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TECHNICAL REPORT

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Calcium status assessment at the population level: Candidate approaches and challenges

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Abstract

Inadequate dietary calcium intake is a global public health problem that disproportionately affects low- and middle-income countries. However, the calcium status of a population is challenging to measure, and there are no standard methods to identify high-risk communities even in settings with an elevated prevalence of a disease caused or exacerbated by low calcium intake (e.g., rickets). The calcium status of a population depends on numerous factors, including intake of calcium-rich foods; the bioavailability of the types of calcium consumed in foods and supplements; and population characteristics, including age, sex, vitamin D status, and genetic attributes that influence calcium retention and absorption. The aim of this narrative review was to assess candidate indicators of population-level calcium status based on a range of biomarkers and measurement methods, including dietary assessment, calcium balance studies, hormonal factors related to calcium, and health outcomes associated with low calcium status. Several promising approaches were identified, but there was insufficient evidence of the suitability of any single indicator to assess population calcium status. Further research is required to develop and validate specific indicators of calcium status that could be derived from the analysis of data or samples that are feasibly collected in population-based surveys.

KEYWORDS
calcium, calcium absorption, calcium balance, dietary assessment, DXA

PURPOSE

In March and April 2021, the Nutrition Science Program of the New York Academy of Sciences in partnership with the Children's Investment Fund Foundation, convened a Calcium Task Force and hosted two virtual meetings. This Task Force is composed of experts in micronutrients, malnutrition, pediatrics, gynecology and obstetrics, biochemistry, public health, supplementation, and food fortification. During these two virtual meetings, the Task Force assessed the evidence on global calcium deficiency and its health consequences as well as useful indicators of calcium status. It also considered potential interventions, such as calcium supplementation for pregnant women, to improve pregnancy outcomes, and associated implementation challenges, as well as food-based interventions, to improve the intake of this micronutrient,

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especially in populations with low calcium intake. The group was also asked to identify the research gaps and provide guidance for interventions and policies based on the most current available evidence. The following narrative review includes the discussions and conclusions of a subgroup of the Task Force on the methods to assess calcium status through dietary intake and biomarkers for calcium and bone health.

INTRODUCTION

Calcium deficiency due to inadequate dietary calcium intake is a global public health concern. Populations in low- and middle-income countries (LMICs), particularly in Asia, Africa, and South America, are most vulnerable to low calcium intakes, though populations in many high-income countries also fail to meet current recommendations.[1] However, in the absence of an observable health condition caused or exacerbated by severely inadequate calcium intake (e.g., rickets), calcium deficiency is not well defined, and efforts to define and address low calcium intakes have been hampered by difficulties in assessing calcium status at a population level.[2]

Calcium status is defined as the extent to which calcium intake meets physiological requirements, which are age, sex, and life-stage dependent.[3] In adults, adequate calcium status reflects a zero-calcium balance, whereas a negative calcium balance occurs when calcium losses (primarily via urine) exceed the amount of calcium absorbed from food or supplements in the intestine. In children, the concept of calcium status is complicated by the need for all growing children to be in positive calcium balance as a consequence of mandatory calcium accretion in growing bones. The magnitude of the requisite positive calcium balance varies with the rate of growth and bone mineralization.[4] Thus, a child may have a suboptimal calcium status, despite being in a positive calcium balance, if the balance is still insufficient to maximize bone growth and mineralization.

Overall calcium status depends on many factors, including consumption of calcium-rich foods and supplements, the bioavailability of the calcium consumed, age, sex, vitamin D status, and genetic variability in calcium retention and absorption.[1,5] Adding to the complexity of assessing calcium status is an inconsistent relationship between low calcium intakes and adverse health outcomes.[6–8] Furthermore, there is no consensus among nutritionists and researchers regarding the health consequences of long-term low calcium intakes and suboptimal calcium status.

Unlike many other micronutrients for which a circulating ion or metabolite concentration may be used as a biomarker of nutritional status (e.g., zinc, retinol, and ferritin), the concentration of calcium in the blood is tightly regulated within a narrow range by endocrine feedback mechanisms and, therefore, cannot be interpreted as a marker of calcium nutriture or status. The term "hypocalcemia" specifically refers to a low total and/or ionized calcium concentration in blood (or serum/plasma) but does not reflect recent calcium intake or total-body calcium status. In fact, hypocalcemia is very rarely (if ever) due to a deficiency of dietary calcium in the absence of other factors that disrupt the homeostatic response to low calcium intake (e.g., vitamin D deficiency and hypoparathyroidism).

The lack of an established biomarker of calcium status is a major barrier to identifying populations at high risk of inadequate calcium intake.[2,9–11] An ideal indicator of population-level calcium status would reflect the proportion of individuals in the population who have calcium intakes that meet or exceed their physiological requirements; alternatively, an estimate of the average value of an index of dietary calcium adequacy (e.g., median calcium intake) may be useful if it can be benchmarked against age-, sex-, and life stage-standardized international references. The ideal indicator would be based on measurements that are specific to calcium (i.e., independent of other closely related factors, such as vitamin D status) and responsive to changes in calcium balance caused by alterations in calcium intake, absorption, or excretion. Furthermore, the collection of data or biological samples required to derive the indicator would need to be feasibly incorporated into population-representative health and nutrition surveys, particularly in LMICs. The lack of a standard calcium status indicator makes it challenging to identify populations with inadequate calcium intake, where interventions to improve calcium intake may yield public health benefits. This also poses challenges in monitoring and evaluating the effectiveness of food fortification or supplementation programs and to advocate for its inclusion in micronutrient surveys.[12,13]

This review aims to assess the most relevant and promising indicators of calcium status at a population level and highlight the evidence gaps that remain to be addressed. Candidate indicators of calcium status range across a spectrum from dietary intake assessments to measurements of fractional calcium absorption, calcium balance, calcium stores, calcium excretion, indicators of hormonal responses, and health outcomes associated with low calcium status (Figure 1 and Table 1). They are assessed with respect to their specificity to calcium status (and independence from other factors, such as vitamin D status), their responsiveness to a change in calcium intake, and their feasibility to be used in a population health and nutrition survey, especially in LMICs.

