Högl W. Complications of vitamin D deficiency from the foetus to the infant: One cause, one prevention, but who's responsibility? *Best Pract Res Clin Endocrinol Metab.* 2015; 29(3):385–398.(246), with permission. © 2015 Elsevier.]

1.2.2. Evidence

Our definition of vitamin D deficiency in the context of skeletal mineralization and mineral ion metabolism for prevention of NR is based on strong evidence (1, 2, 24–27) supported by the increased incidence of NR with 25OHD concentrations <30 nmol/L (1 ng/mL = 2.5 nmol/L). Our definition is consistent with that of the IOM (28). The potential health impacts of maintaining a serum concentration >50 nmol/L are beyond the scope of this review and are addressed elsewhere (29). It should be noted that NR has been reported in children with 25OHD concentrations >30 nmol/L (2, 5, 6, 30) and that NR may not occur with very low 25OHD concentrations but is more likely to occur with deficiency sustained over time, ie, chronic deficiency. Most children with vitamin D deficiency are asymptomatic (15), highlighting the interplay between serum 25OHD level and dietary calcium intake in maintaining serum calcium concentrations and bone integrity (Figure 1).

Although the most significant functional outcome of vitamin D deficiency is the development of osteomalacia and NR, biochemical and bone density associations are also reported. Laboratory observations demonstrate that PTH increases when 25OHD levels drop below 34 nmol/L (7). Moreover, all patients with NR in that study had 25OHD levels <34 nmol/L, and PTH was elevated in all but one patient. Taken together, the evidence suggests that a 25OHD level at 30–34 nmol/L may be the critical cutoff below which NR is more likely to occur.

Seasonal variations in 25OHD of between 13 and 24 nmol/L (31) emphasize the importance of maintaining 25OHD levels >50 nmol/L (ie, sufficient), so as to prevent prolonged periods of 25OHD levels <30 nmol/L, with the risk of developing NR.

1.3. Vitamin D toxicity

1.3.1. Recommendation

- Toxicity is defined as hypercalcemia and serum 25OHD >250 nmol/L with hypercalciuria and suppressed PTH². (1⊕⊕⊕)

1.3.2. Evidence

Intoxication is predominantly seen in infants and young children after exposure to high doses of vitamin D (240 000 to 4 500 000 IU) (32–37). High 25OHD concentrations can cause hypercalcemia, hypercalciuria, and if prolonged, nephrocalcinosis and renal failure. To allow a large safety margin, the consensus group felt it prudent to use the concentration of 250 nmol/L as the recommended upper limit of serum 25OHD — even if symptomatic toxicity from RCTs has only been reported at levels >500 nmol/L (32). In otherwise healthy infants, hypercalcemia and hypercalciuria in the absence of elevated 25OHD concentrations have been reported and may be related to genetic variation in vitamin D metabolism (38, 39).

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1.4. Dietary calcium intake to prevent rickets

1.4.1. Recommendations

- For infants 0–6 and 6–12 months of age, the adequate calcium intake is 200 and 260 mg/d, respectively. (1⊕⊕⊕)
- For children over 12 months of age, dietary calcium intake of <300 mg/d increases the risk of rickets independent of serum 25OHD levels. (1⊕⊕⊕)
- For children over 12 months of age, the panel recommends the following classification of dietary calcium intake: (1⊕⊕⊕)
 - Sufficiency, >500 mg/d
 - Insufficiency, 300–500 mg/d
 - Deficiency, <300 mg/d

² In areas where 25OHD assays are not readily available, suppression of PTH in the presence of hypercalcemia and pharmacological doses of vitamin D may support the diagnosis of vitamin D toxicity. When PTH assay is also unavailable, the possibility of toxicity should be considered in the presence of symptomatic hypercalcemia in association with pharmacological doses of vitamin D.

1.4.2. Evidence

In developing countries where calcium intake is characteristically very low, with few or no dairy products, dietary calcium deficiency is the main cause of NR among children outside the infant age group.

In 2011, the IOM recommended adequate intakes of calcium for infants, children, and adults (16). The adequate intake for infants was based on breast milk calcium content, which is 200 mg/d and 260 mg/d for babies from 0–6 and 6–12 months of age, respectively. For children 1–18 years of age, the IOM set the daily calcium requirement at 700–1300 mg/d, depending on age (28). There is, however, no true definition of dietary calcium deficiency without a reliable biomarker of calcium intake status, and there are little data to indicate what the lowest calcium intake is that prevents NR. Reports from Nigeria, India, and Bangladesh (6, 30, 40–43) highlighted the role of low dietary calcium intake in the pathogenesis of NR among children. Although some of these children also had sub-optimal 25OHD, others had values >50 nmol/L, which points to the interplay between calcium and vitamin D in the pathogenesis of NR (Figure 1). These studies suggest that in children >12 months of age, a dietary calcium intake of <300 mg/d significantly increases the risk of NR independent of serum 25OHD levels, and that at a daily intake of >500 mg, no NR was seen.

1.5. Vitamin D deficiency and fractures

1.5.1. Recommendations

- Children with radiographically confirmed rickets have an increased risk of fracture. (1⊕⊕○)
- Children with simple vitamin D deficiency are not at increased risk of fracture. (1⊕⊕○)

1.5.2. Evidence

Based on evidence from available observational studies and case reports, children with clinical, biochemical, and radiographic evidence of NR are at increased risk of fracture. A retrospective study found that fractures occurred in seven of 45 (17.5%) infants and toddlers with NR, aged between 2 and 14 months (44). However, fractures only occurred in those who were mobile and had severe radiographic evidence of rickets. Although none of the fractures were considered to be characteristic of nonaccidental injury (child abuse), two infants had lateral or anterior-lateral rib fractures. In a national survey in Canada, 11 of 108 cases of NR (11%) had suffered fractures, although details on the bone sites and numbers of fractures were not provided (1). Fractures also have been reported in cases or case series of NR in

toddlers and adolescents (45–50), but details about the number, site, and type of fracture were absent.

