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Recommended calcium intake in adults and children with chronic kidney disease—a European consensus statement

Pieter Evenepoel[1,2], Hanne Skou Jørgensen[1,3,4], Jordi Bover[5,6], Andrew Davenport[7], Justine Bacchetta[8,9], Mathias Haarhaus[10,11,12], Ditte Hansen[13,14], Carolina Gracia-Iguacel[15], Markus Ketteler[16], Louise McAlister[17], Emily White[18], Sandro Mazzaferro[19], Marc Vervloet[20,21] and Rukshana Shroff[22,23]; on behalf of European Renal Osteodystrophy (EUROD), an initiative of the Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) and the European Renal Nutrition (ERN) Working Groups of the European Renal Association (ERA) and the European Society of Pediatric Nephrology (ESPN)

[1]Department of Microbiology, Immunology and Transplantation, Nephrology and Renal Transplantation Research Group, KU Leuven, Leuven, Belgium
[2]Department of Medicine, Division of Nephrology, University Hospitals Leuven, Leuven, Belgium
[3]Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark
[4]Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark
[5]Department of Nephrology, University Hospital Germans Trias i Pujol, Barcelona, Catalonia, Spain
[6]REMAR-IGTP Group, Germans Trias i Pujol Research Institute, Can Ruti Campus, Barcelona, Catalonia, Spain
[7]Department of Renal Medicine, Royal Free Hospital, University College London, London, UK
[8]Pediatric Nephrology Rheumatology and Dermatology Unit, Reference Center for Rare Renal Diseases, ORKID and ERK-Net networks, Lyon University Hospital, Bron, France
[9]Lyon Est Medical School, INSERM1033 Research Unit, Claude Bernard Lyon 1 University, Lyon, France
[10]Division of Renal Medicine, Karolinska University Hospital, Stockholm, Sweden
[11]Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden
[12]Diaverum Sweden, Malmö, Sweden
[13]Department of Nephrology, Copenhagen University Hospital-Herlev, Copenhagen
[14]Institute of Clinical Medicine, University of Copenhagen, Denmark
[15]Department of Renal Medicine, IIS-Fundación Jiménez Díaz UAM University Hospital, Madrid, Spain
[16]Department of General Internal Medicine and Nephrology, Robert-Bosch Hospital, Stuttgart, Germany
[17]Dietetic Team, UCL Great Ormond Street Hospital for Children and University College London, London, UK
[18]Dietetic Team, Royal Free Hospital, University College London, London, UK
[19]Department of Translation and Precision Medicine, Sapienza University of Rome, Rome, Italy
[20]Amsterdam Cardiovascular Sciences, Amsterdam UMC, The Netherlands
[21]Department of Nephrology, Amsterdam UMC, The Netherlands
[22]Renal Unit, UCL Great Ormond Street Hospital for Children, London, UK
[23]Institute of Child Health, University College London, London, UK
Correspondence to: Pieter Evenepoel; E-mail: Pieter.Evenepoel@uzleuven.be

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ABSTRACT

Mineral and bone disorders (MBD) are common in patients with chronic kidney disease (CKD), contributing to significant morbidity and mortality. For several decades, the first-line approach to controlling hyperparathyroidism in CKD was by exogenous calcium loading. Since the turn of the millennium, however, a growing awareness of vascular calcification risk has led to a paradigm shift in management and a move away from calcium-based phosphate binders. As a consequence, contemporary CKD patients may be at risk of a negative calcium balance, which, in turn, may compromise bone health, contributing to renal bone disease and increased fracture risk. A calcium intake below a certain threshold may be as problematic as a high intake, worsening the MBD syndrome of CKD, but is not addressed in current clinical practice guidelines. The CKD-MBD and European Renal Nutrition working groups of the European Renal Association (ERA), together with the CKD-MBD and Dialysis working groups of the European Society for Pediatric Nephrology (ESPN), developed key evidence points and clinical practice points on calcium management in children and adults with CKD across stages of disease. These were reviewed by a Delphi panel consisting of ERA and ESPN working groups members. The main clinical practice points include a suggested total calcium intake from diet and medications of 800–1000 mg/day and not exceeding 1500 mg/day to maintain a neutral calcium balance in adults with CKD. In children with CKD, total calcium intake should be kept within the

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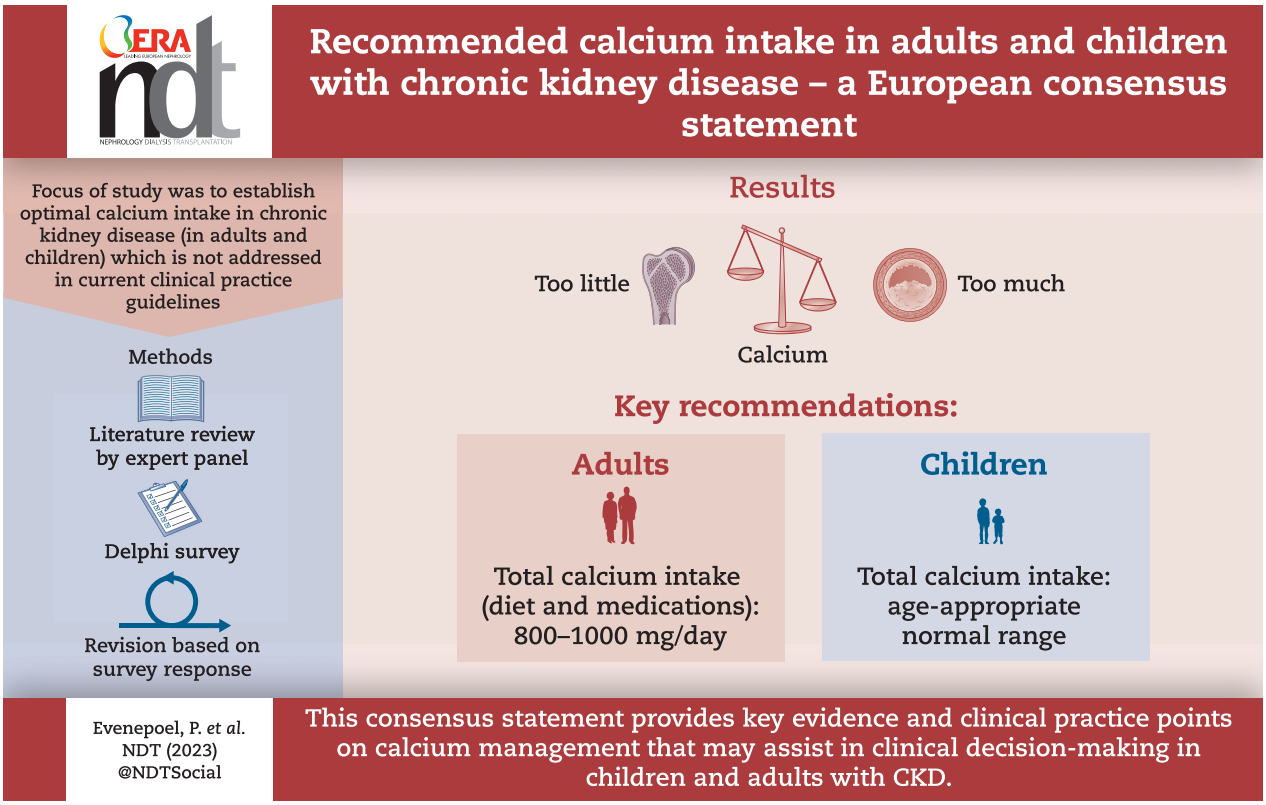
age-appropriate normal range. These statements provide information and may assist in decision-making, but in the absence of high-level evidence must be carefully considered and adapted to individual patient needs.