DIETARY ASSESSMENT

Dietary calcium intake is a widely used measure of calcium status and may be used to derive an indicator of population status (e.g., the proportion of individuals with adequate or inadequate intakes; mean intake).[14] Several methods have been developed for evaluating dietary calcium intakes and assessing the risk of dietary calcium inadequacy for individuals and groups, although no single method is regarded as the gold standard. The reliability of each method depends on inter-rater variability, the extent to which estimates depend on respondent recall (vs. direct observation), the availability of data related to the calcium content of local foods, and the extent to which the consumption of calcium-containing foods varies temporally (e.g., seasonality).[14] Dietary assessment methods can be categorized into indirect methods (such as food balance sheets) that utilize secondary data to estimate food available for consumption at the national and

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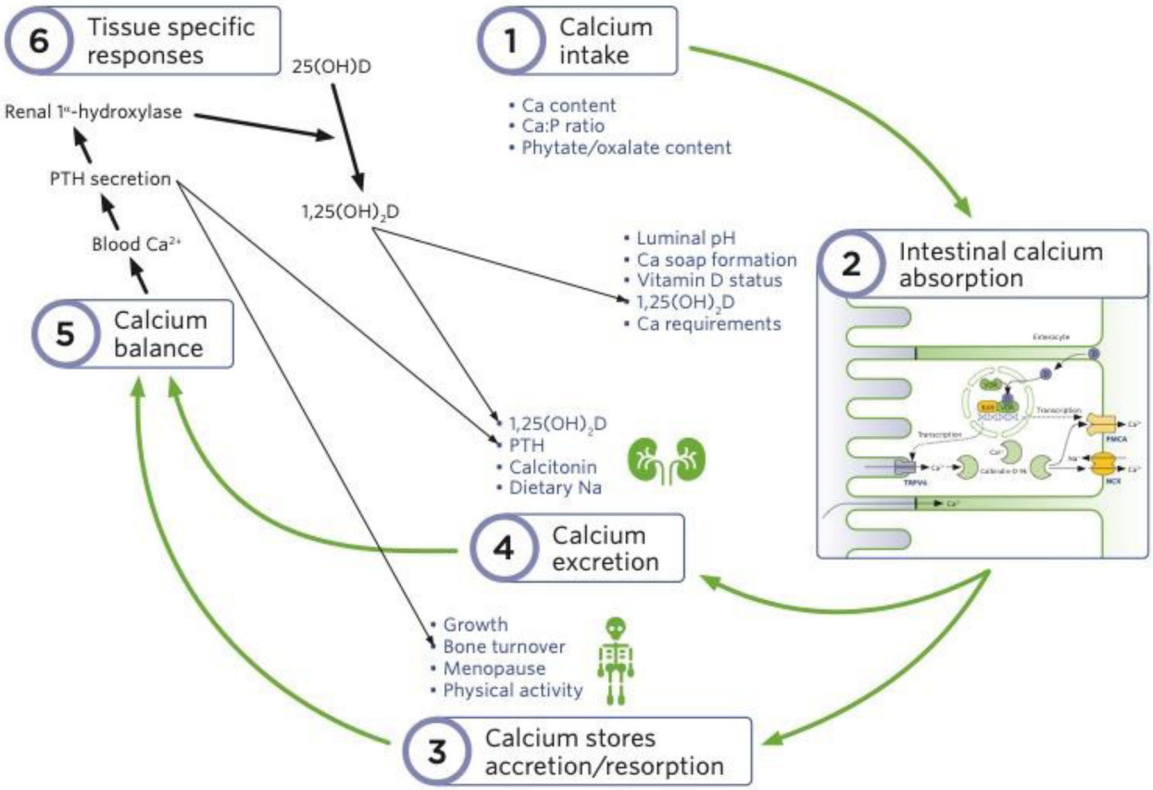

FIGURE 1 Calcium metabolic pathways, including examples of factors that may be measured to assess calcium status. The image of the mucosal cell in the diagram is reproduced from Kopic, 2013.[14]

household levels, and direct methods (such as 24-hour recall), which collect primary dietary data from individuals.[14]

Direct methods

Direct methods using individual-based dietary assessment include retrospective methods that measure food intake from the past (e.g., 24-hour recall and Food Frequency Questionnaires [FFQ]) and prospective methods that assess current food intake (e.g., estimated or weighed food records).[14] The direct dietary assessment methods that are often used to estimate calcium intakes are FFQs, 24-hour recalls, and food records.[1]

FFQs are questionnaires that assess the frequency with which foods are eaten over a certain time period (e.g., previous week or month). Typically, the FFQ is used either in a nutrition survey or in an epidemiological study in order to assess bone-nutrient intakes, such as calcium, often in relation to diseases, such as osteoporosis.[15] Ideally, a calcium-specific FFQ that focuses on assessing calcium intake should be straightforward to implement and validate within the target population[16] given the differences in nutritional habits, food compositions, and preparations across populations. Several calcium-specific FFQs have been developed and evaluated in different settings, with reported correlation coefficients from 0.33 to 0.85 (in comparison with weighed multiple-days food records) across a variety of populations in the United States.[16] The analysis and interpretation of data from FFQs rely on the memory of the respondent, up-to-date knowledge of the calcium content of local foods and recipes, and levels of calcium fortification in the food supply.