It has been suggested that radiographic features of rickets may be mistaken for those characteristic of nonaccidental injury (51, 52), but the necessary biochemical and radiographic data on the cases for validation of the authors' conclusions were absent. In addition, serum 25OHD levels are similar in infants with accidental and nonaccidental injuries (53). Thus, simple vitamin D deficiency, that is, vitamin D deficiency without biochemical or radiological signs of rickets, has not been associated with increased fracture risk in infants and children.

2.0. Prevention and Treatment of Nutritional Rickets and Osteomalacia

2.1. Vitamin D supplementation for the prevention of rickets and osteomalacia

2.1.1. Recommendations

- 400 IU/d (10 μg) is adequate to prevent rickets and is recommended for all infants from birth to 12 months of age, independent of their mode of feeding. (1⊕⊕⊕)
- Beyond 12 months of age, all children and adults need to meet their nutritional requirement for vitamin D through diet and/or supplementation, which is at least 600 IU/d (15 μg), as recommended by the IOM. (1⊕⊕⊕)

2.1.2. Evidence

Few published studies have included the prevention of radiographic or clinical signs of rickets as an outcome. Consequently, we also reviewed studies that assessed the effect of different vitamin D supplementation regimens³ on 25OHD levels and other bone parameters (such as bone mineral density) with the goal of preventing NR by maintaining levels above the rachitic range, ie, >30 nmol/L (54).

In infants and children, 400 IU/d of vitamin D given as a supplement during infancy is sufficient to prevent radiographic signs of rickets in the short term (up to 12 mo) (54). Specifically, an RCT demonstrated that a vitamin D supplement of 400 IU/d was sufficient to prevent radiographic signs of rickets at 6 months of age, even among infants born with vitamin D deficiency (25). Similarly, no cases of radiographically confirmed rickets were seen after administration of 400 IU/d of vitamin D for 12 months, whereas the incidence was 3.8% in Turkish infants and young children who did not receive supplementation (55). In addition, no incident cases of radiographically confirmed rickets were reported in a 2-year surveillance study of Canadian infants who received 400 IU/d of vitamin D (1). Worldwide, there have been no

³ Note that the term "supplementation" may be interpreted to mean additional vitamin D provided from supplements, general multivitamins, or food fortification. In the context of this article, vitamin D supplementation refers to vitamin D above that which is found in standard dietary sources, with the exception of fortified infant formula.

reports of radiographically confirmed rickets in infants or children receiving 400 IU on a regular, daily basis. Furthermore, this dose has been shown in RCTs to achieve 25OHD levels more frequently above the rachitic (severe deficiency) range compared to 100 or 200 IU/d (25).

The prevention of vitamin D deficiency in the absence of NR was also briefly reviewed. In a double-blind RCT of infants without vitamin D deficiency (25OHD > 50 nmol/L), the impact of 400, 800, 1200, and 1600 IU of vitamin D₃ per day was assessed (54). Doses of 400 IU/d maintained 25OHD levels > 50 nmol/L in 97% of infants after 12 months; doses of 800 and 1200 IU/d were of no added benefit to bone mineral density parameters, and 1600 IU/d raised concerns about potential toxicity. A study in infants with vitamin D deficiency (25OHD < 25 nmol/L) found that a single dose of 100 000 IU maintained 25OHD levels above 37.5 nmol/L for 3 months without hypercalcemia, whereas higher doses led to unacceptably high 25OHD levels (56).

Among infants and toddlers with 25OHD levels < 50 nmol/L for whom daily vitamin D supplementation may not be ideal, intermittent bolus doses of 50 to 100 000 IU every 3 months hold promise, although a comprehensive understanding of the safety and efficacy of this approach remains to be studied.

2.2. Target for vitamin D supplementation

2.2.1. Recommendation

- In healthy children, routine 25OHD screening is not recommended, and consequently, no specific 25OHD threshold for vitamin D supplementation is targeted in this population. (1⊕⊕⊕)

2.2.2. Evidence

No studies have specifically examined the best monitoring approach once supplementation has been given to prevent vitamin D deficiency rickets. 25OHD is a reasonable monitoring parameter to ensure levels > 30–34 nmol/L for prevention of NR. Biochemically, a fall in 25OHD concentration < 34 nmol/L is associated with rising PTH levels, but this intersection point depends on the prevailing calcium intake (7).

The frequent coexistence of dietary calcium deficiency and vitamin D deficiency alters the threshold for rickets development (57). Similarly, monitoring 25OHD concentrations as a public health policy for all individuals is impractical; fortunately, high-risk groups can easily be identified based on clinical profile (Table 2).

2.3. Candidates for preventative vitamin D supplementation beyond 12 months of age

2.3.1. Recommendations

In the absence of food fortification, vitamin D supplementation should be given to:

Table 2. Risk Factors for Nutritional Rickets and Osteomalacia and Their Prevention

Maternal factors
Vitamin D deficiency
Dark skin pigmentation
Full body clothing cover
High latitude during winter/spring season
Other causes of restricted sun (UVB) exposure, eg, predominant indoor living, disability, pollution, cloud cover
Low vitamin D diet
Low calcium diet
Poverty, malnutrition, special diets
Infant/childhood factors
Neonatal vitamin D deficiency secondary to maternal deficiency/vitamin D deficiency
Lack of infant supplementation with vitamin D
Prolonged breast-feeding without appropriate complementary feeding from 6 mo
High latitude during winter/spring season
Dark skin pigmentation and/or restricted sun (UVB) exposure, eg, predominant indoor living, disability, pollution, cloud cover
Low vitamin D diet
Low calcium diet
Poverty, malnutrition, special diets
Risk factors are prevented by:
Sun exposure (UVB content of sunlight depends on latitude and season)
Vitamin D supplementation
Strategic fortification of the habitual food supply
Normal calcium intake

- Children with a history of symptomatic vitamin D deficiency requiring treatment. (1⊕⊕⊕)
- Children and adults at high risk of vitamin D deficiency with factors or conditions that reduce synthesis or intake of vitamin D. (1⊕⊕⊕)
- Pregnant women (see *Section 3.1*).