Keywords: calcium, chronic kidney disease–mineral and bone disorder, osteoporosis, renal insufficiency, vascular calcification

GRAPHICAL ABSTRACT



INTRODUCTION

Calcium is an essential nutrient that plays a vital role in neuromuscular function, enzyme-mediated processes and blood clotting, and provides skeletal rigidity by being an essential component of mineralized bone. Its non-structural roles require the strict maintenance of ionized calcium concentration in tissue fluids. In situations of too low exogenous calcium supply, the calcium reservoir in the skeleton can complement the plasma [1]. Whole-body calcium balance refers to the net of calcium influx into the body minus all calcium losses from the body during a given time period [2].

In healthy adults over the age of 25–30 years, the rate of calcium absorption from the gastrointestinal tract must match the losses from the body through the gut, kidneys, skin, hair and nails; so that calcium balance is neutral (Fig. 1). Age, sex, bone disease, hormonal status and exercise all affect calcium balance. In chronic kidney disease (CKD), dysregulated calcium homeostasis renders patients at risk of either a negative or a positive calcium balance.

Hypocalcemia drives hyperparathyroidism, which in turn increases bone turnover, resulting in reduced mineralization and bone loss, compromising bone strength. Along with an increased fall risk and abnormalities in bone quality related to uremia, this sequence of events contributes to the increased fracture risk in CKD [3]. Adults with CKD G5 and on dialysis (CKD G5D) exhibit a 4- to 6-fold higher risk of non-vertebral fractures than age- and sex-matched controls [4, 5], and even children with early CKD (G2–3A) have a 2- to 3-fold higher fracture risk compared with their healthy peers [6].

In the 1990s, exogenous calcium loading through a high calcium dialysate and concomitant use of calcium-containing phosphate binders and active vitamin D derivatives were the first-line approach to control hyperparathyroidism and hyperphosphatemia in CKD. Around the turn of the millennium, increased awareness of the vascular calcification burden in CKD triggered a paradigm shift. Preventing vascular calcification was given priority over controlling hyperparathyroidism [7, 8]. Excessive calcium loading was shown to associate with vascular calcification progression and was assumed to contribute to the increased cardiovascular risk in CKD. Against this background, calcium-free phosphate binders rapidly gained popularity, often completely replacing calcium-based binders. Meanwhile, calcimimetics entered clinical practice and proved very powerful in suppressing

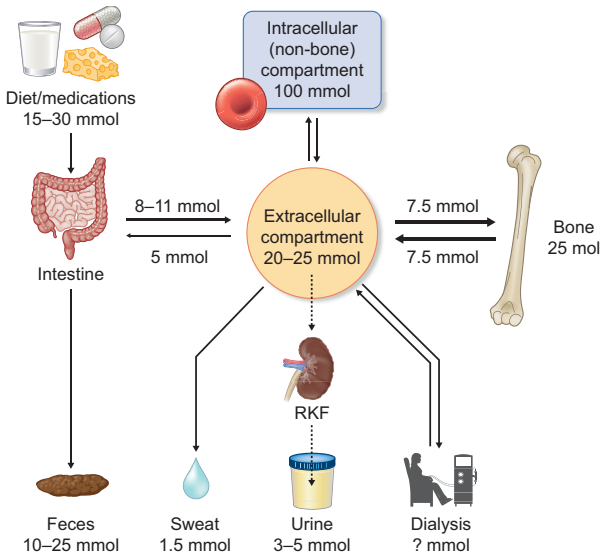


Figure 1: Body calcium fluxes; in patients receiving dialysis, calcium mass transfer to or from the dialysis fluid must also be taken into account. RKF, residual kidney function.

parathyroid hormone (PTH) and unlike active vitamin D derivatives, without increasing calcium levels—rather the opposite. Calcimimetics thus increasingly complemented, if not replaced, active vitamin D derivatives for the control of hyperparathyroidism in patients with CKD G5D. Calcium was inappropriately labeled a "cardiovascular toxin" [9], and clinical guidelines and position papers [10] emphasized the risks of overzealous calcium loading.

This "war on calcium" may have caused collateral damage. An increasing number of patients with CKD may be at risk of overt calcium deficiency, potentially contributing to inadequate control of hyperparathyroidism, worsening of renal bone disease and increased fracture risk. Thus, calcium intake below a lower threshold limit might induce harm, just as exceeding the upper tolerable limit will. An inadequate provision of calcium may go unnoticed for long periods, because commonly available tools for estimating calcium requirements remain crude and unreliable. In current clinical practice, serum calcium levels are our only tool for estimating calcium requirements, but serum calcium accounts for <0.1% of total body calcium, and due to tight negative feedback control, cannot reflect the total body calcium.

Calcium management in CKD remains an area fraught with uncertainties, resulting in wide variations in practice. Notably, the KDIGO guidelines on CKD–mineral and bone disorder (CKD-MBD), published in 2009 [7] and updated in 2017 [11], do not include recommendations for calcium intake for patients receiving maintenance dialysis or living with a kidney transplant. Moreover, expertise from dieticians is often lacking even in tertiary nephrology centers.

Acknowledging the need for a balanced view on calcium management, the European Renal Osteodystrophy (EUROD) initiative, a part of the European Renal Association (ERA) CKD-MBD working group, and the ERA European Renal Nutrition (ERN) working group, together with members of the CKD-MBD and Dialysis working groups of the European Society for Pediatric Nephrology (ESPN), convened a group of nephrologists and nutritionists (expert panel, ExP) with expertise in CKD-MBD management and renal nutrition. The initiative was endorsed by the ERA. The ExP was tasked with developing a consensus statement on calcium management in CKD, especially on the recommended intake of calcium in children and adults with CKD across stages of disease. These recommendations are designed to provide information and assist in decision-making to reduce uncertainty and improve patient outcome. They are not intended to define a standard of care and should not be interpreted as an exclusive course of management. Recommendations for further research are suggested. Following publication of the consensus statement, the ExP has planned a dissemination phase to guide practical day-to-day management of calcium intake.

