Summary of the First Meeting of the Calcium Task Force
By Hallie Kapner

Overview

An estimated 3.5 billion people around the globe are at risk of calcium deficiency[1] due to inadequate dietary intake. While primarily associated with bone health, calcium has also been shown to reduce the risk of preeclampsia and preterm birth, which are leading causes of maternal morbidity and mortality and under-5 mortality. Populations in low- and middle-income countries (LMICs), especially in parts of Asia, Africa, and South America, are at greatest risk of low calcium intakes, yet many high income countries also fail to meet recommendations.

On March 1-3, 2021, the Nutrition Science Program of the New York Academy of Sciences (NYAS), with support from the Children's Investment Fund Foundation (CIFF), convened the first of two meetings of the Calcium Task Force. This international group of experts representing pediatrics, obstetrics, maternal and child health, nutrition science, food fortification and implementation is tasked with developing practical guidance for interventions and policies to improve calcium intake and health outcomes based on available evidence, and to identify areas where further research is needed.

Participants

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Key Takeaways and Research Needs

Calcium supplementation during pregnancy reduces the risk of maternal hypertensive disorders, including preeclampsia, as well as preterm birth. Addressing low calcium intakes in populations at highest risk for preeclampsia will likely require a combination of supplementation and fortification. WHO guidelines on maternal calcium supplementation are not widely implemented due in part to cost and logistical issues related to the large dose and burdensome dosing schedule.

More research is needed in a variety of areas to help policymakers identify whether low calcium intakes should be addressed in their populations, which intervention(s) are most feasible, and how to streamline program implementation.

In the absence of overt health conditions such as rickets, there is no consensus definition of what constitutes low calcium intake or calcium deficiency. Evidence suggests that intakes below 800mg/day are suboptimal. Options for assessing calcium status in relationship to intake are limited by the absence of a well-validated, specific biomarker of calcium status that is "field-friendly," and thus feasible at population level and priced for use in LMICs. Several emerging methodologies may hold promise in this area, but more research is needed. In the interim, research regarding the utility of "sentinel conditions" such as rickets as indicators of population level calcium status may be helpful. As calcium is just one determinant of bone health and is associated with many other aspects of health beyond bone, the group acknowledged that no single biomarker or health outcome will offer a perfect indicator of calcium status.

Fortification is a valid strategy for adding calcium to the diet, but more research is needed to identify region-specific vehicles that are both suitable for calcium fortification and widely consumed in adequate quantity to achieve fortification goals. New studies on the effectiveness of lower-dose calcium during pregnancy may point a path toward simplifying both fortification strategies as well as supplementation programs.

Meeting Summary

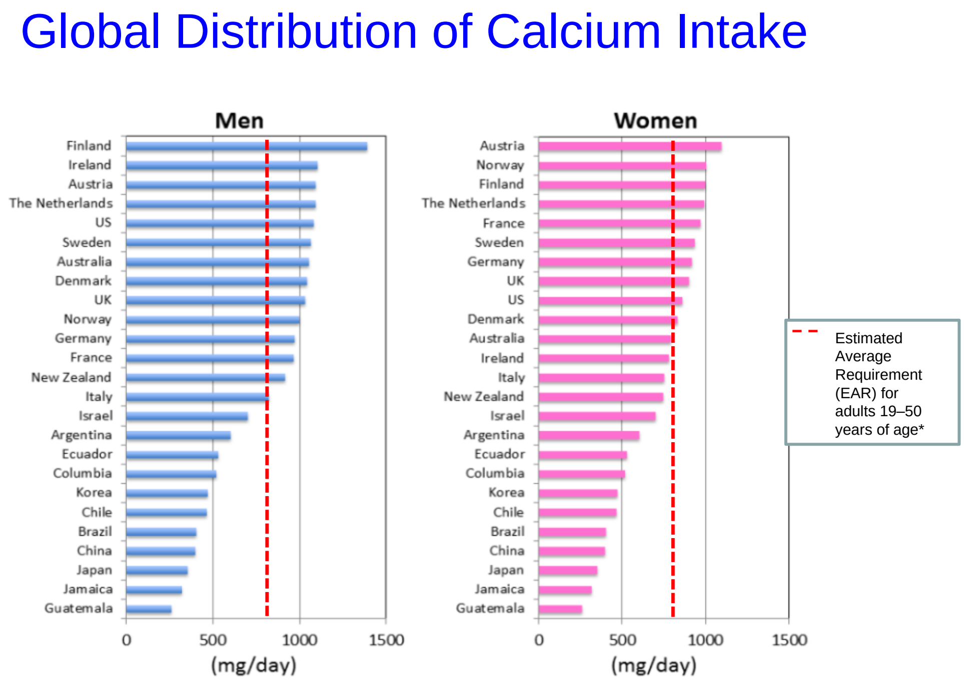
I. Dietary Prevalence and Calcium Intake Recommendations

Global calcium distribution

Dietary reference intakes (DRI) for calcium in the United States and Europe are based on a single outcome: bone health, according to **Connie Weaver**, who provided an overview of calcium intake recommendations and calcium distribution around the globe. Recommendations for calcium intake are designed to maximize bone accretion during the growth periods of childhood and adolescence, and to promote bone retention later in life, particularly among postmenopausal women.