2.3.2. Evidence

Supplementation is a feasible and acceptable way to ensure adequate vitamin D intake independent of nutrition (58). Consensus guidelines for vitamin D supplementation have been drafted from a variety of pediatric/endocrine groups (16, 59–62). Although there are numerous studies regarding vitamin D deficiency in pediatric populations and primary evaluations of the efficacy of various programs for supplementation of pregnant women, breast-feeding mothers, infants, children, and adolescents, there is more opinion than evidence on many aspects of this topic. However, there is strong, high-quality evidence that vitamin D supplementation should be provided for at-risk groups. All at-risk groups (Table 2) are specifically vulnerable and, in the absence of food fortification, require supplementation.

Vitamin D fortification of infant formula is well established and recommended by all European countries, Australia, New Zealand, and the American Academy of Pe-

diatrics (60). Vitamin D fortification of milk is mandated in Canada, and “enriched milk” is voluntarily fortified in the United States (63).

Children with chronic illnesses and conditions affecting vitamin D synthesis/absorption/metabolism may also benefit from supplementation and may require higher doses (58) but are not in the remit of this consensus on NR.

2.4. Dose of vitamin D and calcium for the treatment of nutritional rickets

2.4.1. Recommendations

- For treatment of nutritional rickets, the minimal recommended dose of vitamin D is 2000 IU/d (50 µg) for a minimum of 3 months. (1⊕⊕⊕)
- Oral calcium, 500 mg/d, either as dietary intake or supplements, should be routinely used in conjunction with vitamin D in the treatment regardless of age or weight. (1⊕⊕⊕)

2.4.2. Evidence

Most studies claim that the different doses commonly employed to treat vitamin D deficiency are safe, with hypercalcemia and/or hypercalciuria observed as a side effect only in a few individuals and usually seen in the 300 000 to 600 000 IU range (64). In a small study of children with NR ($n = 17$), doses of 1700 to 4000 IU of vitamin D₂ rapidly increased 25OHD concentrations within 1 week and normalized calcium, phosphate, and ALP levels at 10 weeks (65). In another study in children aged 2–36 months with NR ($n = 19$), 5000 to 10 000 IU of oral vitamin D₃ and calcium 0.5 to 1.0 g daily normalized serum PTH, calcium, and phosphate within 3 weeks, although ALP levels remained elevated (66).

Simultaneous administration of calcium with vitamin D appears to be adequate and recommended by several studies (67, 68). In 123 Nigerian children with NR due to calcium deficiency, the combined endpoint of an ALP level < 350 U/L and radiographic evidence of near-complete healing of rickets was seen in a higher percentage of patients who received a combination of calcium and vitamin D (58%) or calcium alone (61%) than in those who received vitamin D alone (19%) (5). Similarly, in 67 Indian children with NR due to combined calcium and vitamin D deficiency, complete healing at 12 weeks was seen in a higher percentage with combined therapy (50%) than with vitamin D (15.7%) or calcium alone (11.7%) (30).

Combined treatment is justified because studies have shown that the diet of children and adolescents with NR is generally low in both vitamin D and calcium (5, 6, 30, 69).

2.5. Appropriate route of administration and duration of therapy

2.5.1. Recommendations

- We recommend oral treatment, which more rapidly restores 25OHD levels than IM treatment. (1⊕⊕⊕)

- For daily treatment, both D₂ and D₃ are equally effective. (1⊕⊕⊕)
- When single large doses are used, D₃ appears to be preferable compared to D₂ because the former has a longer half-life. (1⊕⊕⊕)
- Vitamin D treatment is recommended for a minimum of 12 weeks, recognizing that some children may require longer treatment duration. (1⊕⊕⊕)

2.5.2. Evidence

Some studies compared IM and oral administration of vitamin D, but most were conducted in adults and, therefore, may not be entirely relevant for children with NR. Oral or IM vitamin D was given to 24 normal volunteers (age, 50–78 y) in a dose of 600 000 IU of D₂ or D₃ (70). Peak levels of 25OHD were seen at 30 and 120 days in those given oral and IM treatment, respectively. Another study in 92 adults with 25OHD < 75 nmol/L compared 300 000 IU vitamin D₃ IM to 50 000 IU D₃ orally given on six occasions over 3 months (71). A higher proportion of subjects receiving oral treatment had 25OHD > 75 nmol/L at 3 and 6 months than IM subjects.

One RCT in 61 children with NR compared a single IM dose of 600 000 IU vitamin D₃ to a weekly oral dose of 60 000 IU D₃ for 10 weeks (72). There were no differences at 1, 4, and 12 weeks between groups in bone profiles, 25OHD concentrations, or side effects. A meta-analysis of studies comparing the administration of vitamin D₂ and D₃ concluded that, when given as bolus doses, vitamin D₃ was more effective at raising 25OHD concentrations, but no significant differences were seen with daily doses (73).

There are no RCTs on the duration of treatment for children with NR, and most of the literature consists of review articles. The review commissioned by the PES recommends that daily oral treatment be given for 8 to 12 weeks (74). Similar durations between 8 and 12 weeks of daily treatment are recommended in reviews from the United Kingdom (75, 76). A duration of 3 months is recommended in a consensus statement from Australia and New Zealand (77). Given the limited evidence, we recommend minimum treatment duration of 12 weeks to achieve a comprehensive healing and normalization of ALP, recognizing that some children may require longer treatment.

Several studies explored the concept of “stoss therapy,” ie, the administration of a large dose given as a single dose or in divided doses over several days. This approach has been advocated for ease of use and compliance with therapy. Three different single oral doses (150 000, 300 000, or 600 000 IU) in 56 Turkish children aged 3–36 months with NR did not affect the rate of improvement of rickets at 30 days (64).