Other direct methods for estimating the calcium intake of individuals include a 24-hour recall (where respondents are asked by an interviewer to recall and report all foods and beverages consumed over the preceding 24 h), and a weighed or an estimated food record (whereby respondents are instructed to document all foods and beverages consumed during a predefined period [e.g., 1–7 days] and food portions can be either estimated or weighed).[1,14] Most national nutrition surveys use the 24-hour recall method, and both 24-hour recall and food record methods are frequently used in randomized clinical trials and cohort studies.

A single-day, 24-hour recall or food record (per respondent) can be used if the purpose is to aggregate the data across individuals to describe the average dietary intake of a group or population. It is, however, unreliable to use the result of a single 24-hour recall or food record to characterize an individual's usual intake of food and nutrients.[17,18] For this purpose, multiple, nonconsecutive 24-hour recalls or food records on the same individual are required in order to capture daily variability, and ideally, these should be conducted at different times of the year to account for seasonal variation in dietary intakes.[14] The number of days required depends on the intake variability of the nutrient and the desired level of precision.[19] For

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TABLE 1 Summary of candidate calcium status indicators

Indicator type	Aspect of calcium intake, metabolism, or related outcome that is measured	Measurement modality or biomarker	Specific to calcium (more checks indicate greater specificity)	Responsiveness to a change in calcium balance (more checks indicate greater responsiveness)	Feasibility for field settings and in LMICs (more checks indicate greater feasibility)	Limitations
1. Dietary assessment	Amount of calcium available or ingested	Food Frequency Questionnaire	✓✓	✓✓	✓✓✓	Wide-ranging correlation coefficient across a variety of populations; needs tailoring to the local context
		24-hour recall or Food Record	✓✓✓	✓✓✓	✓✓✓	Calcium absorption or bioavailability is not considered; labor intensive; requires multiple days recall for precise estimates at the individual level
		Food Balance Sheets or Household Consumption Expenditure Surveys	✓	✓	✓✓✓✓	Not based on individual intake; can provide an overestimate of intake
2. Calcium absorption	Proportion of ingested calcium that is absorbed	Stable isotope signature	✓✓✓✓	✓✓✓✓	✓✓	Influenced by vitamin D status; needs sophisticated and expensive equipment
		Radiotracer	✓✓✓✓	✓✓✓✓	✓	Expensive and may require controlled dosing; cannot be used in children or pregnant women
3. Calcium stores	Absolute quantity of bone mineral in the skeleton	DXA	✓✓✓	✓	✓✓	Many genetic and environmental determinants of BMC; DXA is not readily implemented in large-scale surveys
		QCT	✓✓	✓	✓	Higher radiation dose than DXA. Not suitable for large-scale surveys
4. Calcium excretion	Amount of calcium excreted in urine	Urinary calcium excretion (24 h or UCa/Cr)	✓✓✓	✓✓✓	✓✓	Poor measure of Ca status for the general population; affected by various internal determinants

(Continues)

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TABLE 1 (Continued)

Indicator type	Aspect of calcium intake, metabolism, or related outcome that is measured	Measurement modality or biomarker	Specific to calcium (more checks indicate greater specificity)	Responsiveness to a change in calcium balance (more checks indicate greater responsiveness)	Feasibility for field settings and in LMICs (more checks indicate greater feasibility)	Limitations
		Urinary metabolomics	✓✓✓	✓✓✓	✓	More validation is required on the repeatability of biomarkers
5. Calcium balance	The net result of absorption versus excretion	A combination of methods for measuring absorption and excretion	✓✓✓✓	✓✓✓✓	✓	Time-consuming and expensive; not appropriate for population-based studies
6. Hormonal factors	Circulating concentrations of calciotropic hormones or other secreted molecules for which the regulation of their secretion is related to calcium status	PTH	✓✓	✓✓✓	✓✓	High variability; affected by vitamin D status
		$1,25(OH)_2D$	✓✓	✓✓✓	✓	Influenced by vitamin D status
		Bone turnover markers (ALP, OC, PINP, DPD, etc.)	✓	✓✓✓	✓✓	High variability; affected by age
7. Health outcomes	Population prevalence or incidence of diseases associated with low calcium intake	Nutritional rickets	✓✓	✓✓	✓✓	Also caused by vitamin D deficiency
		Osteoporosis	✓✓	✓	✓✓	Multifactorial disease; not always associated with calcium intake
		Preeclampsia	✓	✓	✓✓	Multiple risk factors

Abbreviations: ALP, alkaline phosphatase; BMC, bone mass content; Ca, calcium; DPD, deoxypyridinoline; DXA, dual-energy X-ray absorptiometry; LMIC, low- and middle-income countries; OC, osteocalcin; PINP, procollagen type I N-terminal propeptide; PTH, parathyroid hormone; QCT, quantitative computed tomography; Uca/Cr, urinary calcium, creatinine ratio; 1,25 (OH)2D, 1,25-dihydroxyvitamin D; 25OHD, 25-hydroxyvitamin D.

calcium, the number of days that have been suggested to estimate an individual's true intake varied between 4 and 17 days, depending on the age, gender, and within-subject variation.[16] If calcium-fortified foods are consumed but only occasionally, then this number of days would increase, as within-subject variability increases.[16]

Assessments of nutrient intake or dietary pattern assessment based on FFQs, 24-hour recalls, or food records are prone to imprecision due to recall bias, day-to-day variability, the effect of seasonality, and lack of specific information about local food composition and recipes.[20,21] Furthermore, estimates of nutrient intake do not typically take into account the extent to which the nutrient is absorbed. This is an important issue for calcium, for which absorption is substantially affected by the food matrix and the presence of other specific dietary components (e.g., phytates) that interfere with calcium absorption.[22] However, in contrast to most other calcium biomarkers discussed below, the estimation of calcium intake based on the dietary recall may have the

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advantage of being relatively independent of vitamin D status, particularly in settings where dairy products are not vitamin D-fortified and, therefore, where major sources of vitamin D and calcium are distinct.