Primary dietary sources of calcium in Western countries include dairy products such as milk, yogurt, and cheese, as well as fortified cereals, flours, orange juice, and soy beverages. While beans, broccoli, and leafy greens such as spinach contain calcium, these foods also contain high levels of oxalates and phytates, which lower bioavailability by binding to calcium and inhibiting absorption.

Populations in countries where dairy products and fortified foods are widely consumed are likelier to meet calcium requirements. Perhaps unsurprisingly, much of the world has calcium intakes well below the requirement,[2] especially in LMICs and those where dairy is not a typical component of the diet, such as Japan.



Shin CS and Kim KM. J Cell Biochem. 116:1479-1805;doi 10.1002/jcb.25119, 2015.

Understanding calcium requirements

Calcium comprises nearly two percent of adult human body weight and is a constant proportion of bone mineral. “The more calcium you have in bone, the higher the bone mineral density,” Weaver said. Bone mineral density (BMD) is linearly linked to fracture risk, and intake requirements vary by age and sex. “Each life stage has a different goal,” Weaver said. Calcium intake requirements peak in adolescence to support periods of rapid growth, then decrease in adulthood, only to rise again for women following menopause and in all populations after the age of 70, as calcium retention decreases with age.

A variety of methods have been used to calculate calcium requirements, all of which, Weaver explains, result in similar outcomes in terms of the amount of calcium needed to maintain bone health throughout life. The Institute of Medicine (IOM) has established the following DRIs for calcium by life stage[3]:

Age	AI	EAR	RDA
0-6 months	200mg	-	-
6-12 months	260mg	-	-
1-3 years		500mg	700mg
4-8 years		800mg	1000mg
9-18 years		1100mg	1300mg
19-50 years		800mg	1000mg
51-70 years (Men)		800mg	1000mg
51-70 years (Women)		1000mg	1200mg
Over 70		1000mg	1200mg

While calcium intake guidelines do not vary by race, studies show racial and ethnic differences in calcium retention and bone mineral density. Weaver reported that among American adolescents, Black females had higher calcium retention, more efficient absorption, and lower urinary calcium excretion than white males and females[4], a trend that persists into adulthood.[5] Task force member **John Pettifor** noted that Black African populations have lower bone mass than Black Americans, perhaps owing to lower calcium intakes, yet they suffer far fewer fractures. It is not known whether this is an adaptation in response to prolonged low calcium intakes or a genetic advantage geared to maximize calcium absorption. Asian females had the highest calcium retention at the lowest intake levels among groups studied.[6]

Ethnic differences in calcium absorption may partially account for differences in recommended intakes in some countries. **Anuradha Khadilkar** explained that Asian countries, including India, have lower recommended calcium intakes than Western nations. It is noteworthy that many Indians consume very little dairy and follow a vegetarian diet, often including vegetables with significant oxalate levels.[7]

Calcium retention also varies with body mass index (BMI), such that those with higher BMI have higher calcium retention than those with lower BMI, but only in the setting of adequate calcium intake. In settings of low calcium intake, those with higher BMI are noted to have lower bone mineral density and increased risk of fracture.[8]

Defining calcium deficiency

Due to difficulties in measuring calcium status and an inconsistent relationship between low calcium intakes and health outcomes—not all populations with low calcium suffer negative consequences— there is no widely accepted definition of calcium deficiency. According to Weaver, agencies including the IOM and the European Food Safety Authority generally consider calcium intakes below the country's EAR as suboptimal.

II. Calcium and Health Outcomes

Bone Health and Rickets

Premature infants and low birth weight

Premature infants have been largely left out of discussions about optimizing calcium intakes, said **Steven Abrams**. Due to insufficient calcium and phosphorus accrual *in utero*—which peaks late in the third trimester— preterm babies have the highest incidence of rickets worldwide. Rickets in this population is distinct from the disease in toddlers and young children, which is primarily associated with low vitamin D intake. Babies who are small for gestational age (SGA)—which is approximately one third of babies born in LMICs— are also at elevated risk for rickets.

Premature infants are not included in the IOM or WHO calcium guidelines. The American Academy of Pediatrics does offer guidance on calcium, phosphorus, and vitamin D intakes for preemies[9], and additional reference materials detail the nutritional needs of this population.[10] Abrams reports that without fortification, neither breast milk, infant formula, or even total parenteral nutrition formulations used for premature infants can meet the calcium and phosphorus levels required for bone health and growth. As a result, rickets still occurs among preemies in the United States, and more commonly in LMICs.

Infants at highest risk of rickets (birth weight <1000g) are monitored by assessing peak serum alkaline phosphatase activity, a "reasonable but imperfect biomarker" for the development of rickets, said Abrams.[11] Much like older children with rickets, rachitic babies are at high risk of fracture and bone deformity.