However, eight subjects (two in the 300 000-IU group, six in the 600 000-IU group) developed hypercalcemia. A recent study in India compared single oral doses of 300 000 vs 600 000 IU of vitamin D₃ in 76 rachitic children aged 6 months to 5 years (78). At 12 weeks, all children demonstrated radiographic healing with comparable decreases in ALP and PTH. However, hypercalcemia occurred in five children (6.5%)—two receiving 300 000 IU and three receiving 600 000 IU. Several review articles advocate different recommendations with stoss therapy that are not supported by evidence (75–77). The few studies comparing daily treatment to stoss therapy contained groups with different subject characteristics. Although we recommend daily treatment as the first line of management, we recognize that in some situations, stoss therapy may be more practical. Therefore, we provide vitamin D dose recommendations for both treatment options (Table 3). Any treatment needs to be followed by supplementation (see Sections 2.1 and 2.3).

3.0. Prevention of Nutritional Rickets/Osteomalacia: Identification of Risk Factors

3.1. Dietary practices and nutrient intakes among mothers associated with nutritional rickets in infants

3.1.1. Recommendations

- Maternal vitamin D deficiency should be avoided by ensuring that women of childbearing age meet the intakes of 600 IU/d recommended by the IOM. (1⊕⊕⊕)
- Pregnant women should receive 600 IU/d of vitamin D, preferably as a combined preparation with other recommended micronutrients such as iron and folic acid. (2⊕⊕⊕)

3.1.2. Evidence

Maternal diet and nutrient intake as a predictor of infantile rickets have not been addressed in the literature as an *a priori* hypothesis. However, available data have been

collected during vitamin D intervention studies, case studies, or case series in women during pregnancy.

Many cases of NR included data on maternal 25OHD and, in some cases, dietary information (79–81). Neonatal vitamin D deficiency is always caused by maternal deficiency and can have life-threatening consequences such as hypocalcemic seizures and dilated cardiomyopathy in unsupplemented infants (11). Hypocalcemia (see Section 4.1.2) or other early biochemical signs of rickets (such as elevated ALP and PTH) are present before radiographic signs of NR occur in unsupplemented neonates and infants (82, 83). A high percentage of mothers of infants with symptomatic vitamin D deficiency are from high-risk groups who are vitamin D deficient and exclusively breastfeeding (11, 24, 83–85).

In a Canadian case series, six First Nation infants presented with hypocalcemic seizures within the first 30 days of life, with suspected or confirmed maternal vitamin D deficiency and a lack of supplementation during pregnancy (86). All were formula fed, which suggests that although their intake of vitamin D would have been sufficient in normal circumstances, in these infants the oral vitamin D supply via formula milk was insufficient to treat their pre-existing severe neonatal deficiency.

Prevention of maternal deficiency is critical, and all mothers should meet their nutritional requirement for vitamin D, which is currently set at 600 IU/d, although this value is not based on direct evidence from RCTs of vitamin D supplementation in pregnant women (28). Potentially, a higher intake of vitamin D may be required to prevent both maternal and neonatal deficiency (87). Prevention of congenital vitamin D deficiency is described in Section 4.4.

3.2. Early feeding, supplementation, complementary feeding, and nutrient intake associated with NR in infants

3.2.1. Recommendations

- In addition to an intake of 400 IU/d of vitamin D, complementary foods introduced no later than 26 weeks should include sources rich in calcium. (1⊕⊕⊕)
- An intake of at least 500 mg/d of elemental calcium must be ensured during childhood and adolescence. (1⊕⊕⊕)

3.2.2. Evidence

There is abundant, yet low-quality evidence from multiple case reports, case series (11, 48, 49, 88), and observational studies (1, 2, 45, 50, 85, 89–99) that exclusive breast-feeding without vitamin D supplementation is a major risk factor for NR in infants. Furthermore, prolonged breast-feeding with late introduction of complementary feeding is associated with NR in infants not re-

Table 3. Treatment Doses of Vitamin D for Nutritional Rickets

Age	Daily Dose for 90 Days, IU	Single Dose, IU	Maintenance Daily Dose, IU
<3 mo	2000	N/A	400
3–12 mo	2000	50 000	400
>12 mo to 12 y	3000–6000	150 000	600
>12 y	6000	300 000	600

Abbreviation: N/A, not available. Reassess response to treatment after 3 months as further treatment may be required. Ensure a daily calcium intake of at least 500 mg. For conversion from IU to μ g, divide by 40.

ceiving vitamin D supplements (26, 100–105). Abundant observational data (55, 106–111) and one RCT (25) suggest that infants receiving vitamin D supplementation in the first year of life are not at risk of developing NR. Evidence for providing 400 IU/d vitamin D to infants is presented in Section 2.1.

Evidence primarily from developing countries demonstrates that traditional diets low in calcium cause NR (30, 43, 69, 93, 112–114). Therefore, special diets during infancy such as those that avoid milk and dairy products, those using soy or rice milk that are not specifically designed for infants, and/or vegan and macrobiotic diets may predispose infants to NR (115–120). Recommendations on sufficient calcium intake are presented in Section 1.4.

3.3. Association of sunlight exposure to nutritional rickets

3.3.1. Recommendations

- Because UVB rays trigger epidermal synthesis of previtamin D₃, restricted exposure to sun increases the risk of vitamin D deficiency and nutritional rickets. (1⊕⊕⊕)
- Environmental factors such as latitude, season, time of day, cloud cover, and pollution affect availability of UVB, whereas personal factors such as time spent outdoors, skin pigmentation, skin coverage, age, body composition, and genetics affect the dose-response to UVB exposure and circulating 25OHD. (2⊕⊕⊕)
- No safe threshold of UV exposure allows for sufficient vitamin D synthesis across the population without increasing skin cancer risk. (2⊕⊕⊕)

3.3.2. Evidence

Solar radiation (UVB band of 290 to 315 nm) stimulates synthesis of previtamin D from epidermal 7-dehydrocholesterol, which isomerizes to cholecalciferol and is subsequently metabolized to 25OHD. Sun exposure increases circulating 25OHD (121–123). Assuming UVB availability, an individual's capacity to synthesize vitamin D increases with longer epidermal exposure. However, exposure can be affected by environmental factors such as latitude, altitude, season, time of day, cloud cover, and air quality (123–129) as well as personal factors such as occupation, lifestyle, culture such as clothing, and preference which may modify time spent outdoors and/or the surface area of skin exposed to sunlight (130–133). Finally, the dose-response of circulating 25OHD to cutaneous UVB exposure is dependent on skin pigmentation, age, body composition, genetic factors, and baseline 25OHD levels, among others (121, 131, 134–138).