Indirect methods

Indirect methods provide insights into dietary patterns and nutrient intake by identifying trends in food availability and consumption across different geographical regions and times.[14] Food balance sheets are compiled by FAO annually and provide total food availability estimates, which are usually expressed by kilograms of food commodities per capita per year. Using data from food balance sheets, the availability of calcium in the food supply can be estimated for a country's or a region's population.[16] An analysis of global food balance sheet data from 2011 showed that most LMICs do not have sufficient levels of calcium in the national food supply to meet the suggested requirements of the population.[23] The approach does not, however, offer information about the calcium distribution at the household or individual level.

Household consumption and expenditure surveys measure the total amount of food available for consumption in the household, through records of expenses and foods consumed during a specific time period (1–4 weeks).[14] These data are largely publicly available for most countries and can be used to estimate calcium intakes at the household level.[24] These estimates are calculated by multiplying the average food consumption data by the corresponding nutrient values, which are obtained from food composition tables.[14] In some LMICs, this is the only resource available to calculate estimates of nutrient intakes.[14] However, information on the distribution of food consumption between family members, cooking methods, or food losses cannot be obtained from these surveys,[14] and methods for estimating individual intakes can lead to an overestimation of nutrient intakes, especially for young children.[24] Nevertheless, household consumption and expenditure surveys have shown to have a good agreement with individual 24-hour recalls assessed in 12- to 23-month-old children, and identified calcium as a problem nutrient in most of the analyzed regions.[25]

Dietary assessment methods can be validated against biomarkers.[14] However, this is particularly challenging for calcium, given the lack of a reliable calcium biomarker (discussed in the next sections).

CALCIUM ABSORPTION

Calcium absorption is measured in terms of the proportion of an amount of ingested calcium that is absorbed from the intestinal lumen. The mean percent calcium absorption, referred to as fractional calcium absorption, is 25–30% of calcium intake in adults.[3] There is typically an inverse relationship between calcium intake and fractional calcium absorption. When calcium intake is reduced, fractional calcium absorption usually increases adaptively via active absorption (as opposed to passive) mechanisms in the intestine.[26] The adaptation typically occurs within 1–2 weeks and is often accompanied by an increase in serum parathyroid hormone (PTH) and $1,25(OH)_2D$ concentrations.[4] However, many factors influence absorption efficiency, including the bioavailability of the calcium consumed (e.g., foods with high phytic and oxalic acid are usually considered a poor source of bioavailable calcium), calcium requirements, age, and vitamin D status.[27–29] Several isotopic methods have been developed to measure fractional calcium absorption utilizing stable isotopes (^{40}Ca, ^{42}Ca, ^{43}Ca, ^{44}Ca, ^{46}Ca, and ^{48}Ca), radioactive isotope tracers (^{45}Ca and ^{47}Ca), or combinations of both.[21,30] Isotope enrichment in biological specimens is then measured over several days to weeks.

Radiotracer techniques have historically been used to assess calcium absorption and metabolism. Kinetic analysis and compartmental modeling can provide a picture of calcium metabolism as well as the perturbation in response to an intervention.[31] In a whole-body counter, gamma-emitting isotopic tracers are used to measure absorption and retention. The principles employed for radioactive tracers are similar to those described for stable isotopes.[31] Calcium pool sizes and turnover rates in the body can be measured with isotopic tracers in conjunction with classical balance techniques. However, radiotracers cannot be used in children and pregnant women due to ethical concerns about irradiating the bone marrow or in facilities where food is prepared for commercial use. As a result, other isotopic methods have been developed to measure calcium absorption.

A dual stable isotope method, based on natural isotopic enrichment in a 24-h urine collection, has been shown to be the most accurate and reliable method currently available for measuring fractional calcium absorption.[21] Following isotope administration, urine is collected over a 24-h period. The relative fraction of the oral compared to the intravenous dose of the isotope in the urine represents the amount of the oral dose that was absorbed. The inconvenience of 24-h urine collection has led some methods to be developed that use single collections (of either serum or urine) at least 20 h after isotope administration.[32]

The use of the rare, long-lived radioisotope, ^{41}Ca, can overcome some of the limitations of classic radiotracers. ^{41}Ca has an exceptionally long half-life of over 10^5 years that permits its treatment as a quasi-stable isotope, and the excretion of ^{41}Ca can be measured after one dose in single urine samples for many years due to the sensitivity of accelerator mass spectrometry and the limited natural presence of ^{41}Ca.[31,33] Due to its ability to monitor bone metabolism over many years, ^{41}Ca is an efficient method for monitoring changes in bone metabolism resulting from changing conditions or in response to an intervention, disease, or medications. However, it is a time-consuming process as it first requires stabilization of the ^{41}Ca in bone, which can take up to 6 months. Changes in calcium metabolism also alter the urinary ^{41}Ca:Ca ratio. Changes in the urinary ^{41}Ca:Ca ratio are inversely related to bone balance. Although ^{41}Ca offers the greatest sensitivity to monitor changes in bone calcium balance, some practical disadvantages curtail its widespread application, such as the requirement to label the skeleton prior to intervention, the expense of sample preparation, the availability of the method, and longer analysis time.[33]

Ratios of $\delta^{44/40}Ca$ calcium isotopes can also be used to evaluate bone turnover under various conditions or interventions without dosing subjects with isotope-enriched supplements. This method uses the principle of kinetic isotope fractionation, in which stable isotopes are

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separated from one another based on mass during unidirectional biochemical processes.[34] During bone remodeling, the lighter isotopes are preferentially taken up into bone, while the heavier isotopes circulate in bodily fluids and tissues. During bone resorption (or break down), lighter isotopes circulate in the fluids and tissues of the body at higher rates.[35] Thus, major calcium compartments in our body, including blood and soft tissues, bones, urine, and feces, have a unique isotopic "fingerprint" that can be used to evaluate changes in a bone turnover under various conditions as with administered isotopes. However, when using urine $\delta^{44/40}$Ca as a marker for net bone balance, fractionation of Ca isotopes occurs during urine generation, which strongly depends on the amount of calcium reabsorbed by kidneys.[35]

Calcium absorption studies are often difficult to conduct because they can rely on costly materials or analytical equipment that are challenging to implement in the context of large-scale population studies, particularly in LMICs, and they may require long-term follow-up of participants.[33] There are also numerous factors that can perturb calcium absorption, but there are no current standards or reference ranges to correct for these factors. As a result, these methods are not ideal for population-based studies of calcium status.