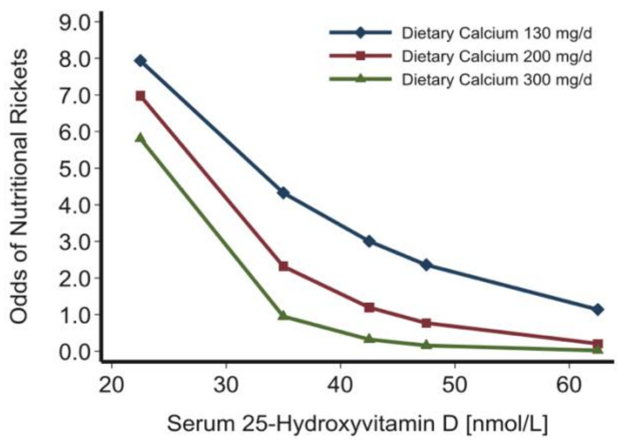
Vitamin D vs Calcium-Predominant Rickets

Rickets in early childhood and adolescence was once considered to result strictly from low vitamin D intake. However, the interaction of calcium and vitamin D is now seen as central to both types of rickets.[12] A comparison of vitamin D rickets versus calcium-predominant rickets reveals that children with vitamin D rickets are likelier to be breastfed infants or toddlers with low endogenous vitamin D production due to dark skin pigmentation or insufficient sun exposure. Outside of the premature infant cohort, calcium-predominant rickets mainly afflicts malnourished children and teenagers with normal or slightly low vitamin D levels, but extremely low calcium intakes (<300mg/day). Extended breastfeeding without complementary food sources of calcium, as well as extremely restrictive diets, including vegan diets, also increases the risk of rickets.[13]

Genetic and environmental risk factors

Calcium and vitamin D intakes unquestionably influence the risk of developing nutritional rickets, but little is known about other risk factors, including genetic and environmental influences. **John Pettifor** described research efforts to elucidate these potential links. One study of Nigerian children[14] revealed a nearly 15% incidence of family history of rickets among a cohort of rachitic children, compared to a 3% incidence in a control group. Similarly, mothers who have previously had a child with rickets had lower calcium concentration in breastmilk than control mothers.[15] Whether these findings are the result of a genetic difference in calcium homeostasis in mothers of rachitic children or some other predisposing factor remains to be seen.

Researchers have long hypothesized that the degree of calcium deprivation plays a role in the risk of rickets. A recent study[16] adds what Pettifor describes as "good evidence" that calcium status plays a "major role" alongside vitamin D status in the likelihood of developing rickets. Analyses of rachitic children compared to controls shows that while the majority of the rachitic cohort had 25(OH)D levels ≥30 nmol/L, the IOM cut point for deficiency, the risk for rickets was higher among those with low 25(OH)D *and* low calcium intake. As calcium intakes decrease, Pettifor said, "you need substantially higher 25(OH)D to maintain normal calcium homeostasis."



Cardiovascular and Other Health Outcomes

Preeclampsia

One of the most well-documented benefits of calcium supplementation beyond bone health is a significant reduction in the risk of preeclampsia, as **Gabriela Cormick** detailed in a review of calcium's relationship to cardiovascular and other health outcomes. A Cochrane review[17] of the effects of high-dose calcium supplementation (1.5-2g/day) during the second half of pregnancy shows a more than 50% reduction in the risk of preeclampsia. While WHO guidelines[18] recommend high-dose calcium supplementation for pregnant women in settings of low calcium intake, implementation of this recommendation is low. Cormick reports that pregnant women in LMICs have mean calcium intakes of 687mg/day, compared to 948mg/day in high income countries.[19]

Several recent studies have assessed the potential benefits of low-dose calcium supplementation in pre-pregnancy and early pregnancy. The Calcium and Preeclampsia (CAP) trial tested the impact of a 500mg daily calcium supplement from pre-pregnancy through 20 weeks' gestation in women with a history of preeclampsia in Argentina, South Africa, and Zimbabwe. Women who adhered to at least 80% of the supplementation regimen had a 34% reduction in preeclampsia risk with no adverse side effects reported.[20] Following the CAP trial, WHO amended their recommendation to recognize the importance of improving calcium status before pregnancy.[21]

Other cardiovascular outcomes

"The relationship between calcium supplementation and reduction in preeclampsia risk seems to be mediated by a decrease in blood pressure,"[22] said Cormick. Calcium supplementation also shows a "small but consistent effect" in preventing primary hypertension[23] and reducing body weight[24] in a variety of age groups. Calcium supplementation is associated with favorable changes in cholesterol metabolism,[25] including a reduction in LDL and increase in HDL, possibly due to calcium binding with triglycerides and bile acids.

Health benefits for offspring

Calcium supplementation during pregnancy may have benefits to offspring beyond birth and the postnatal period. Children whose mothers were supplemented with calcium during pregnancy have a reduced risk of dental caries at age 12[26] and lower systolic blood pressure.[27] These aspects have not been well-studied, and the mechanisms of these potential benefits are unclear.

Concerns

Short-term studies have shown that high-dose calcium supplementation can inhibit iron absorption, but Cormick explained that long-term studies of hemoglobin status show no ill effects from interactions between iron and calcium. Supplementation of postmenopausal women is controversial in some regions due to an association between myocardial infarction and calcium supplementation in this population. However, meta-analyses[28] [29]show no increase in all-cause mortality or cardiovascular disease mortality among postmenopausal women taking calcium supplements.