METHODS

Developing the PICO questions

Clinical practice recommendations are most useful when they provide specific actionable advice on choosing between alternative approaches in particular clinical situations. We developed clinical questions to be addressed and framed them in a searchable format, with specification of the patient group (P) to whom the statement would apply; the intervention (I) being considered; the comparator (C) (which may be "no action" or an alternative intervention); and the outcomes (O) affected by the intervention. Our PICO terms were as follows:

Population: patients (children and adults) with CKD G2–5D
Intervention: nutritional requirement for calcium at different ages and stages of CKD
Comparator: nutritional requirements for calcium in age-matched healthy controls
Outcomes: bone pain and deformities, fracture risk, calcium balance, bone (de)mineralization (on imaging or bone histology), development of hypo- or hypercalcemia, PTH control, changes in bone turnover markers, development of vascular calcification (on imaging or vessel biopsy), all-cause and cardiovascular mortality

We have included children, adolescents and adults in this consensus document as physiological changes in bone development constitute a continuum through the ages, with the skeletal turnover and mineralization in young adults being more similar to the growing bones of children with accrual of calcium rather than the slow demineralization of the skeleton of older adults [12, 13]. The Paediatric Renal Nutrition Taskforce have recently published clinical practice recommendations on the dietary management of calcium and phosphate in children with CKD G2–5D [14], which will be referred to for specific details on the dietary management of childhood CKD-MBD. No distinction was made between sexes, given the paucity of sex-specific data. Calcium requirements in pregnant and lactating women is beyond the scope of this document.

Literature search

Given the paucity of systematic reviews, meta-analyses and randomized controlled trials (RCTs) specifically dealing with the topic of calcium management in CKD, original research manuscripts have mainly been used to provide the evidence base for this consensus. Existing guidelines on nutritional requirements of calcium in healthy individuals of all ages were reviewed. Clinical practice recommendations are based on an in-depth review of the available evidence, but in the absence of applicable studies, guidance is based on the opinion of experienced dietitians and nephrologists from the ExP.

Framing advice

This consensus presents "Key evidence points" providing a concise summary of available evidence, and "Clinical practice points" presenting our clinical practice recommendations. Using the

Delphi method, voting group members were sent an e-questionnaire to provide a level of agreement on a 5-point scale (strongly disagree, disagree, neither agree nor disagree, agree, strongly agree) and given the opportunity for re-wording of the practice points if appropriate. Participants for the Delphi survey were board and ordinary members of the ERA CKD-MBD (including EUROD) and ERN working groups, and the ESPN CKD-MBD and Dialysis working groups. It was agreed *a priori* that at least a 70% level of consensus was required for each statement, failing which the recommendation would be adapted after discussion in the ExP, and reviewed again.

QUESTION 1: WHAT IS THE RECOMMENDED INTAKE OF CALCIUM IN HEALTHY INDIVIDUALS OF DIFFERENT AGES?

Calcium requirements in healthy individuals

Key evidence points

- Adequate calcium intake is defined as the amount that meets the needs of 97.5% of healthy people in the age-related population.
- Calcium requirements are expressed in milligrams of elemental calcium intake per day (mg/day).
- Calcium requirements are described as a range based on evidence from balance studies and clinical trials on fracture risk reduction.
- Calcium requirements vary considerably throughout the lifespan, being highest during periods of rapid growth in infancy and adolescence.
- International recommendations have set a reference intake of 800–1000 mg/day for healthy adults over 25 years of age.

Background and rationale

It is important to define calcium requirements in healthy individuals before modifications to the calcium intake are considered in patients with CKD. Recommendations for calcium intake for the general population of children and adults have been reported by many countries and international authorities including the Institute of Medicine (IOM) [15] in the USA and the European Food Safety Authority (EFSA) [16].

Several different terms have been used in international recommendations to describe nutrient adequacy; these include Population Reference Intake, Recommended Dietary Allowance (RDA), Recommended Nutrient Intake (RNI) and Estimated Average Requirements. To avoid potentially confusing terminology, we describe calcium requirements in milligrams of elemental calcium intake per day, and we suggest avoiding terms such as RDA/RNI, etc. However, to compare different guidelines and benchmark nutritional intake against KDIGO and KDOQI guidelines, it is worth noting that the RDA is used in both.

Calcium requirements vary throughout the lifespan, being highest in infancy and adolescence [17–19] and lower in older age. Adequate dietary calcium intake is essential for normal skeletal growth and mineralization as the calcium content of the skeleton increases from 25 g at birth to >1000 g in adults. Calcium requirements are highest during periods of rapid growth, including the first year of life and during puberty [20]. Approximately 25% of the total skeletal mass is laid down during the 2-year interval of peak height velocity during adolescence [21], but bone calcium accrual continues, at a slower pace, until peak height is reached at ∼30 years of age [12]. Calcium requirements in healthy children of different ages have been described by the Paediatric Renal Nutrition Taskforce [14].

The IOM, EFSA and others use a factorial approach to determine optimal calcium requirements, based on carefully conducted calcium balance studies in healthy individuals and on data from RCTs on calcium intake and skeletal outcomes. Both the IOM and EFSA have used the pooled analyses of studies published by Hunt and Johnson [22], who determined the dietary calcium intake required to maintain neutral calcium balance. Calcium balance data [calcium intake—(fecal calcium + urinary calcium)] were collected from 155 healthy adults (73 women, mean age 47 years, and 82 men, mean age 28 years) who participated in 19 rigorously controlled feeding studies. Daily intakes of calcium ranged from 415 to 1740 mg. The models predicted a neutral calcium balance at 741 mg/day (507–1035 mg/day). Assuming that a neutral balance is achieved with this average requirement of 741 mg/day, and taking into account the variation in calcium requirements in the population, both the IOM and EFSA have set a reference intake of 800–1000 mg/day (corresponding to the average requirement +2 SD) for adults >25 years of age. However, there are also notable differences between these two international recommendations:

- EFSA allows a marginally higher calcium intake of 1150 mg/day in young adults up to 25 years to account for the higher bone calcium accretion until peak bone mass is reached.
- The IOM recommends a higher calcium intake (1200 mg/day) in women >50 years and men >70 years based on reduced calcium absorption with age.

The higher calcium requirement in older age is difficult to reconcile with the Hunt and Johnson study. Women were not stratified for menopausal status, and there were only two men above 70 years, with no evidence of changes in skeletal maintenance with older age. In addition, due to a lack of calcium balance studies in adults >70 years, RCT data were used instead. However, these trials are inconsistent, lack information on dietary calcium intake and show a poor dose–response relationship between calcium intake and skeletal outcomes [22].

Two meta-analyses explored the association between calcium intake and fracture risk in otherwise healthy adults. Bolland *et al.* concluded that dietary calcium intake is not associated with fracture risk and that there is no evidence that increasing calcium intake from dietary sources prevents fractures [23]. In a recent meta-analysis by Zhao *et al.*, which included 33 randomized trials with >50 000 participants, there was no significant association between calcium intake and risk of hip fracture as compared with placebo or no treatment [24]. Thus, as there is no clear evidence that a higher calcium intake leads to either a reduced bone loss or a lower fracture risk, we do not recommend increasing the calcium intake in older adults, in line with EFSA recommendations.