CALCIUM STORES

Although calcium is present in all tissues, over 99% of body calcium is found in bones and teeth.[3] Therefore, a direct measure of the absolute amount of calcium stored in bone is a reasonable candidate biomarker of calcium status, if there are standards against which any individual or group-average value or population distribution can be compared. However, to be practically useful as the basis for a population indicator in a public health context, measures of calcium stores would also need to be responsive to modifiable determinants of calcium status, including dietary calcium intake.

Since calcium is a constant fraction of bone mineral content (BMC), an assessment of BMC effectively provides a measure of total body calcium. In large-scale studies, BMC and bone mineral density (BMD) are typically measured by dual-energy X-ray absorptiometry (DXA), whereby BMD is a two-dimensional measure of areal BMD equivalent to BMC divided by bone area. In population-based national nutrition surveys, DXA has been used successfully, but it has primarily been used in these settings to estimate the prevalence of osteoporosis[36,37] or sarcopenia,[38] by assessing BMD[39,40] and body fat composition.[41] These studies, however, did not attempt to correlate these outcomes with calcium intake. DXA remains the major bone densitometry method in clinical settings due to its use in diagnosing osteoporosis, assessing fracture risk, and monitoring treatment responses.[42] BMC and BMD derived from a DXA scan are translated into Z-scores and T-scores that are based on a reference population. T-scores are used only for adult populations over the age of 50 years, while Z-scores are created from age, sex, and race-matched controls.[43] The average values acquired from a DXA scan differ between groups by age, sex, and ethnicity; therefore, reference data are used to compare the individual to a population.

However, there is a lack of standardization between DXA manufacturers in bone and soft tissue measurements due to various methodological limitations. The use of DXA in children and growing young adults has additional challenges; BMC magnification, due to the widespread use of fan beams, is particularly problematic, and there is ongoing debate as to whether these projection methods are appropriate for children. BMC is considered to be the more appropriate DXA-derived measure of bone mass in children because areal BMD can overestimate true volumetric mineral density in larger children and underestimate it in smaller children.[44–46] Furthermore, since DXA is unable to differentiate where the calcium is deposited (within the bone or overlying blood vessels), an increase in BMC or BMD, especially in the spine, may overestimate BMC/BMD, particularly in elderly adults with atherosclerosis or osteophytes.[47] Also, DXA is still a relatively expensive method and not readily transportable. Although transportable models of DXA instruments are available, DXA is most suitable for studies or surveys in which participants are able to visit a centralized assessment center rather than for studies that rely entirely on home visits.[48]

Quantitative computed tomography (QCT) relies on more X-ray exposure than DXA but can provide estimates of true volumetric density.[49] Several cross-sectional studies have demonstrated that QCT is more sensitive than DXA at detecting changes in BMD.[50,51] Peripheral QCT and high-resolution peripheral QCT are often used in small-scale studies, sometimes to complement DXA measurements, but their application is much less frequent in large-scale epidemiologic studies or surveys.[49,52] Currently, osteoporosis in adults is diagnosed based on the WHO definition, which uses the DXA-derived BMD T-score. However, no equivalent and comparable measurement have been developed for diagnosing osteoporosis with QCT.[49] This lack of standardization, the high cost of equipment, its lack of portability, and the higher radiation exposure associated with QCT limit its use in population surveys, but these are areas of active research that may make QCT more feasible in the future.[49,52]

Although not correlated with recent dietary intakes of calcium, BMC and BMD can reflect long-term adequacy of calcium intake and are strong predictors of bone fracture risk.[3] Interventions to increase calcium intake through either diet or supplementation, in participants aged over 50, have been associated with an increase in BMD, and those increases were similar in trials with calcium doses of ≥1000 versus <1000 mg/day and ≤500 versus >500 mg/day. However, the supplementation resulted in a small and likely clinically insignificant change in BMD, and the response to intervention often plateaus after about a year.[53] In children, interventions to improve calcium intake (most of which lasted 12–24 months) have shown to increase BMC, but only in children with low calcium intakes at baseline.[54] Although BMD and BMC measurements have been shown to reflect long-term adequacy of calcium intake in trials of selected populations, they are also highly dependent on factors independent of calcium intake, including genetics, estrogen and PTH levels, intake of other nutrients (such as vitamin D), and calcium absorption, which makes these challenging methods to assess calcium status in a population-level survey.[3] Despite these limitations, BMD was used by the Institute of Medicine as an

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indicator of calcium adequacy in older adults (during the stage when bone loss is expected) in the derivation of the 2011 dietary reference intakes (DRIs) for calcium.[29]

CALCIUM EXCRETION

Unlike serum/plasma calcium concentrations, urinary calcium concentrations vary greatly in response to short-term changes in calcium intake and absorption, dietary protein intake, urinary output, and calcium requirements.[21,55,56] Furthermore, urine can be relatively easily sampled in a serial manner without the need for invasive techniques required for blood collection. However, the correlation of urinary calcium excretion with calcium intake is low, and the wide range of nondietary factors that influence calcium excretion limit its reliability as a measure of calcium status.