III. Biomarkers and Assessment of Calcium Status

Assessing calcium status

Efforts to define calcium deficiency and address low calcium intakes are hampered by difficulties in assessing calcium status. Calcium intake assessments rely on dietary recall questionnaires, which often focus on dairy and calcium supplements.[30] Such surveys are less relevant in LMICs with little access to calcium-rich foods or supplements. Calcium is tightly regulated in the body, and many biochemical markers tied to calcium status are also associated with other nutrient deficiencies. Dual-energy x-ray absorptiometry (DXA) is the gold standard for determining total body bone content and bone mineral density, but it is costly and can only detect bone changes associated with later stages of deficiency. The search for a "sensitive and specific" marker of calcium status has yielded several intriguing techniques, according to **Victor Owino**, who discussed both existing and emerging methods of assessing calcium.

Biomarkers of calcium status

Several hormonal markers associated with bone metabolism can provide insight into calcium status,[31] yet none are strictly specific to calcium. Reduced intestinal absorption of calcium and inorganic phosphate triggers increased levels of parathyroid hormone (PTH): however, elevated PTH is also associated with low vitamin D status. Similarly, low serum insulin-like growth factor 1is seen in the setting of protein or vitamin D deficiency, as well as low calcium. While not a measurement of calcium status, markers of bone resorption and formation can also be assessed as indicators of bone health, as accelerated bone turnover is associated with increased risk of fracture.

Urinary metabolomics is a relatively new frontier in assessing calcium status. A study[32] exploring the potential for urinary metabolite analysis to indicate calcium status identified 27 biomarkers of interest in animal models. Metabolite levels are far more sensitive to shifts in calcium intake than bone mineral density, vitamin D levels, or even calcium itself, Owino explained. "The researchers suggest that you could use these metabolites in combination to determine the stage and severity of calcium deficiency....as some markers appear early in deficiency, and some appear later," he said.

Calcium status can also be assessed by measuring total urinary calcium excretion over a 24-hour period. While accurate, this method is overly burdensome. To avoid the need for 24-hour urine collection, one study[33] tested a thrice-daily spot collection schedule and determined that it is possible to measure calcium status by calculating the urinary calcium/creatinine ratio of these samples. Accuracy varied based on the time the spot samples were collected—for example, the evening and first morning urine samples correlate most closely with measures of 24-hour urine calcium.

Stable calcium isotopes have been recently proposed as a novel biomarker of bone health[34] that could be used as a highly sensitive indicator of changes in bone metabolism that occur well before decreases in bone mineral density. This method uses thermal ionization mass spectrometry to measure the ratio of heavier to lighter calcium isotopes in urine. During bone formation, lighter isotopes, including ^{40}Ca, are preferentially taken up by bone tissue, while heavier isotopes such as ^{44}Ca are excreted in urine. In bone resorption, the process reverses—lighter isotopes leach from bone and present as a higher ratio in urine. This approach has been validated in a study of women with DXA-diagnosed osteoporosis.[35] One downside is the complex equipment required for this type of analysis. Some studies also suggest that in settings of adequate calcium intake, the isotope ratio in urine may be less applicable.

IV: Preeclampsia and Preterm Birth

Maternal hypertensive disorders are the single largest cause of maternal death worldwide, accounting for an estimated 21% of obstetric deaths and linked to 1.5-2 million neonatal deaths annually. **José Belizán** noted that as maternal deaths from other complications, such as hemorrhage, have plummeted over the past 30 years, rates of maternal hypertensive disorders remain unchanged.

Preeclampsia is a multifactorial condition marked by what **Erick Boy** characterized as "an onslaught of immune and inflammatory responses" and placental dysfunction, all of which contribute to hypertension in pregnancy. The only preeclampsia treatment that is 100% effective is the delivery of the baby and placenta. Considerable efforts have been focused on preventing preeclampsia, but "no preventative strategy is effective if there is no identification of risk," said Boy. The International Federation of Gynecology and Obstetrics (FIGO) recommends[36] universal first-trimester preeclampsia screening using a combination of maternal history risk factors and biomarkers including mean arterial pressure (MAP), serum placental growth factor, and uterine pulsatility index. This assessment is "almost impossible" in low-resource settings, said Boy, although maternal history and MAP alone have some predictive value.

Prophylactic measures

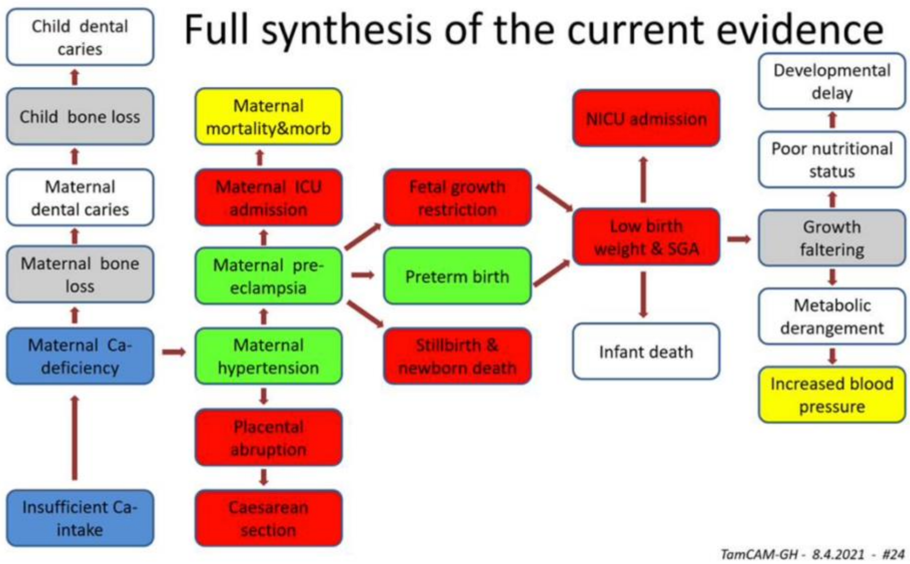
There is significant evidence that low-dose aspirin can reduce the risk of preeclampsia. The effect size varies among clinical trials due to differences in the timing of initiation of aspirin therapy (early pregnancy vs. later) and dose, but a recent meta-analysis showed a 70% reduction in preterm preeclampsia among women who take ≥100mg aspirin daily starting in the first trimester.[37] Guidelines from FIGO as well as the American College of Obstetrics and Gynecology recommend 100-300mg of aspirin daily *only for women identified as high-risk for preeclampsia*, beginning at 11-16 weeks of gestation and continuing through 36 weeks.[36] To increase compliance, counseling patients on the risks of preeclampsia and benefits of treatment, as well as normalizing common aspirin side effects, are also recommended.