Of note, in the Bolland meta-analysis, those on calcium supplements had an average total daily calcium intake of 1780 mg/day (range 1230–2314 mg/day) [23], which is considerably higher than the average population intake [25]. Elderly people in residential care have much lower baseline dietary calcium intakes (mean 513 mg/day) together with low baseline vitamin D concentrations. When such vulnerable adults were given calcium and vitamin D supplements (1200 mg/day + 800 IU/day), the risk of hip fractures was reduced by 23% and all fractures by 17% over 3-year follow-up [26]. Similarly, a cluster RCT showed that when vitamin D–replete elderly in care homes were given calcium supplementation by high calcium, high protein dairy foods, those on a

higher calcium intake [1142 (±353) mg/day vs 700 (±247) mg/day in controls] had a risk reduction of 33% for all fractures, 46% for hip fractures and 11% for falls [27]. In populations with a naturally lower dietary calcium intake (mean 522 mg/day in men and 507 mg/day in women), there was a 6% reduction in the vertebral fracture risk for every 100 mg increase in dietary calcium intake in women, with no association seen in men [28]. These data suggest that with an insufficient calcium intake, supplementation with calcium (and/or vitamin D) has positive effects on skeletal health, reducing fracture risk.

Dietary sources of calcium and bioavailability

Key evidence points

- The main dietary sources of calcium for children and adults are dairy products, cereals if fortified with calcium and beverages, with considerable variation across geographic regions and ethnic groups.
- Statutory or voluntary fortification with calcium can increase the calcium content of other foods.
- Calcium bioavailability in healthy individuals averages 30%.

Background and rationale

The contribution of different foods to the average daily intake of calcium varies with age, the individual's food preferences and national guidelines on food fortification. Dairy products are the largest contributor to dietary calcium intake in most children [29]. The main dietary sources of calcium in healthy adults are dairy products, cereals and beverages (non-alcoholic), although the contribution from dairy varies from 37% to 67% across different countries [30]. Of note, hard water from taps and some mineral waters can be important sources of calcium, contributing up to 500 mg/L [31]. The typical calcium content per portion of calcium-rich foods and the bioavailability of calcium [32] from these sources are shown in Table 1.

Calcium is often added to foods by manufacturers, either for fortification or as a food additive (used as food color or preservative) [33]. Calcium fortification of foods such as bread and wheat flour is mandated in some countries like the UK. Also, calcium is often added to breakfast cereals and drinks, particularly those consumed by children, which contributes variable amounts to the dietary intake. The actual calcium content of processed products vary considerably depending on the production methods and brand, and nutrient composition tables may not provide accurate estimates of the added calcium.

In healthy individuals, approximately 30% of dietary calcium is absorbed [34], but this depends on the food source and subject-related factors, ranging from 5% to 82% (Fig. 2). Physiological variations in calcium absorption are strongly influenced by age, being highest in infancy and adolescence [20], virtually doubling during pregnancy [35], and decreasing after the age of 40 years [36].

Balance studies have shown that the fractional calcium absorption is inverse to calcium intake when the intake is very low and reaches a threshold at higher intakes; approximately 45% absorption was seen at low intakes (200 mg) and 15% at intakes over 2000 mg [36]. Vitamin D status may also influence calcium absorption and is discussed in subsequent sections. Milk, dairy products, some mineral waters and fortified foods have a calcium bioavailability between 30% and 40%, whereas it is <10% for vegetables and fruit [37, 38]. Phytates, oxalates, phosphate and fatty acids bind calcium in the gut to form insoluble calcium salts thereby reducing calcium absorption. Studies investigating whether the fractional calcium absorption is related to gastric acidity show heterogeneous results in healthy controls [39–44]. Case-mix, variable test conditions, proton pump inhibitor (PPI) use and analytical issues likely explain this heterogeneity. Recent data demonstrating low calcium absorption in patients after gastric bypass surgery or sleeve gastrectomy emphasize the role of the stomach in calcium bioavailability [45, 46]. Importantly, individuals on a phosphate-restricted diet are likely to have a low dietary calcium intake as most foods that contain phosphate are also natural sources of calcium [29].

Estimating an individual's calcium intake

Clinical practice points:

- An estimate of the total calcium intake should consider contributions from diet and medications (including calcium supplements and calcium-containing phosphate binders).
- A self-administered questionnaire or diet history of a typical 24-h period can be used to rapidly identify the main sources of dietary calcium.
- A 3-day prospective diet diary (food intake record) can be used when detailed information is required.
- The calcium bioavailability from different foods should be considered when estimating net absorption.

Background and rationale

An individual's usual calcium intake can be estimated using a variety of tools—these are described in Table 2 together with their relative advantages and disadvantages [47–49]. For a rapid bedside estimation, self-administered on-line calculators or a retrospective diet history of a typical 24-h period can be useful tools. The International Osteoporosis Foundation (https://www.osteoporosis.foundation/educational-hub/topic/calcium-calculator) and the Royal Osteoporosis Society (https://webapps.igc.ed.ac.uk/world/research/rheumatological/calcium-calculator) provide free on-line calculators [50, 51] that are quick and easy to use. Other national societies provide similar tools that take into account regional food choices and fortification practices.

For detailed analyses, a 3-day prospective diet diary/food intake record or a food frequency questionnaire can give a clinically useful estimate of intake [47], but can be time-consuming to administer and assess. A more detailed account of the consumption of specific dietary sources of calcium (such as milk, fortified cereals and additive-rich foods), together with portion sizes, can be determined by direct questioning, followed by analysis using country specific food composition databases or dietary analysis software. Importantly, the calcium intake from supplements or calcium-containing phosphate binders can contribute significantly to enteral calcium intake and must be considered in the overall calcium intake.

QUESTION 2: WHAT ARE THE DETERMINANTS OF CALCIUM BALANCE IN CKD?

Calcium intake and bioavailability in CKD

Key evidence points

- The average dietary calcium intake is 500–900 mg/day in adults with CKD G3–4 and 400–800 mg/day in CKD G5–5D. The average dietary calcium intake in children with CKD varies with age.
- The dietary intake of calcium decreases with the progression of CKD.
- The dietary intake of calcium shows regional variability, with notably lower intake in Asian countries.

Table 1: A guide to the calcium and phosphorus (phosphate) content of foods.