Abundant global observational data report an association between restricted epidermal exposure and NR as a consequence of vitamin D deficiency (85, 139–143). UV

radiation causes skin cancer, and exposure to UV radiation from sunlight and artificial sources early in life elevates the risk of developing skin cancer (144). Without firm evidence to account for variations in age, skin color, latitude, time of day, and time of year, it is currently impractical to provide prescriptive advice on safe solar exposure to the population as a whole. All risk factors are summarized in Table 2.

4.0. Prevention of Osteomalacia During Pregnancy and Lactation and Congenital Rickets

4.1. The relationship between vitamin D during pregnancy and infant growth and bone mass

4.1.1. Recommendations

- Pregnant women should receive 600 IU/d of supplemental vitamin D. This will ensure adequacy of maternal 25OHD, especially in women at risk of deficiency, to prevent elevated cord blood ALP, increased fontanelle size, neonatal hypocalcemia and congenital rickets, and to improve dental enamel formation. (2⊕⊕⊕)
- There is little evidence that maternal supplementation with vitamin D will protect or improve birth anthropometry (2⊕⊕⊕), and there is no evidence that supplementation with vitamin D will protect or improve short- or long-term growth or bone mass accretion. (2⊕⊕⊕)

4.1.2. Evidence

There is moderate evidence that low maternal vitamin D status during pregnancy is associated with elevated cord blood ALP and larger fontanelle size at birth (145, 146). Moderate to strong evidence from two RCTs (145, 147), two controlled trials (148, 149), and one observational study (150) indicated that low maternal vitamin D status during pregnancy increases the risk of neonatal hypocalcemia; however, a smaller RCT and a controlled trial did not support these findings (146, 151). A single large controlled trial suggests that vitamin D supplementation during pregnancy improves dental enamel formation of offspring (148).

There are conflicting data about the association between maternal vitamin D status during pregnancy and birth anthropometry. Three RCTs of moderate to high quality using daily dose or single high-dose regimens did not find an association (151–153), whereas two controlled trials of moderate-grade evidence found a positive association (146, 147). Three low- to high-quality RCTs did not find any difference in birth anthropometry in offspring of mothers supplemented with 400, 2000, or 4000 IU/d; none of the studies had a placebo group (87, 154, 155).

There are inconsistent data on the association between maternal serum 25OHD levels and linear growth during the first year of life (152, 157, 162) and insufficient to weak evidence for an association between maternal serum 25OHD levels and bone mass or density at birth (150, 158–161) or in later childhood (162–164).

4.2. The effect of calcium supplementation during pregnancy on infant bone mass

4.2.1. Recommendation

- Pregnant women do not need calcium intakes above recommended nonpregnant intakes to improve neonatal bone. (1⊕⊕⊕)

4.2.2. Evidence

Calcium supplementation studies in pregnancy have not had congenital or neonatal rickets as an outcome, but three RCTs of maternal calcium supplementation during pregnancy measured neonatal bone (165–167). These RCTs were conducted in West Africa where typical dietary calcium intakes are 250–300 mg/d (165), in the United States with an average intake of about 2000 mg/d (166), and in a multicenter World Health Organization study in populations with dietary calcium intake of approximately 600 mg/d (Argentina, Peru, India, Egypt, Vietnam, South Africa) (167). Maternal calcium supplementation had no effect on neonatal bone mineral assessed by dual-energy x-ray absorptiometry in the Gambian and US studies, except in the latter study in offspring of women in the lowest quintile of dietary calcium intake (<600 mg/d). There was no effect of maternal calcium supplementation on neonatal or infant anthropometry, a finding consistent with observational studies.

4.3. Influence of calcium or vitamin D supplementation in pregnancy or lactation on breast milk calcium or vitamin D

4.3.1. Recommendations

- Lactating women should ensure they meet the dietary recommendations for vitamin D (600 IU/d) for their own needs, but not for the needs of their infant. (1⊕⊕⊕)
- Lactating women should not take high amounts of vitamin D as a means of supplementing their infant. (2⊕⊕⊕)
- Pregnant and lactating women should meet the recommended intakes of calcium. Maternal calcium intake during pregnancy or lactation is not associated with breast milk calcium concentrations. (1⊕⊕⊕)

4.3.2. Evidence

Maternal vitamin D intake during lactation correlates with milk vitamin D activity. Several double-blind

RCTs found that high maternal intakes of vitamin D (2000, 4000, and 6400 IU/d) were associated with higher breast milk vitamin D concentration (Figure 2) (168–171).

Supplementing mothers with high amounts of vitamin D has been suggested as a means of increasing both maternal (Figure 3) and infant serum 25OHD concentrations (172–175). Maternal vitamin D intakes up to 4000 IU/d are likely safe during pregnancy and lactation (16). However, the finding that infants of mothers supplemented with 2000 IU/d or more have similar serum 25OHD concentrations as infants receiving 400 IU/d (Figure 4), as well as safety concerns, and our own recommendation that all infants receive 400 IU vitamin D per day lead us to advise that mothers should take recommended amounts (600 IU/d) rather than higher doses of vitamin D.

Maternal calcium intake during pregnancy or lactation does not influence breast milk calcium concentrations. Only one observational study found a weak association between maternal calcium intakes during pregnancy and breast milk calcium level at day 40 (mature milk) (176). Numerous studies, including two RCTs (177, 178) and two observational studies (179, 180) have not found a relationship between maternal calcium intake and breast milk calcium concentrations.

No studies have investigated the effect of maternal vitamin D intake during pregnancy on either milk calcium or vitamin D concentrations. Two double-blind RCTs found that maternal serum 25OHD concentration or maternal intake of vitamin D (up to 4000 IU/d) during lactation was not associated with milk calcium concentrations (181, 182).