Although a 24-h urine collection is the most accepted method of assessing calcium excretion, it is challenging to implement outside of a clinical environment.[57] An untimed urinary calcium to creatinine ratio (UCa/Cr) based on a single "spot" urine sample appears to be an acceptable alternative to a 24-h urine collection for estimating calcium excretion. In addition to normalizing calcium output values for variations in urine volume and concentration, UCa/Cr ratios correct for differences in lean body mass as well as timing errors in urine collection sessions.[56,58] The majority of studies suggest using the first-morning urine spot sample collected in order to assess UCa/Cr since it is easy to collect and correlates well with 24-h urinary calcium excretion. However, UCa/Cr has low sensitivity for detecting adequate calcium intake, and reference ranges based on race and age are required to interpret the data.[59,60]

Overall, calcium intake only accounts for about 1–6% of the variance in urinary calcium.[62,63] Urinary calcium excretion is affected by numerous other extrinsic (water supply composition and geographical location) and intrinsic (sex, age, and ethnicity) factors.[64] Given the numerous sources of variability in urinary calcium excretion, including responsiveness to many factors (such as sodium overload and increased protein intake[65,66]) that may not directly reflect calcium balance, it is unlikely that measurement of urinary calcium on its own would provide a useful approach for the assessment of population calcium status.

Urinary metabolomics is a relatively new frontier in assessing calcium status. A study in rats on either low calcium or normal calcium diet for 2 weeks identified 27 biomarkers indicating potential calcium deficiency from urinary metabolite analysis.[11] As some metabolites are far more sensitive to shifts in calcium intake than BMD, metabolomics was used in combination with BMD measurements, to determine the stage and severity of calcium deficiency, as some metabolites appear early in deficiency, and some later. Examining the effect of calcium supplementation on the urinary metabolic profiling of calcium deficiency, Wang *et al.* grouped the biomarkers into three different categories that correlated with various stages of calcium deficiency from markers of early and late stages and those that were persistent throughout.[11] A follow-up study by the same research group looked at urinary metabolites in children with and without nutritional rickets (NR).[61] They found 31 urinary metabolites that were associated with NR and that a combination of phosphate and sebacic acid could be used to differentiate between the two groups, given their high sensitivity (94.0%) and specificity (71.2%) to diagnose this condition. As this research field is in its early stages, further application and validation are required. Importantly, the associations of metabolic signatures with calcium intake need to be validated in large-scale human studies before they can be recommended for use in population surveys.

CALCIUM BALANCE

Calcium balance is the equilibrium of the body's calcium stores over an extended period of time. It is assessed by measuring the difference between the total calcium inputs and total body calcium losses and assumes that the body retains the amount of calcium needed.[3] Results of calcium balance measurements can be either positive, indicating accrual of calcium usually in bones; neutral, suggesting bone mineral maintenance; or negative in cases of bone loss.

In theory, the measurement of calcium balance provides a comprehensive assessment of the extent to which calcium intake meets calcium requirements at different life stages. In the derivation of the 2011 DRIs for calcium, average calcium accretion and retention were used to derive estimated average requirements for infants and children (although averages are not necessarily optimal considering average calcium intakes for most populations are below recommended intakes), and neutral calcium balance was considered an indicator of calcium adequacy in adults.[29] However, there is inconclusive evidence of a positive association between calcium intake and bone remodeling in adults due to the confounding effects of vitamin D status along with other dietary factors.[67] There are two other major considerations that limit the application of calcium balance studies to population calcium status assessment: (1) Lack of feasibility: In contrast to most of the other measurement approaches considered, calcium balance studies are highly resource intensive and very unlikely to be feasible for population surveys; (2) Lack of age/stage-specific standards: Even if feasibility issues could be overcome, a calcium balance measurement can only be interpreted in the context of age and life-stage-specific standards. A positive calcium balance in a growing child (or an average of a set of values for children in a population) is insufficient evidence of adequate calcium status since the net calcium retention (i.e., accretion) may still be too low to optimize skeletal growth. In women, even within the normal menstrual cycle, calcium balance can fluctuate based on sex steroid levels and other factors affecting bone resorption and formation. Calcium balance over a range of calcium intakes has been used to determine the intake where calcium retention is maximal,[62,63] but this approach is even more resource intensive. Later in life, an increase in bone resorption caused by menopause and age-related bone loss results in a net loss of calcium. Therefore, calcium balance studies are appropriate for the characterization and validation of other biomarkers of calcium status, but on their own are unlikely to be suitable for use as population-level measures of calcium adequacy.

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HORMONAL FACTORS

Assessment of hormones involved in the regulation of bone mineral metabolism may reflect the extent to which sufficient calcium is available for bone formation or remodeling, and therefore may be responsive to interventions aimed at improving calcium nutriture.[68,69] PTH, the major circulating metabolite of vitamin D (25-hydroxyvitamin D; 25(OH)D), and the active metabolite of vitamin D (1,25-dihydroxyvitamin D; $1,25(OH)_2D$) play important roles in bone metabolism and calcium homeostasis.[70] Numerous assays are available to measure plasma/serum concentrations of 25(OH)D, $1,25(OH)_2D$, and PTH, and can, therefore, be used to assess the changes in their concentrations in response to dietary changes or other interventions.[10,71]

Serum PTH is a primary endocrine regulator of bone remodeling and a marker of fracture risk.[72] PTH governs serum calcium levels, stimulates the release of calcium from the skeleton, and increases renal reabsorption of calcium, thereby maintaining serum calcium within relatively narrow ranges.[73] Several studies have shown that calcium intake can modulate PTH levels for a given 25(OH)D value.[69,74] PTH is very responsive to calcium intake as both acute, postprandial increases in calcium intake or longer-term calcium supplementation have also shown favorable effects on bone metabolism through reduced PTH levels.[75,76] However, decreases in either calcium intake or 25(OH)D concentrations into the vitamin D deficiency range can increase serum PTH concentrations;[70] 25(OH)D should ideally be measured concurrently to use PTH as a marker of calcium status.