Food	Portion size [237]	Elemental calcium, mg per portion [238]	Calcium bioavailability (%)	Phosphate, mg per portion [238]
Dairy and dairy products				
Cow's milk	100 mL	120	32	94
Oat, hemp, coconut, rice and almond milk (fortified)	100 mL	120		48
Custard or rice pudding	120 g	170		136
Hard cheese	30 g	240	37	212
Soft cheese (e.g. brie, mozzarella)	30 g	93	30	75
Yogurt	150 g	189	32	207
Dairy-free yogurt (fortified)	125 g	150		90
Egg				
Egg, cooked	50 g (1 egg)	28		103
Soya products				
Soya milk, cheese and desserts	Check product for degree of calcium fortification		24	
Calcium-set tofu	50 g	60	31	48
Fortified orange juice				
Calcium-fortified orange juice	100 mL	120	20–40	[a]
Cereal (grain) and cereal products				
Bread—white calcium fortified	33 g slice	58		31
Bread—wholemeal	33 g slice	35		67
Fortified breakfast cereals	30 g pt	1–131		14–26
Fruit				
Apricots, dried	50 g	29		33
Apricots, raw	80 g	12		16
Figs, raw	55 g	126		45
Currants	2 tbsp	50		38
Orange	120 g	29		19
Fish (soft bones eaten)				
Anchovies, canned	5 (15 g)	45	24	45
Sardines (tinned in oil)	100 g	679	27	545
Whitebait, fried	80 g	688	24	688
Salmon, tinned	100 g	164	27	291
Nuts and seeds				
Almonds[a]/brazil nuts/hazelnuts/walnuts	30 g	28–72	21[a]	90–177
Sesame seeds	1 tbsp (12 g)	80	21	86
Spreads				
Peanut butter	20 g	7		66
Hummus	60 g	25		96
Tahini paste	1 tsp	129		139
Vegetables				
Broccoli	85 g	30	58	50
Watercress	20 g	34	67	10
Kale	90 g	135	41	41
Okra, boiled	7 pcs (35 g)	42		19
Spinach	90 g	144	5	25
Chickpeas	90 g	39		73
Red kidney beans	90 g	64	20	117
Green beans	90 g	50		37
Baked beans	205 g	86	22	180
Water				
Tap water	100 mL	8–15		
Mineral water	100 mL	1–48	23–48	

[a]The exact amount of calcium (and phosphate) present in a food will vary depending on the food source, production methods, degree of fortification and analytical technique. Calcium-fortified dairy replacement products usually have a similar calcium content to their cow's milk alternatives. Values for bioavailability (when available) were obtained from a range of published data [31, 34, 37, 239–248] but will be influenced by many factors including: cooking method, phytate and oxalate content, the total calcium load of a meal [249], the calcium salt used for fortification, and the calcium and vitamin D status of the consumer. The approximate absorption from a mixed meal has been estimated to be 30% [34].
pcs, pieces; pt, portion; tsp, teaspoon; tbsp, tablespoon.

- Calcium salts may account for 60%–70% of total calcium intake if calcium-containing phosphate binders are used.
- Calcium bioavailability is impaired in CKD, averaging 15%.

Background and rationale

In patients with CKD G3–5, whole-body calcium influx depends on calcium intake and bioavailability. In patients with CKD G5D, dialytic calcium mass transfers must additionally be accounted for.

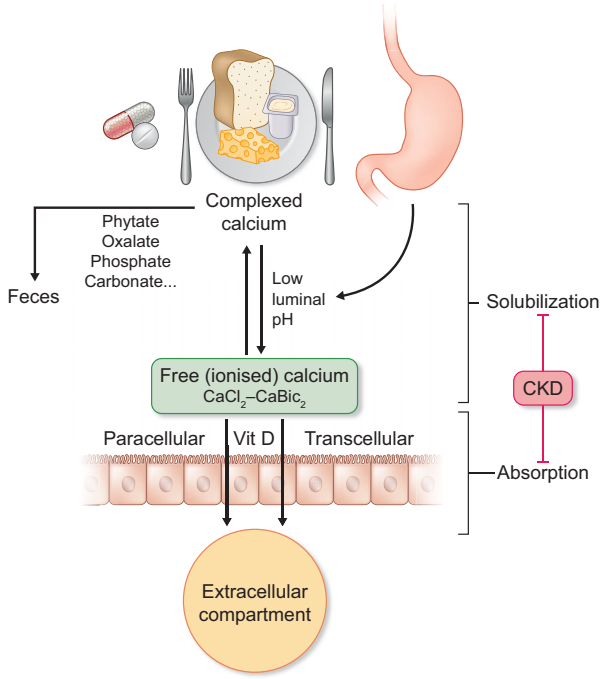


Figure 2: Calcium absorption and bioavailability. The bioavailability of calcium from different food sources is influenced by many factors, including cooking method, phytate and oxalate content, the total calcium load, and the solubility of the complexed calcium. Calcium salt solubility is pH dependent, emphasizing the role of gastric acidity. Transepithelial and transcellular transport towards the circulation (extracellular compartment) is enhanced by vitamin D. CKD may impair calcium bioavailability by hampering both calcium solubilization and absorption.

Data from cohort studies in patients with CKD show a daily dietary calcium intake of 400–900 mg/day (Fig. 3) [52–72]. The main dietary sources of calcium are bread (when fortified with calcium) and dairy foods [29, 66]. As for most nutrients, dietary calcium intake decreases with the progression of CKD [53, 59]. Besides uremic anorexia, dietary restrictions likely account for this decrease, since dietary phosphate restriction limits food items with high calcium content and bioavailability [29, 34]. As in the general population [73], the dietary calcium intake varies across geographic regions and ethnic groups [72], with notably lower intake in Asian countries [59, 70], reflecting the dietary preferences. Calcium-containing phosphate binders are an important source of calcium in patients with CKD G4–5D and can constitute up to 70% of the overall calcium intake [29, 53, 66, 67].

Many direct and indirect methods may be used to evaluate calcium bioavailability [74]. They have inherent limitations, and results obtained with different methods are not interchangeable and need to be interpreted cautiously. Furthermore, characteristics of the study population (age, sex, habitual dietary calcium intake) [36, 75] and of the test meal (composition, calcium content, extrinsically or intrinsically labeled, tracer carrier compound) may cause variability. Single and double stable or radioisotope tracer techniques are most often used in clinical research studies and inform on the apparent fractional absorption; analysis of concomitant stool collections allow for the calculation of net fractional absorption. Acknowledging that results have not been unequivocal, available clinical evidence indicate that calcium bioavailability by gastro-intestinal absorption decreases along the progression of CKD, with the apparent fractional absorption averaging 15% in the CKD population as a whole, i.e. about half the value obtained in healthy controls [76–78]. Reasons for this decreased calcium bioavailability in CKD may include altered gut physiology, hypovitaminosis D, vitamin D hyporesponsiveness, hypogonadism or combinations thereof, as detailed below.

Gastric acid secretion may be impaired in CKD, both by idiopathic and iatrogenic mechanisms [79]. Reduced expression or dysfunction of the calcium-sensing receptor is a common finding in CKD [80], and based on recent experimental data, associates with impaired H^+-ATPase-mediated gastric acid secretion [81]. In addition, up to 90% of patients with CKD are treated with PPIs [82], which are potent blockers of the H^+-K^+-ATPase. Thus, multiple factors leading to gastric acid secretion blockade may account for pronounced hypochlorhydria, if not achlorhydria, in patients with CKD. Given that a low gastric pH is critical for solubilization and ionization of calcium salts present in foods (discussed above), uremic and iatrogenic hypo- and achlorhydria may be an important factor contributing to calcium malabsorption.

CKD associates with low circulating levels of 1,25 dihydroxy vitamin D, which is known to enhance transepithelial calcium transport. Active vitamin D derivatives increase, but do not normalize, calcium absorption in patients receiving hemodialysis [83]. Conversely, nutritional vitamin D supplements fail to improve calcium absorption, both in healthy controls [84, 85] and in patients with CKD [86]. These findings challenge the importance of nutritional vitamin D in intestinal calcium absorption. Most likely, nutritional vitamin D supplementation only has a clinically meaningful positive impact on calcium absorption when vitamin D is severely depleted and calcium intake is low [10, 87]. Rather than increased gastrointestinal absorption, an increased renal tubular calcium reabsorption and/or skeletal calcium release may be hypothesized to explain the increased calcium levels in individuals treated with active vitamin D derivatives.