4.4. Causes and therapy of congenital rickets

4.4.1. Recommendation

- Supplementing mothers with 600 IU/d of vitamin D and ensuring they receive recommended calcium intakes, or appropriate therapy of maternal conditions predisposing to hypocalcemia or vitamin D deficiency, prevents congenital rickets. (2⊕○○)

4.4.2. Evidence

Approximately 80 cases of congenital rickets, defined as babies presenting within the first 4 weeks of life with biochemical and radiographic signs of rickets, have been described in the medical literature. Typically, mothers of babies with congenital rickets have osteomalacia with severe vitamin D deficiency, low calcium intake, and hypocalcemia at delivery and had not taken vitamin D supplementation during pregnancy (83, 183–197). In rare

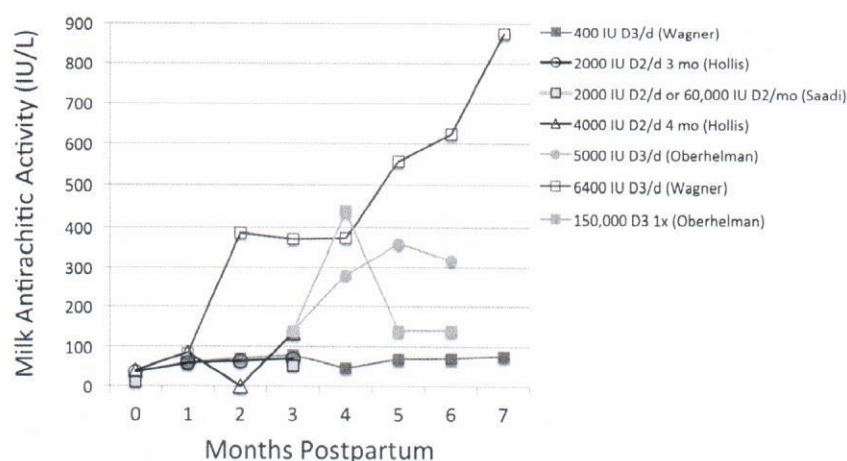


Figure 2. Double-blind RCTs have shown that maternal intakes of 1000–6400 IU/d of vitamin D are associated with increased breast milk vitamin D concentrations (156, 168, 169, 171). Lines of similar color represent the same study, and the legend provides the vitamin D supplementation dose (IU/d unless otherwise stated). Oberhelman et al (171) reported milk concentrations of cholecalciferol only.

cases, congenital rickets can occur when mothers have had severe prolonged hypocalcemia not primarily caused by vitamin D deficiency such as poorly treated hypoparathyroidism (198–201), renal failure (202–206), received phosphate-containing enemas (207), or iatrogenic hypermagnesemia (208).

The mechanisms for the development of congenital rickets remain poorly understood, especially how diminished maternal calcium supply as the common primary maternal abnormality in all cases affects fetal mineralization. Clearly, congenital rickets only occurs in extreme metabolic situations. It is fair to state that all reported cases of congenital

rickets could have been prevented by vitamin D supplementation, normal calcium intake during pregnancy, and adequate therapy of maternal conditions associated with prolonged hypocalcemia or vitamin D deficiency. Evidence is very limited on the therapy for congenital rickets, but rickets generally is responsive to vitamin D with or without calcium supplementation.

5.0. Assessing the Burden of Nutritional Rickets and Public Health Strategies for Prevention

5.1. Assessment of disease burden

5.1.1. Recommendations

- The prevalence of rickets should be determined by population-based samples, by case reports from sentinel centers, or by mandatory reporting. (1⊕⊕⊕)
- Screening for nutritional rickets should be based on clinical features, followed by radiographic confirmation of suspected cases. (1⊕⊕⊕)
- Population-based screening with serum 25OHD, serum ALP, or radiographs is not indicated. (1⊕⊕⊕)

5.1.2. Evidence

NR has been increasingly reported in high- and low-income countries (55, 209–213). Using different methodology, the incidence of NR has been reported as 2.9, 4.9, 7.5, and 24 per 100 000 in Canada (1), Australia (2), the United Kingdom (3), and the United States (99), respectively. Many studies are hospital based but provide additional insight into the burden of NR. Infants with NR may present with hypocalcemic seizures. The incidence of dilated cardiomyopathy associated with NR and hypocalcemia is unknown, but it is potentially the deadliest and most economically costly complication of NR (11). The methods used for the diagnosis of NR in case reports (102) and small to large case series (104, 214–217) are widely variable and many lack radiographic confir-

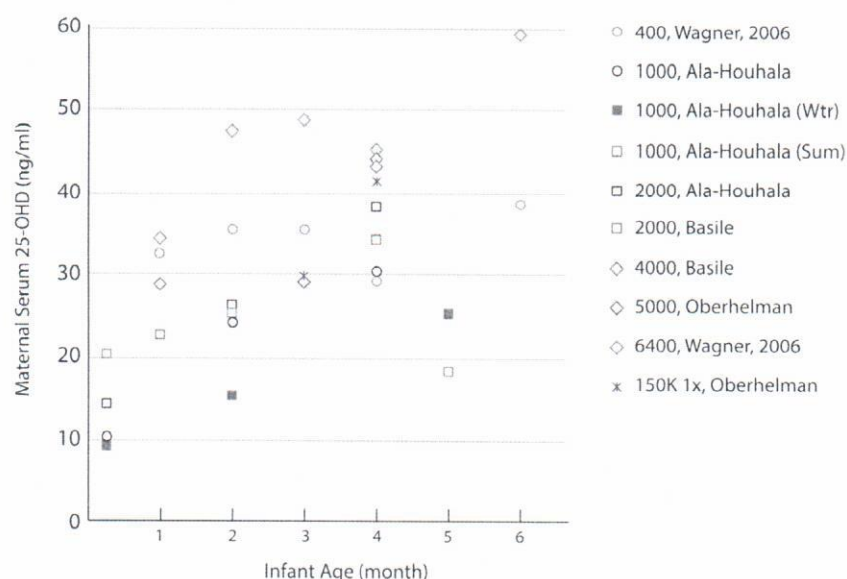


Figure 3. Double-blind RCTs have shown that maternal serum 25OHD concentrations are increased with vitamin D supplementation (169, 171, 174, 182). Most trials began supplementation shortly after birth. Markers of similar color represent the same study, and the legend provides the vitamin D supplementation dose in IU/d unless otherwise stated. 1 ng/mL $\approx$ 2.5 nmol/L. Wtr, winter; Sum, summer.