High dose calcium supplementation during pregnancy can reduce preeclampsia risk by half in settings where women are likely to have low calcium intakes, and this is reflected in the WHO guidelines. WHO has cited insufficient evidence to recommend supplementation for all women pre-pregnancy, although studies show a benefit to pre-pregnancy calcium supplementation for women with a history of preeclampsia.

Data on the potential benefits of Vitamin D supplementation in preventing preeclampsia is inconclusive, with older meta-analyses showing a mild protective effect, and a more recent study[38] showing a greater effect. "The jury is still out on vitamin D," said Boy, "but the evidence is not consistently strong."

Lessons from antenatal calcium trials

Per Ashorn reviewed the cascade of maternal and fetal complications that have been potentially linked to low calcium intake during pregnancy. Synthesizing information from Cochrane reviews as well as other systematic reviews and meta-analyses, Ashorn reported that solid evidence exists to support that calcium supplementation positively impacts many of these outcomes.



Green positive effect likely
Yellow positive effect possible
Red positive effect unlikely
Gray effect unknown, inconclusive research
White effect unknown, insufficient research

The strongest evidence[17] shows an impact of supplementation with high-dose calcium (≥1g day) on maternal hypertension (35% risk reduction), preeclampsia (55% risk reduction) and preterm birth (24% reduction in preterm birth overall, 55% among women identified as high-risk for preeclampsia). A 20% reduction in maternal morbidity was also reported.

Little evidence exists to support a benefit of calcium in reducing fetal outcomes including neonatal death and stillbirth, NICU admission, growth restriction, and low birth weight/SGA, as well as maternal complications including placental abruption, ICU admission and Cesarean birth.

Ashorn and his collaborators conducted meta-analyses and systematic reviews to ascertain the impact of calcium supplementation on infant and child outcomes (e.g. growth, cardiovascular, metabolic, neurodevelopmental)[39], as well as potential benefits to maternal and child bone and dental health.[40] Data support a potential benefit for decreased systolic blood pressure among children whose mothers were supplemented during pregnancy, and a possible decrease in the likelihood of the children´s dental caries.[26,27]

Either a lack of data or conflicting results prohibit a determination on whether calcium can benefit growth faltering, infant death, developmental delay, poor nutritional status, metabolic issues, or maternal and child bone loss.

The potential of low dose calcium supplements during pregnancy

Calcium supplementation programs and clinical trials often utilize a high-dose regimen, typically 500mg dosed 3 times daily. **Wafaie Fawzi** offered a brief history of this dosage regimen, relaying that early trial designers selected the dose because it was "thought to be big enough to have an impact, and not because lower doses were looked at and excluded." For years, calcium trials simply followed the lead of the initial trials, with variations in geography and sample size.

Yet, as Fawzi said, despite convincing evidence on the benefits of high-dose calcium to prevent preeclampsia and preterm birth, "in most settings where there is a need for this intervention, it has not been implemented." One reason for this is the costly and demanding thrice-daily dosing schedule. A simplified regimen with fewer pills is an appealing option, and according to Fawzi, previous studies indicate "limited but promising" data on calcium supplements ranging from 500-800mg/day.[17]

Fawzi and a team of collaborators are currently conducting a non-inferiority trial[41] among nulliparous women <20 weeks' gestation in Tanzania and Bangalore. Their protocol compares the effectiveness of high-dose (500mg 3x/day) and low-dose (500mg plus two dummy pills) calcium to prevent preeclampsia and preterm birth. The trial will follow the cohorts until 6 weeks postpartum and will also monitor for gestational hypertension, SGA, and perinatal mortality. To further understand the mechanisms by which calcium acts on these outcomes, the team is collecting blood samples from a subset of trial participants, examining angiogenic and inflammatory markers, endocrine regulators, and metabolic mediators.