Most of the dietary calcium is absorbed in the small intestine, while the large intestine accounts for only 6%–10% of the total calcium absorbed. Carbohydrate fermentation may foster colonic calcium absorption, but may be very low in CKD given a restricted intake of potassium-rich fruit and vegetables, which have a high content of dietary fiber and fermentable carbohydrates.

Calcium losses in CKD

Key evidence point

- Urinary calcium excretion decreases early in the course of CKD prior to homeostatic hormonal changes and parallels kidney function decline, to average 40 mg/day at CKD G3.
- Endogenous fecal calcium losses are estimated at 100–200 mg/day.

Background and rationale

In patients with CKD G2–5 not yet on dialysis, whole-body calcium efflux occurs through urinary and fecal losses, with small amounts also lost through the skin, hair and nails (limited to ~40–60 mg/day, and probably not affected by CKD). The 24-h urinary calcium losses show a stepwise decline across CKD stages, reaching amounts as low as 22 mg/day in patients with CKD G4 [53, 88, 89]. A low degree of calciuria is seen even in CKD G2–3, before any changes in regulatory calciotrophic hormones are detected. This observation points to a decreased filtered calcium load as a main driver of low calciuria. The fractional urinary excretion of calcium also decreases with CKD severity. Urinary

Table 2: Comparison of some practical dietary assessment methods.

Method	Description	Advantages	Disadvantages
Diet history/recall (retrospective)	• Individual recalls recent usual food and drink intake • Face to face or indirectly by telephone	• Reports usual intake • Minimal participant burden • No literacy skills required • Able to estimate portion size and frequency • Can describe cooking methods and cultural eating habits • Allows classification of nutrient intake into broad categories (low, medium, high)	• Relies on accurate recall • Underreporting or recall bias • Interview can be time consuming • Method not standardized • Trained interviewer required • Interviewer bias • Inaccurate estimation of portion size
FFQ (retrospective); includes semi-quantitative FFQ if portion estimated included and short frequency questionnaires	• Report of frequency of consumption of specific food and drink from a list over a given period • Can be adapted to include portion sizes • Uses closed questions • Historically method of choice for epidemiologic studies [250]	• Can be tailored to assess specific food groups or nutrients • Provides information on food consumption patterns • Can be adapted to be population/culture specific • FFQs can be self-completed (depending on complexity) • Simple FFQs impose a low respondent burden • Users can take photographs to record portion sizes • Easy to collect and assess • Reliable tool for micronutrient assessment [251]	• Relies on accurate recall • Time consuming depending on number of food items included • Literacy and numeracy skills required • Tailored software programs required for processing data
Diet diary/food intake record (current)	• Record of all food and drink consumed over a specified period (3–7 days) • Intake can be weighed, described or photographed • Can include product labels • Can either be used to reflect usual intake or include special events • Data are analyzed by reference to food composition tables (or data analysis software)	• No recall required • Minimizes analysis error if recipes and product labels included • Reproducible • "Gold standard" against which other dietary assessment methods are compared [252] • Reliable tool for assessment of micronutrient intake [49]	• High participant burden • Incomplete/selective recording • Literacy skills required • Interpretation bias • Can alter usual food intake

FFQ, food frequency questionnaire.

calcium losses in patients with CKD G3–4 average 40 mg/day [90]. It is debatable whether this low degree of calciuria is maladaptive or homeostatic. In healthy, middle-aged women, a urinary calcium <40 mg/day is indicative of either calcium malabsorption, very low calcium intake, excessive digestive juice secretion or bone hunger (e.g. from osteoblastic metastases) [91]. Preliminary data from stable isotope studies indicate that even in children and young adults with CKD, bone resorption prevails [92]. The low urinary calcium in CKD patients could therefore suggest a low intestinal calcium absorption, even to such a degree that endogenous losses exceed intestinal absorption, at least in a subset of patients.

Fecal calcium losses include malabsorbed calcium and endogenous intestinal losses originating from sloughed epithelial cells and digestive juice secretion. The latter losses are estimated at 100–200 mg/day [93, 94]. Determinants remain poorly defined [93]. It is probable that endogenous fecal calcium loss is a largely unregulated drain on the calcium economy [91]. Data on endogenous intestinal calcium losses in CKD are very limited [94].

Dialytic calcium mass transfer in CKD G5D

Key evidence points

- In addition to the calcium load from diet and medications, dialytic calcium mass transfer must be considered when assessing calcium balance in maintenance dialysis patients.
- Dialytic calcium mass transfer is determined by plasma-to-dialysis fluid ionized calcium gradient, dialysis session duration, ultrafiltration rate and skeletal remodeling rate.

Background and rationale

In patients receiving maintenance dialysis therapy, calcium balance is more complex; in addition to calcium contributed from diet and medications, dialytic calcium mass transfer must be considered. Major determinants include plasma-to-dialysis fluid ionized calcium gradient, dialysis session duration,

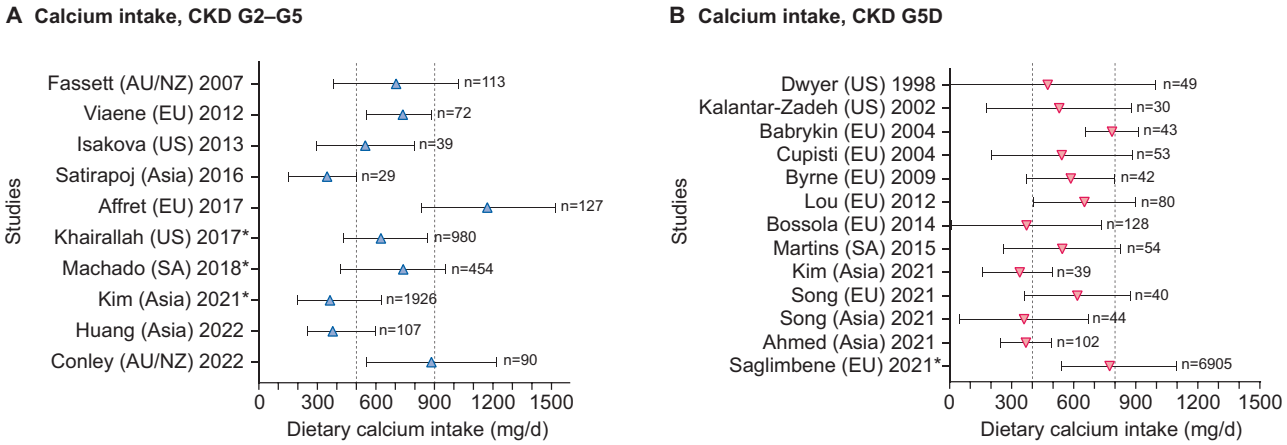


Figure 3: Reported dietary intake of calcium in patients with CKD.