Levels of PTH have been measured in some national nutrition surveys[77–81] and have been inversely correlated with calcium intake,[77,79] although there are a number of challenges that would need to be addressed. PTH is most often measured by immunoassays, but variations in the assay methodology have made it challenging to set reference ranges, which would also need to consider vitamin D status and time of day of sample collection.[82–84] For a population-based survey, there are also challenges associated with measuring a peptide, which is sensitive to degradation, although this has been done successfully in some national nutrition surveys.[84]

One of the most significant factors affecting intestinal calcium absorption is $1,25(OH)_2D$, and the concentration of this active metabolite in a vitamin D replete individual is influenced by calcium intake, PTH concentrations, and serum phosphate levels.[85] While 25(OH)D is the major circulating vitamin D metabolite and the most relevant biomarker of vitamin D status, $1,25(OH)_2D$ is much less commonly measured in population surveys, and studies examining the association of $1,25(OH)_2D$ concentrations with bone health parameters have shown contradictory results.[86,87] Fractional calcium absorption was well correlated with $1,25(OH)_2D$ in young women (~28 years old) but not in older women (~72 years old).[88] While this shows the age-dependent response in calcium absorption, it may also demonstrate that $1,25(OH)_2D$ could not be readily used as a marker of calcium intake in a national nutrition survey. Additionally, there is a general lack of correlation between different immunoassay platforms that make data across studies difficult to compare.[85,89] This is largely due to a lack of validation studies between methodologies and across laboratories and standardized methods.

Serum 25(OH)D is a robust measure of recent vitamin D ingestion and cutaneous synthesis but does not directly reflect calcium status. Although some studies have suggested calcium intake may contribute to variation in 25(OH)D,[90] this phenomenon is not well established and would likely have a minor effect compared to the direct influence of vitamin D inputs. Therefore, 25(OH)D was not considered a candidate biomarker of calcium status in this review.

Bone turnover markers (BTMs), such as alkaline phosphatase (ALP), osteocalcin, procollagen type I N-terminal propeptide, collagen C-terminal–telopeptide, and deoxypyridinoline, provide insight into bone turnover dynamics and can be used to determine fracture risk or to monitor treatment for bone disorders.[9,59] BTMs can detect changes in bone microarchitecture that contribute to fracture risk resulting from increased bone turnover and may, therefore, be considered as complementary measures to bone mass.[91,92] In order to correlate hormonal changes with bone metabolism, BTMs may be measured concurrently with dietary assessment. However, BTM measurements have several limitations with respect to their utility for the assessment of calcium status. They may be perturbed by changes in calcium intake, especially if bone formation or resorption is being altered.[92] However, BTMs, such as ALP, deoxypyridinoline, pyridinoline, and hydroxyproline, do not consistently reflect differences in response to calcium intake.[93–96] Importantly, most studies comparing calcium intake with BTMs have been conducted on women in higher income settings and using calcium supplementation. Differences in biomarker concentrations based on age and life stage would require age- and sex-specific reference ranges in order to use them as biomarkers of calcium intake. As well, many BTMs are measured by immunoassays and can suffer from the same shortcomings in standardization and comparison across studies as described previously.[68]

While some of the hormone biomarkers discussed above may be influenced by calcium intake, they are also affected by other factors that confound their use in calcium status assessment. However, among these markers, PTH seems to be more responsive to calcium intake and the most promising candidate for inclusion in a population-based survey, despite the pitfalls of sensitivity to degradation and influence by vitamin D status.

HEALTH OUTCOMES

Inadequate calcium intake has been associated with numerous adverse health outcomes, including cancer, cardiovascular disease, hypertension, metabolic syndrome, falls, cognitive function, rickets in children, osteoporosis, and preeclampsia.[4] Ideally, the prevalence of a specific disease that is associated with calcium intake would be a good indicator of calcium status in that population. However, there are several limitations in assuming an association between average calcium intake and the prevalence of certain diseases (discussed in more detail in this Special Issue[8]):

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1. There are limited high-quality datasets that include both dietary calcium intake and disease prevalence parameters. Moreover, when data are available, they are more likely to be from high resource settings, which tend to have greater proportions of older adults (who, in turn, are more prone to osteoporosis and bone fractures).
2. Diseases are multifactorial, and as such there are many other risk factors (e.g., genetics, physical activity, and vitamin D status) that modify the association between calcium intake and these diseases.
3. There are associations that may be real at the individual level but might not be apparent or consistent at the population level.

As a result, this section will focus on three key health conditions that are mostly related to calcium: NR, osteoporosis, and preeclampsia.

The use of bone health outcomes as an indicator of calcium adequacy is long-standing. NR in children and infants is characterized by suboptimal bone mineralization at the growth plate, hypocalcemia, hypophosphatemia, and secondary hyperparathyroidism, which permanently alters bone structure.[3] Rickets manifests as stunted growth and bowing of the extremities in children.[97] Prolonged calcium insufficiency, combined with inadequate vitamin D exposure, could lead to rickets in young children.[98] In some LMICs, low calcium intake is a significant contributor to NR, along with inadequate exposure to vitamin D.[99]

Screening and diagnosis of rickets are based on an assessment of vitamin D and calcium intake from diet and supplements, sun exposure, clinical signs, biochemical testing, and radiographs.[98,100] Conventional biochemical parameters and imaging studies do not identify whether low dietary calcium intake or vitamin D deficiency, or both, is the principal cause of NR. However, in settings in which there is evidence of vitamin D adequacy, the prevalence of rickets may be a surrogate of dietary calcium inadequacy.[101]

An aging-related bone disorder linked to reduced bone mass and bone quality, osteoporosis compromises bone strength and bone mass.[3] Bone fragility increases with a decrease in bone mass, increasing fracture risk, especially in the vertebrae, hips, and forearms.[4] Osteoporosis primarily affects women, but it can occur in males as well.