VI. Calcium Supplementation Programs

Implementation challenges and strategies

WHO guidelines for calcium supplementation in pregnancy are not widely implemented due to cost, local supply issues, and the somewhat "daunting" dosing regimen, according to **Kate Dickin**. The agency has recognized a need to identify factors that hinder or enable adherence to calcium supplementation programs. Dicken offered considerations to guide future calcium supplementation efforts, based on qualitative studies of calcium and IFA supplementation in Kenya[42] and Ethiopia.[43]

Education and instruction are important elements of compliance. The women in Dickin's studies were highly adherent to supplementation (70-100%), and most were unfazed by the pill burden as long as they were provided clear instruction and education on the benefits of supplementation.[44] This information is especially important as both women and health care workers often had little awareness of preeclampsia. "There was no word for it in either local language," Dickin said. Other factors that boosted compliance were keeping pills readily accessible and recruiting a family member as a supportive "adherence partner."[45]

Factors that hindered compliance often had little to do with calcium itself. Rather, women missed doses due to forgetting, working outside the home, or not having easy access to food or water at dosing times. Women were likelier to stop taking supplements if family members were unsupportive, or if they feared being stigmatized—in some countries, taking pills during pregnancy is associated with HIV.

Dickin also addressed the challenging reality that many women in LMICs do not seek early antenatal care (ANC) unless they have specific concerns. Training community health workers to conduct outreach is one strategy that could accomplish a greater goal of boosting utilization of ANC services and increasing the likelihood of supplementation program success.

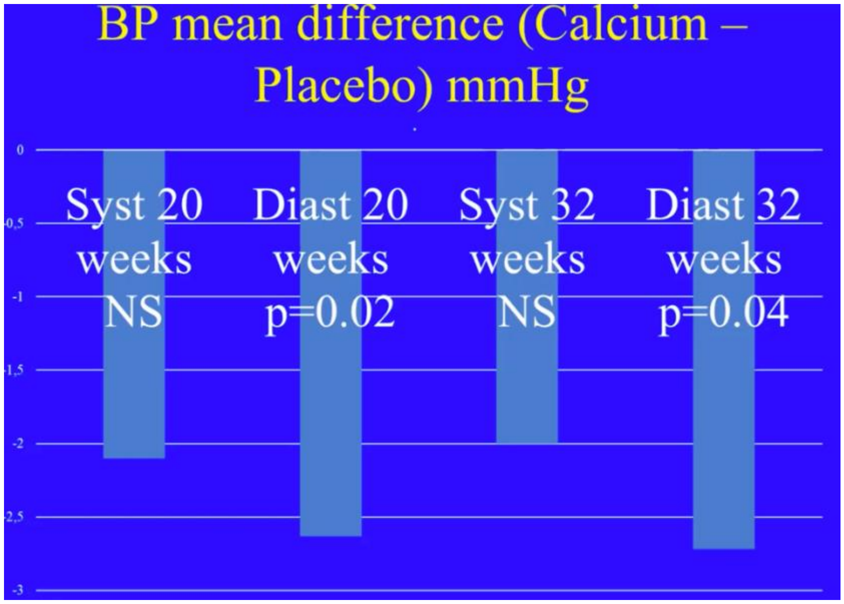
Targeting populations at high risk of preeclampsia

Demographic considerations

Justus Hofmeyr reviewed a "hierarchy of targets" for calcium supplementation programs aimed at preventing preeclampsia. Women at highest risk are adolescents and young women, women having their first baby with a current partner, and women with a history of preeclampsia. Women outside these categories with low calcium intake should also be considered.

Timing considerations

Most trials testing the effect of calcium on preeclampsia begin in the second half of pregnancy, but Hofmeyr emphasized that the underlying pathophysiology begins much earlier. "If calcium actually impacts preeclampsia [itself] rather than just being a mild antihypertensive, it needs to be given in the first half of pregnancy," he said. Unpublished data from the CAP trial[20] support the idea that calcium supplementation before pregnancy impacts the origins of preeclampsia, even at low doses. An experimental group of women with previous preeclampsia who were dosed with 500mg calcium starting in pre-pregnancy had a significant drop in diastolic blood pressure (-2.5mmHg) at 20 weeks compared to controls. This effect persisted during the second half of pregnancy, when all participants were supplemented with high-dose calcium. "We felt this was an indicator that low-dose calcium in early pregnancy...had some persisting effect on the process of developing preeclampsia," Hofmeyr said.



Resource considerations

In settings with no resource constraints, Hofmeyr advocates following WHO guidelines. Yet many countries with low calcium intakes are resource-constrained. "If we can only afford so much calcium, I would like to suggest that giving 500mg to 3 times the number of women is likely to have a much greater public health impact," Hofmeyr said, acknowledging that more research[41] is needed to confirm this approach.

Lack of demand for ANC services among pregnant women in many LMICs is likely to hamper any antenatal supplementation program and complicate efforts to reach women early in pregnancy, especially high-risk women. Hofmeyr noted that staple food fortification may be the most feasible route to improving calcium intakes pre-pregnancy and in early gestation.

Potential impacts of calcium supplementation at scale

Chris Sudfeld shared the results of a novel modeling exercise that aims to estimate the human capital benefits of scaling up calcium supplementation. Previous studies[46] have considered the impact of childhood nutrition programs across the life course, linking them to outcomes including school performance, social emotional development, work capacity, and productivity.

While calcium has not been previously modeled in this context, Sudfeld commented that calcium's impact on preterm birth—the leading cause of under-5 mortality worldwide—warrants this type of exercise.