ultrafiltration rate and the state of bone turnover [95]. It should be acknowledged that the ionized (free) dialysis fluid calcium concentration is only 80%–95% of the calcium concentration indicated on the label, and even lower when using citrate as an acid buffer [96–98]. Compared with acetate-based dialysis fluid, citrate-based dialysis fluids reduce serum calcium [99], and this effect may be exaggerated in online hemodiafiltration [100]. Of note, the balance of serum ionized to complexed calcium is affected by pH, which can be modified by the buffer concentration in the dialysis fluid; decreasing the bicarbonate content may decrease calcium mass transfer by reducing the patient plasma-to-dialysis fluid ionized calcium gradient. A dialysis fluid calcium of 1.25 mmol/L (2.5 mEq/L) associates with a neutral [101], if not negative [102, 103], dialytic calcium mass transfer in hemodialysis patients. In peritoneal dialysis patients, dialytic calcium mass transfer is generally neutral with a dialysis fluid calcium of 1.25 mmol/L, depending upon ultrafiltration [104, 105], with higher likelihood of a positive mass transfer when the peritoneal dialysis program includes icodextrin exchanges (dialysis fluid calcium 1.75 mmol/L, or 3.5 mEq/L) and when ultrafiltration is low [105]. Taken together, a dialysis fluid calcium of 1.25–1.50 mmol/L (2.5–3.0 mEq/L) should achieve a near-neutral calcium transfer during dialysis in most patients.

It is unclear whether hemodiafiltration results in a greater calcium efflux through convective clearance and a larger fluid exchange compared with hemodialysis for a given dialysis fluid calcium concentrations. Studies suggest that post-dilution hemodiafiltration shows similar results on calcium balance as hemodialysis [96, 106]. However, pre-dilution hemodiafiltration, achieving even larger volumes of fluid exchange and convective clearance, may result in greater shifts in calcium, depending on the calcium and bicarbonate concentrations of the dialysis fluid [98]. It has been demonstrated that PTH decreases, and ionized calcium increases, when bicarbonate is used as the dialysate buffer, whereas the opposite is seen with acetate [99]. Patients on long hours of daily or nocturnal hemodialysis are prone to hypocalcaemia and may need a higher dialysis fluid calcium concentration: a randomized study in patients on nocturnal hemodialysis who received either "normal" (1.3 mmol/L, $n = 24$) or high (1.6 or 1.75 mmol/L, $n = 26$) calcium in the dialysis fluid for 1 year showed a significant decrease in serum calcium and increase in PTH in the low calcium group, with no change in the abdominal aortic calcification score in either group [107].

QUESTION 3: WHAT IS THE RECOMMENDED DAILY INTAKE OF CALCIUM IN PATIENTS WITH CKD ACROSS STAGES AND AGE/SEX CATEGORIES?

Recommended daily intake of calcium in CKD

Key evidence points

- Whole-body calcium balance studies, although difficult to perform, are essential to make conclusive recommendations for calcium intake from diet or medications.
- Whole-body calcium balance is unrelated to (soft or bone) tissue calcium balance. Skeletal demineralization may maintain serum calcium levels within a normal range, but this internal shift of calcium would not be reflected in whole-body calcium balance studies.

Clinical practice points

- In children with CKD, we suggest a total elemental calcium intake within the age-appropriate normal range.
- In adults with CKD, we suggest a minimum total elemental calcium intake of 800–1000 mg/day to maintain a neutral calcium balance.
- In adults with CKD, we suggest not to exceed a total elemental calcium intake of 1500 mg/day to avoid hypercalcemia and risk of vascular calcification.
- In children or adults with CKD, a higher calcium intake may be appropriate in special circumstances such as for patients with re-mineralization of the skeleton ("hungry bone syndrome"), those on intensified dialysis regimens or in physiological conditions requiring additional calcium supply (rapid growth in infancy or adolescence and during pregnancy and lactation).

Background and rationale

A careful medical and nutritional history may provide some insight into the adequacy of calcium intake. However, due to the multifactorial nature of dysregulated calcium homeostasis in CKD, determining the optimal dietary calcium requirement is challenging and depends on the investigation of calcium balance.

Formal balance studies are the gold standard to evaluate the calcium balance but are complex and difficult to conduct. They require timed collections of urine and feces, often combined with isotope techniques to assess kinetics, and should be performed

Table 3: An example of the factorial approach to recommended daily calcium intake—a estimation of calcium losses based on available evidence and a calculation of the intake of calcium that would be needed to counteract these losses.

	Skeletal Ca accretion	Urinary Ca, mg	Endogenous intestinal Ca, mg	Dermal Ca, mg	Total Ca loss, mg	FACa, %	Recommended daily intake, mg
Adult, non-CKD	0	–120	–100	–50	–270	30%	900
Adult CKD	0	–40	–100	–50	–190	20%	950
Adult CKD	0	–40	–100	–50	–190	15%	1250
Adult CKD	0	–40	–200	–50	–290	20%	1450
Adult CKD	0	0	–200	–50	–250	15%	1650

Ca, calcium; FA, fractional absorption.

in steady state to allow for proper interpretation. Formal balance studies are thus cumbersome and limited to only two studies in patients with CKD [94, 108]. In a crossover study, six patients with CKD G3–4 consumed controlled high- (2000 mg/day) or low-to-normal calcium diets (800 mg/day) for 9 days. Calcium balance was slightly negative to neutral in both patients and healthy controls on the low-calcium diet (−91 ± 113 vs −144 ± 174 mg/day, $P > .05$) and more positive in patients than in controls on the high-calcium diet (759 ± 120 vs 464 ± 225 mg/day, $P < .05$). Serum calcium and phosphate concentrations were unchanged, and intact PTH and 1,25 dihydroxy vitamin D levels decreased in subjects on the high-calcium diet [108]. A further study examined eight patients with CKD G3–4 in a 3-week crossover trial. Patients were randomly assigned to a controlled calcium intake of 2457 mg/day (1500 mg of elemental calcium from calcium carbonate used as phosphate binder +957 mg/day of dietary calcium) or placebo (957 mg/day of dietary calcium). Calcium balance was neutral in the placebo group and positive in the calcium carbonate group (61 vs 508 mg/day, $P = .002$). Serum calcium, phosphate and intact PTH concentrations were unchanged in both groups [94].

Despite major limitations including small sample size, questionable steady state conditions and analytical shortcomings, these balance studies represent the highest level of evidence currently available. In aggregate, they indicate that a dietary calcium intake of 800–1000 mg/day may be adequate to maintain calcium balance in patients with CKD G3–4 who are not receiving active vitamin D derivatives. These values are identical to the estimated requirement for healthy adults >25 years of age and to the recommendation by the 2020 KDOQI clinical practice guidelines on nutrition [109].