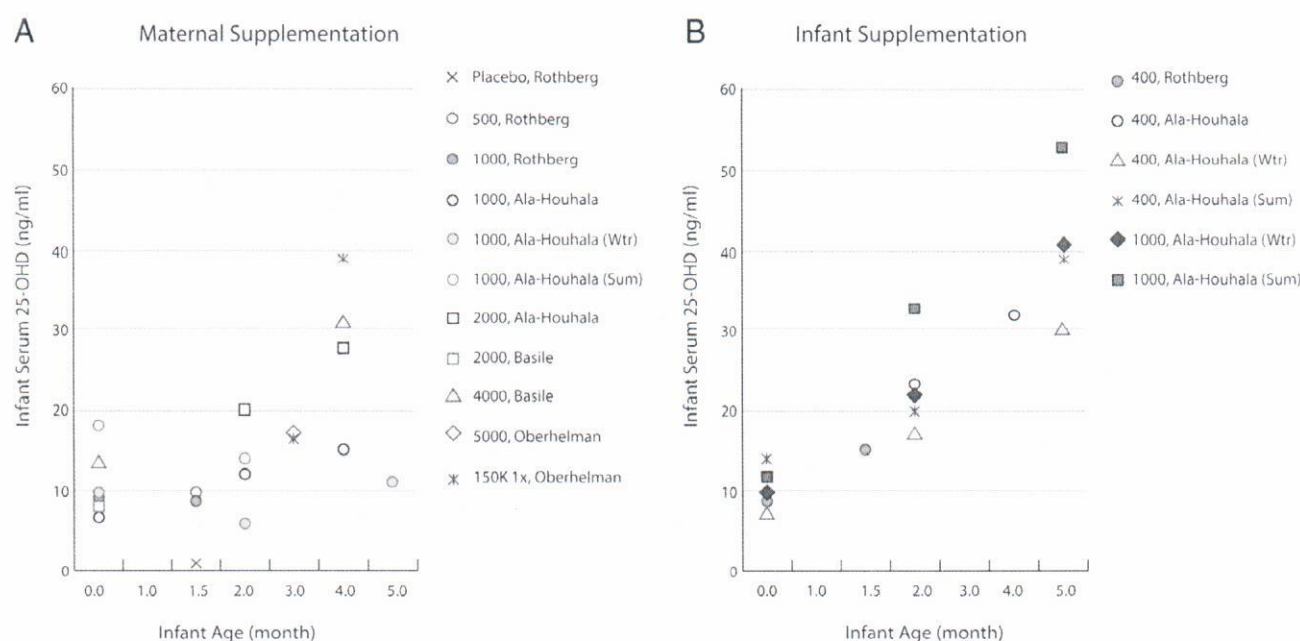


Figure 4. Infant serum 25OHD concentrations by age in RCTs where either the mother was supplemented with vitamin D (A) or the infant was supplemented (B) (171,173–175–182). Markers of similar color represent the same study, and the legend provides the vitamin D supplementation dose in IU/d unless otherwise stated. 1 ng/mL $\approx$ 2.5 nmol/L. Wtr, winter; Sum, summer.

mation (209). Physician-based surveys can estimate the burden of disease, but few have been done (1, 2). Population-based studies provide the most accurate assessment of the disease burden (3, 99, 211, 218–221). Despite differing methodologies, published reports indicate the greatest burden of NR is in Africa, Asia, and the Middle East due to sun avoidance or dietary calcium insufficiency (209, 213).

Even high-income countries have observed a resurgence of NR, mainly among immigrants of African, Asian, or Middle-Eastern origin. This overall increase in the incidence of NR in high-income countries corresponds to an increase in the number of individuals in ethnic minority, immigrant, and refugee groups (1–4, 99, 222). The incidence among established Caucasian populations is stable or decreasing. In regions with a low prevalence of NR, inclusion of NR as a reportable disease is potentially the most cost-effective means of case identification and surveillance (1, 2, 4, 99, 222).

Measurement of serum 25OHD is useful for the diagnosis of vitamin D deficiency in NR, but not for population screening (223, 224). Raised serum ALP has been used as a screening tool for NR (225). However, acute illness, drugs, liver disease, growth spurts, and transient hyperphosphatasemia of infancy and childhood can all elevate ALP values. Because of the invasiveness of venipuncture, high cost, and low positive predictive values, serum ALP and 25OHD cannot be recommended for population screening. Although radiographs of the wrists and knees provide definitive confirmation of active rickets (226), radiation exposure

precludes recommending screening radiographs in asymptomatic children.

5.2. Public health strategies for rickets prevention

5.2.1. Recommendation

- Universally supplement all infants with vitamin D from birth to 12 months of age, independent of their mode of feeding. Beyond 12 months, supplement all groups at risk and pregnant women. Vitamin D supplements should be incorporated into childhood primary health care programs along with other essential micronutrients and immunizations (1⊕⊕⊕), and into antenatal care programs along with other recommended micronutrients. (2⊕⊕⊕)
- Recognize nutritional rickets, osteomalacia, and vitamin D and calcium deficiencies as preventable global public health problems in infants, children, and adolescents. (1⊕⊕⊕)
- Implement rickets prevention programs in populations with a high prevalence of vitamin D deficiency or limited vitamin D and/or calcium intakes and in groups of infants and children at risk of rickets. (1⊕⊕⊕)
- Monitor adherence to recommended vitamin D and calcium intakes and implement surveillance for nutritional rickets. (1⊕⊕⊕)
- Fortify staple foods with vitamin D and calcium, as appropriate, based on dietary patterns. Food fortification can prevent rickets and improve vitamin D status of infants, children, and adolescents if appropriate foods are

used and sufficient fortification is provided, if fortification is supported by relevant legislation, and if the process is adequately monitored. Indigenous food sources of calcium should be promoted or subsidized in children. (1⊕⊕⊕)

- Promote addressing the public health impact of vitamin D deficiency as both a clinical and a public health issue. (1⊕⊕⊕)

5.2.2. Evidence

Vitamin D supplementation

Infants aged 0–12 months and adolescents are at increased risk of NR and osteomalacia from vitamin D deficiency due to rapid growth. Vitamin D is found in a limited number of foods, and dietary intakes apart from fortified foods have little impact on overall vitamin D status. Programs that deliver micronutrient supplements provide the fastest improvement in micronutrient status of individuals or targeted populations (227, 228).