Sudfeld and his collaborators paired data on the effects of calcium supplementation on pregnancy and preterm birth with observational cohort data[47] showing an association between prematurity and lower schooling attainment. The group also factored in estimates[48] of global returns on education and the impact of schooling on future income to calculate the lifetime income gained by preventing preterm birth.

Results varied widely based on the average annual income in countries and the relative benefit of additional schooling. Modeling the reduction in preterm birth if calcium supplementation was scaled to 90 percent coverage in Bangladesh, Sudfeld's model showed total income gains of $213M USD annually. In South Africa, the same exercise yields an additional $1B USD each year. Across 32 LMICs, the total gain is almost $19B. "We recognize this is an estimate, but it's what we've got today," Sudfeld said.

Research gaps related to supplementation

The task force identified several areas where more work is needed related to calcium supplementation during pregnancy, with a focus on those that may increase compliance or make programs more widely accessible. **Jean Humphrey** led a discussion of needs that she deemed "implementation science-heavy," commenting that the evidence that calcium, along with multiple micronutrients and low-dose aspirin, greatly impact preterm birth is plentiful, "we just haven't figured out how to do it."

The group agreed that the greatest benefits of supplementation can only be achieved if women begin supplementation early and comply with the regimen. Among the ideas that surfaced to overcome these hurdles is equipping community health workers with at-home pregnancy tests, empowering women to learn their status at home, in private, which may increase likelihood of earlier ANC attendance. Another is adherence packaging, which provides pregnant women with daily dose packets including calcium, MMS, and potentially aspirin, for the duration of pregnancy.

The discussion also touched on ideas for increasing calcium absorption by adding prebiotics to calcium supplements, an approach that has been shown successful in some studies.[49]

VII. Increasing Calcium Intake Through Food Fortification and Processing

Food sources of calcium and bioavailability

All food sources of calcium are not created equal, and the key difference is bioavailability. Nutrient databases and food labels can be misleading, listing the total calcium content of a food without noting the quantity of *absorbable* calcium. Through that lens, spinach can be considered a high calcium food, despite the fact 15 cups of spinach are needed to equal the bioavailable calcium in a single cup of milk.[50] Good food sources of calcium should provide at least 30mg of absorbable calcium in a ≤100 calorie serving.[51]

Food	Serving	Ca per Serving (mg)	Ca per 418 kJ (100 kcal) (mg)	Ca Absorb Serving (mg)	Energy per Serving (kJ)	Ca Absorp (%) [B]
Orange Juice [★,A] (calcium fortified CCM)	237 mL	300	268	90	468	30
Milk [★] (whole)	237 mL	276	189	89	610	32
Kale [○]	85 g	47	448	23	46	49
Spinach [○,B]	85 g	122	595	6	88	5
Soybean [●] (cooked)	86 g	88	59	21	623	24
Carrots [○] (raw, sliced)	1 cup	42	52	22	221	53
Potato [●] (baked)	1 med	26	161	6	675	22 [□]

(Yang, et al, 2012)

In plants, calcium content is influenced by both genetic and environmental factors, including soil properties.[52] Various calcium compounds in soil are taken up by the roots, transformed into calcium oxalate or calcium maleate, and translocated mainly to the leaves, although stems, grains, and seeds also contain calcium.

Biofortification

Keith Lividini reviewed the potential for using biofortification to create calcium-rich varietals of staple crops. Agronomic biofortification relies on the application of fertilizers to soil or leaves to boost micronutrient content.[53,54] Soil management, including the use of mycorrhizal fungi, can also be used to maximize uptake.

Strategies for agronomic fortification focus on increasing bioavailable calcium in the edible parts of the plants, with a special focus on fruits and seeds, rather than leaves. Successes include calcium-enriched durum wheat,[55] Rocha pears,[56] sunflower sprouts, mustard and lettuce.[57] However, Lividini said, "the physiology that underlies calcium transport throughout the plant has not been completely elucidated," thus more work remains to determine how to best accomplish this goal across a greater range of crops.

Agronomic biofortification can improve general soil health,[53] but it is costly, and as calcium fertilizers do not impact crop yield, there is little incentive for farmers to apply them.[58] Experts in agronomic fortification for calcium advocate for its use in "niche areas," and encourage implementation alongside breeding programs.

Traditional biofortification programs require an understanding of genetic variations that promote the desired trait—in this case, increased calcium. Little is known about the genetic control or physiologic mechanisms that contribute to high calcium in staple crops. "We're in a discovery phase," Lividini said. Target crops of interest include finger millet, which is already high in calcium and can be sustainably grown and easily stored, as well as other millets and cereal crops including wheat, rice, maize and sorghum.

Genetically modified crops represent opportunities for creating varietals with improved calcium transport or lower levels of antinutrients including oxalate and phytic acid. However, GM crops can be controversial, and little is known about the potentially detrimental impacts on plant health as a result of increased calcium or decreased phytic acid.