A population-based osteoporosis risk assessment strategy could include the Fracture Risk Assessment Tool (FRAX score), the Fracture Index, as well as more simple screening tools, such as Osteoporosis Screening Tool (OST). While the Fracture Index estimates six clinical risk factors, the OST only considers age and weight.[102,103] These tools do not require BMD measurements. OST, the most widely tested predictor of osteoporosis, has comparable performance characteristics with high sensitivity.[102] A high sensitivity may offer cost savings by eliminating unnecessary BMD assessment, but these tools have yet to be well validated in men.

Furthermore, it is unclear whether OST is valid in multi-ethnic populations. FRAX index helps address this limitation by estimating fracture risk by race, although it is influenced by age when stratifying patients. Additionally, T-scores in bone density reports vary depending on the type of analysis compared with controls of the same race and sex.[43] Using FRAX with BMI would allow for the more targeted allocation of testing, including BMD, to high-risk individuals for osteoporosis or those at high fracture risk in resource-limited settings.[104] Once an intervention threshold has been established, fracture probabilities assume clinical utility. The intervention thresholds would need to be established depending on local priorities for osteoporosis and the absolute fracture risk in a region or country.

Nonetheless, it should be noted that some LMICs with known suboptimal calcium intakes have lower osteoporotic fracture rates in comparison to North America and Europe (with higher intakes of calcium)—a phenomenon that has been described as the calcium paradox.[8] Moreover, other longitudinal cohort studies failed to show an association between higher intakes of dietary calcium and reductions in fracture risk and osteoporosis.[105] This may be explained by the fact that osteoporosis is a multifactorial disease, and in addition to inadequate calcium intake, osteoporosis can be caused by genetics, hormones, and other risk factors.[106,107]

Preeclampsia is a complex and potentially life-threatening condition, manifested by high blood pressure and signs of organ damage during the second half of pregnancy. In populations with low calcium intake, it is recommended to supplement calcium during pregnancy to reduce the risk of preeclampsia.[6] Although limited data are available, several studies have examined whether low calcium intake can lead to preeclampsia.[6] Yet, a biological mechanism explaining how this can cause preeclampsia has not been elucidated. Moreover, there are inconsistencies in the results of observational studies and no causal relationship has been established for both calcium and vitamin D,[4] which may be explained by the multiple risk factors of this disease (e.g., previous preeclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease, and multiple pregnancies).[6] Thus, the prevalence of preeclampsia or pregnancy-induced hypertension cannot be considered a reliable indicator of calcium status in a population.

In conclusion, none of these health conditions have been consistently linked to calcium status that would enable a specific disease prevalence to be a robust indicator of calcium status at the population level.[4] Future research might provide further support for such associations, but the available evidence is limited.[4]

RESEARCH GAPS AND RECOMMENDATIONS

A reliable indicator of calcium status would inform public health policy decisions and enable monitoring of the effectiveness of calcium-related interventions. Many of the potential indicators of calcium status discussed here have important limitations, including a lack of specificity or sensitivity for assessing calcium status and low feasibility for population studies. For example, current indicators of bone health and calcium balance have not been shown to be highly correlated with changes in calcium intake, perhaps due to the short-term nature of many studies or the relatively slow response of these indicators. Most indicators of calcium absorption or metabolism are also responsive to vitamin D status, suggesting that future applications of these indicators would ideally need to account for vitamin D status through concurrent measurement of 25(OH)D. Additionally, most of the available data related to calcium intakes and bone health or other health

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outcomes are from higher-income settings where average calcium intakes are relatively high.

Genetics, sex and gender, life stage, socioeconomic status, dietary patterns (beyond calcium intake), and physical activity all contribute to long-term bone health and other calcium-related health outcomes and, therefore, need to be considered in biomarker validation and establishment of cutoffs for candidate calcium status indicators. Despite a low calcium diet, some populations do not appear to have the same adverse effects on bone health that are observed in many high-income settings where higher calcium intakes are more common.[108] The majority of studies have been conducted among older adults or postmenopausal women, and data related to calcium adequacy are sparse for children and younger adults, yet it is likely that meaningful clinical targets and interventions will differ by life stage for any of the candidate biomarkers.

Until any of the candidate biomarkers are further validated, the dietary assessment remains the most feasible and useful approach in population-based surveys for assessing calcium intakes. Dietary recalls and analyses of food balance sheets have demonstrably served the purpose of highlighting global inequities in the availability and intake of calcium-rich foods.[6–8] However, it is important to acknowledge that assessment of dietary intake is not a biomarker of calcium status as it does not directly address calcium adequacy and, therefore, the use of such methods may be combined with clinical indicators for which data can be feasibly ascertained through household or facility-based surveys, including the prevalence of rickets (children) and fracture rates (older adults).

In settings where blood collection and processing are feasible, consideration should be given to the use of PTH, with concurrent measurement of 25(OH)D, to assess population-average calcium status. This approach could be used to identify subgroups at the highest risk of suboptimal calcium status (e.g., elevated PTH despite normal 25(OH)D), to track changes in median PTH over time or in response to calcium interventions, and to compare PTH distributions across populations. However, further research is needed to validate PTH assays for these applications and to define PTH cutoffs that are suitable for identifying suboptimal calcium status at different life stages.

CONCLUSIONS

To assess calcium status, a variety of candidate methods are currently available, including dietary assessment, calcium-balance studies, biochemical analyses, and radiological examinations. However, these methods are either not specific to calcium intake or are poorly suited to the large-scale screening of calcium status assessment in populations. Further research is required to develop and validate a specific indicator of calcium status that could be derived from the analysis of data or samples that are feasibly collected in population health and nutrition surveys.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

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