Food fortification with vitamin D

Food fortification of commonly consumed staple foods safely provides adequate intake to prevent deficiency at minimal cost. Mandatory fortification of staple foods with vitamin D and calcium ensures nutritional adequacy (229). After vitamin D fortification of milk in North America and of milk, margarine, and cereals in the United Kingdom, the prevalence of NR dramatically declined, so much so that it was considered almost eradicated (16, 63, 228).

Studies in adults and children highlight the need for appropriate foods (230) to be adequately fortified and consumed by the at-risk segments of the population (231) so that vitamin D intakes of most members of a population approach dietary recommendations (232, 233). Because vitamin D fortification of foods rich in calcium is optimal for bone health, dairy products are commonly fortified. In countries where dairy products are not widely consumed, flour, margarine, cooking oil, or soy-based foods can be fortified with vitamin D.

Although several studies have assessed the effectiveness of vitamin D fortification of food to increase 25OHD concentrations in different age groups and communities, relatively few fortification studies have targeted children. A systematic review and meta-analysis concluded from food-based RCTs that vitamin D-fortified foods increase serum 25OHD and reduce the prevalence of deficiency (<30 nmol/L) in adults, provided appropriate vehicles are chosen based on analysis of habitual diet (234). Fortification of chupatty flour (6000 IU/kg) raised 25OHD from approximately 12.5 nmol/L to approximately 48 nmol/L in children over a 6-month period (235). Fortification of fluid milk and margarine was estimated to increase vitamin D intake in 4-year-old children

from 176 to 360 IU/d (4.4 to 9 µg/d) and 25OHD concentrations from 55 to 65 nmol/L (236). Milk fortification has also been a successful strategy to improve the vitamin D status of schoolchildren in India (237). Fortification and supplementation requirements may vary with population exposure to sunshine (see Section 3) (238).

Food fortification with calcium

Inadequate dietary calcium intake is a risk factor for NR in children over the age of 12 months with low dairy product intake, a common situation in low-income countries. The IOM recommends a calcium intake of 500 mg/d in children ages 1–3 years when children are at the greatest risk of NR, based on calcium retention in absorption studies (16). In populations with low dairy intake such as in Africa and parts of Asia, indigenous food sources of calcium or fortification of staple foods with calcium can provide adequate calcium intake in children (213, 239). Calcium salts can be used to fortify infant formulas, complementary foods, and staple food in areas where dairy intake is low. Calcium carbonate for food fortification is available at very low cost (227).

Food fortification effectively increased dietary calcium intakes by using calcium-fortified laddoos in the diet of underprivileged Indian toddlers (240) and by calcium fortification of cereal for 7- to 12-year-old children (241). More than 1100 foods are calcium fortified in the United States, yet dairy food makes up more than 65% of adolescents' calcium intake (242). In the United Kingdom, calcium fortification of flour is an important source of calcium intake (16% of total) for young adolescent girls (243). There are limited data from studies on calcium fortification or the acceptability of dietary diversification to include locally available and affordable calcium-rich foods in developing countries. Periodic monitoring for NR is important to determine the effectiveness of fortification and/or supplementation programs in preventing NR.

Health promotion

Education of medical providers and organizations, health insurers, policy makers, governments, public health officials, and the general public is vital to address the public health issue of NR and vitamin D deficiency. They should be provided with guidelines on the importance of adequate vitamin D and calcium intakes in children, adolescents, and pregnant and lactating women (244). National and global public health promotion strategies are essential to raise professional and community awareness, and global action to protect all children from vitamin D and calcium deficiency is imperative.

5.3. Economic cost/benefits of prevention programs

5.3.1. Recommendation

- The cost-effectiveness of supplementation and food fortification programs needs further study. (1⊕⊕○)

5.3.2. Evidence

Very weak evidence supports a policy of providing vitamin D supplementation to Asian children in the United Kingdom for the first 2 years of life (245). However, this report had methodological limitations that preclude any conclusions.

Urgent research is required to model the cost-effectiveness of alternative vitamin D supplementation strategies and food fortification programs. Future economic models should include:

- Resources associated with different supplementation strategies
- Indirect costs of treatment and complications
- Resource use of current practice
- Effectiveness of different approaches
- Expected adherence
- Outcomes such as quality of life associated with 25OHD levels, and
- Health care costs of disease caused by both skeletal and extraskelatal effects of vitamin D deficiency.

Costs of vitamin D supplementation and/or fortification programs will differ depending on the target 25OHD level and population characteristics. Subgroup analyses targeting high-risk groups, such as people with darkly pigmented skin, limited sun exposure, and low calcium intakes, should be conducted.

Conclusion

Vitamin D deficiency should be considered a major global public health priority. NR can have severe consequences, including death from cardiomyopathy or obstructed labor, myopathy, seizures, pneumonia, lifelong deformity and disability, impaired growth, and pain. NR is the “the tip of the iceberg,” and its resurgence indicates widespread vitamin D deficiency with important public health implications. NR and osteomalacia are fully preventable disorders that are on the rise worldwide and should be regarded as a global epidemic. We advocate for the eradication of NR and osteomalacia through vitamin D supplementation of all infants, pregnant women, and individuals from high-risk groups and the implementation of international food fortification programs to ensure nutritional sufficiency of vitamin D and calcium for the whole population. This consensus document provides policy makers with a reference framework to work toward the global eradication of rickets.

Appendix A: Affiliations of Consensus Group Members

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