Improving calcium through food processing

Commercial fortification is the most far-reaching method for increasing the amount of calcium in food. Yet, methods for fortifying with calcium or boosting bioavailability also exist outside commercial production pipelines. **Salvador Villalpando** reviewed food processing techniques from cultures around the world that enhance calcium intakes. For millennia, populations in Mexico and Central America have added calcium salts to corn before making it into dough. This process, known as nixtamalization, decreases the amount of phytic acid in maize, increasing bioavailable calcium by as much as 18x in some studies.[59] Researchers have also developed low phytate varietals of corn, and comparisons of mean fractional calcium absorption following meals containing native corn vs low phytate corn show higher rates of absorption among those who ate the varietal.[60]

In Bangladesh, small indigenous fish are dried and eaten with bones intact, or ground for use in condiments that can provide as much as 360mg of calcium per 30g serving.[61] In Tanzania, the calcium-rich shells of chicken eggs may be dried, ground to a powder, and added to other foods.[62]

Dietary prebiotic fiber has been proposed as a method to increase calcium absorption.[63] Fermentation of these indigestible carbohydrates by microbes in the lower gut reduces local pH, which is believed to inhibit the complexation of minerals that can reduce calcium absorption. This approach is still experimental and would require regular consumption of prebiotics to both maintain increased calcium absorption and foster populations of intestinal microbiota that facilitate the process.

Identifying practical vehicles for food fortification

Calcium fortification programs are “sparse”[64] compared to other micronutrients, and according to **Cristina Palacios**, this is due to both technical and practical issues. Due to low bioavailability, large quantities of calcium salts are required to achieve fortification goals, and some forms of calcium can change the color, acidity, or taste of fortified foods, with potentially negative impacts on acceptability and shelf life.[65]

While there is no “clear-cut, silver bullet answer” for selecting a vehicle, Palacios suggests that the best options are foods that are regularly consumed, and in adequate quantities, by target population(s). Staple crops, bread, breakfast cereals, dairy products, infant formula and cereals, orange juice and tofu are common fortification vehicles. Emergency and therapeutic foods recommended by the World Food Programme are also fortified with calcium.

Few examples exist to illustrate the impact of fortification on population-wide calcium intakes. Britain is the only nation with a mandatory calcium fortification program (wheat), which supplies 13-14% of calcium intakes across the population.[66] Without that program, an estimated 10-12% of adolescents would fall short of intake requirements.[67] Dozens of other countries have regulations for calcium fortification, but participation is voluntary. One study on the impact of voluntary calcium fortification shows that in the United States, 54% of those who do not consume calcium-fortified products have intakes below the recommendation, compared to 38% of people who consume fortified foods.[68] The impact of calcium fortification programs in LMICs has been minimally studied, and this remains an area for greater research.

Potential for Impactful Calcium Fortification

"Fortification is conceptually very simple, but the devil's in the details," said **Lynnette Neufeld,** who offered a frank overview of the implementation challenges of staple food fortification programs, with a focus on unresolved questions that should be addressed prior to initiating calcium fortification.

As a population-level intervention, staple food fortification would, with no special effort or change in behavior, reach groups for whom calcium intake is especially important—young women before or during pregnancy, children, women with a history of preeclampsia, and others with low intakes. But this ideal scenario only comes to fruition if the fortified vehicle is widely accessible, adequately fortified, and regularly consumed *in quantity* to meaningfully raise calcium intakes. As Neufeld explained, current guidelines suggest that large doses are needed to prevent preeclampsia and preterm birth, especially among women with low intakes. "Is fortification a way to move those women from low intake to adequate intake to the point where supplementation would no longer be needed? And if so, would this put other population subgroups at risk of excess intake?"

These questions can be answered using modelling exercises that include information about current dietary intake of calcium, and the potential contribution from fortification. The data needed for such modelling is now being collected and models developed for several micronutrient fortification programs but additional data will be needed for calcium.[69] [70]

Lastly, while mandatory fortification programs are a longer process (5-7 years) than voluntary ones, requiring legislation and monitoring, as well as public guidance and education, Neufeld asserts that it is the only approach that assures that fortified products will be equitably available. "In the meantime, if we're concerned about calcium intake, there may be other actions that are needed while such programs are set up," Neufeld said.

Bioavailability of calcium and interactions with other components in supplements or fortificants

Carolina Diaz Quijano illustrated the "intricate network" of factors that influence calcium bioavailability. Even in regions where calcium intake is high, calcium status can be low due to the effects of antinutrients in the diet, food preparation techniques that decrease bioavailability, or even the form of calcium consumed. The interplay of these factors should be considered in the context of calcium fortification or supplementation programs.

The interactions of greatest concern are between calcium and oxalates, phytates, tannins, and sodium. Oxalates and phytates are present in many otherwise healthy foods, including green leafy vegetables, nuts, cereals, oilseeds, wheat bran, and berries. Emerging research on what Diaz Quijano deems an "elegant solution" to this challenge involves the use of probiotics that degrade oxalates[71] or phytates[72] and could be incorporated into supplements or used as fortificants alongside calcium. Cooking, fermenting, or pre-soaking high-phytate foods can also reduce phytate levels. The amount of sodium in the diet can negatively affect calcium absorption by increasing urinary calcium excretion.

The selection of the calcium salt used for supplementation or fortification can influence many aspects of the final product, from tablet size to the taste, appearance, shelf life, and public acceptability of a fortified food. Cost is also a factor. Diaz Quijano compared the most commonly used calcium salts for these applications, noting that while their calcium content and solubility differ, the fractional absorption is surprisingly similar. "Are we willing to pay such a premium on a calcium salt just because its fractional absorption is marginally better?" she asked, suggesting that these types of analyses be considered before implementing supplementation or fortification programs.

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