At a calcium intake of 1500–2000 mg/day, calcium balance turns positive. Given the huge burden of vascular and soft tissue calcification in CKD, it is tempting to speculate that extraosseous sites are the primary repository for excess exogenous calcium. However, there is no conclusive evidence to support this assumption, and it should be considered whether (re)-mineralization of bone occurs initially, or in parallel. It could be hypothesized that the risk of vascular calcification is highest when the skeletal compartment is "saturated" or unresponsive, fostered by (episodic) hypercalcemia [110].

While children and young adults require a positive calcium balance to mineralize the growing skeleton, a neutral calcium balance should be aimed for in mature adults after the peak bone mass is achieved in the mid-30s. This implies that the rate of calcium absorption from the gastrointestinal tract should match the rate of losses from the body through the bowel, kidneys, skin, hair and nails. Whole-body calcium balance studies and factorial iteration may help to define the recommended daily calcium intake. In the latter approach, the recommended elemental calcium intake is calculated by imputing estimated average losses modeling different scenarios. Using this approach, an estimated recommended daily intake of elemental calcium would be in the range of 950 to 1650 mg/day in patients with CKD (Table 3). These figures should be interpreted cautiously, considering the multiple assumptions.

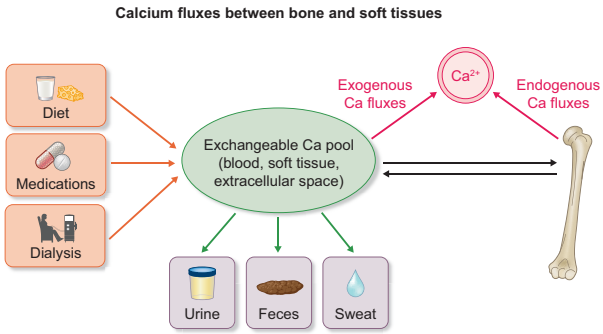


Figure 4: Exogenous and endogenous calcium fluxes; calcium loading can occur through diet, medications, mass transfer during dialysis—or as an internal shift from the skeleton due to bone resorption.

Importantly, whole-body calcium balance needs to be distinguished from tissue calcium balance (Fig. 4). Bone mineral density (BMD) is lower in patients with CKD as compared with age- and sex-matched healthy individuals [111, 112]. Along with recent data from stable isotope studies [92], this points to a negative skeletal calcium balance in CKD. Skeletal calcium efflux, mediated by osteoclastic bone resorption, may be crucial to maintain normocalcemia in patients with CKD, as illustrated by the rapid drop of serum calcium in a substantial proportion of patients following potent antiresorptive therapy [113]. Conversely, progression of vascular calcification paralleling the decline of kidney function denotes a positive vascular calcium balance in CKD. Of interest, bone demineralization and vascular calcification are closely linked and referred to as the calcification paradox of CKD [114, 115]. It may be speculated that internal calcium shifts from bone to vasculature, rather than exogenous calcium loading account for the huge vascular calcification burden in CKD.

A mere handful of studies have investigated the effect of calcium supplementation against placebo or no treatment in CKD, all of them small, of short duration (<6 months) and focused on mineral metabolism parameters [116–119]. Additionally, three studies of calcium vs non-calcium based phosphate binders included a placebo or dietary intervention group, allowing for a comparison of calcium vs control [120–122]. These studies all show that calcium supplementation ameliorates secondary

hyperparathyroidism and decreases the prevalence of hypocalcemia, at the cost of an increased risk of hypercalcemia.

A number of studies have compared calcium- and non-calcium-containing phosphate binders, most of which focused on safety outcomes, i.e. vascular calcification progression (Table 4). No increased risk of vascular calcification progression seems to be present with elemental calcium supplementation <1000 mg/day [120, 122–124]. At elemental calcium supplementation >1200 mg/day, that is, on top of dietary calcium intake, 9 out of 10 studies found an increased risk of vascular calcification progression with calcium supplementation, along with an increased risk of hypercalcemia.

For hard endpoints, two larger studies failed to demonstrate a survival benefit of non-calcium- vs calcium-containing phosphate binders [125, 126]. In the Dialysis Clinical Outcomes Revisited (DCOR) trial study, 2103 US patients receiving hemodialysis were randomized to sevelamer vs calcium-containing phosphate binders in the form of calcium acetate (70%; mean elemental calcium 1325 mg/day) or calcium carbonate (30%; mean elemental calcium 1960 mg/day), and 1068 patients completed the study with a median follow-up of 20 months. There were no differences in all-cause or cardiovascular mortality in the overall cohort, but patients >65 years had a lower mortality rate with sevelamer [125]. In the recently published Outcome Study of Lanthanum Carbonate Compared With Calcium Carbonate in Hemodialysis Patients (LANDMARK) Study, 2374 Japanese patients receiving hemodialysis, with more than one risk factor for cardiovascular disease, were randomized to lanthanum or calcium carbonate (median elemental calcium 600 mg/day), and 1851 patients completed the trial with a median 3.2 years of follow-up. There was no difference in all-cause mortality, but patients treated with lanthanum carbonate had increased risk of cardiovascular death, i.e. challenging the initial hypothesis [126]. Systematic reviews and meta-analyses differ in their conclusions regarding any survival benefit of non-calcium vs calcium containing phosphate binders (Table 5) [127–132]. The most consistent finding, in both CKD G3–5 and CKD G5D, is a survival benefit with sevelamer use [128, 129, 131].

Limitations of these studies should be acknowledged. Information on dietary calcium intake is generally not included, preventing an evaluation of total calcium exposure. Furthermore, there is evidence of pleiotropic benefits of sevelamer (lowering lipids, advanced glycation end-products and inflammatory parameters) which could contribute to the survival benefit with this specific binder. Interestingly, in the Calcium Acetate Renagel Evaluation-2 (CARE-2) Study, the addition of a statin to control low-density lipoprotein cholesterol resulted in no difference in the progression of vascular calcification between patients receiving calcium acetate (1375 mg/day elemental calcium) vs sevelamer [133].

Overall, these studies focused on safety outcomes and did not assess skeletal endpoints. Calcium supplementation consistently decreases PTH to a greater degree than non-calcium containing phosphate binders despite similar control of phosphate [122, 125, 126, 134–141] and also lowers bone turnover, both as assessed by bone biopsy [142–145] and by biomarkers [138, 146, 147]. Although this effect is most consistent in studies with higher doses of supplemented calcium, it is also reported with lower doses and without overt hypercalcemia [122]. Reduced severity of secondary hyperparathyroidism may explain the increase in BMD seen in some studies [117, 121], though this is not a consistent finding [124, 146, 148]. In the LANDMARK trial [126], supplementation with 600–1200 mg/day of elemental calcium did not decrease the risk of hip fractures in Japanese patients receiving hemodialysis [126]; no other studies investigating fracture endpoints are currently available.

In aggregate, clinical trials indicate excess risk with elemental calcium supplementation >1200 mg/day added to the dietary calcium intake (which averages 400–900 mg/day), and calcium balance studies demonstrate a positive calcium balance with total elemental calcium intake >1500 mg/day in patients with CKD. We consider 1500 mg/day to be the safe upper limit of daily calcium intake. Of note, this is lower than the safe upper limit of 2000 mg/day set by the 2003 KDOQI guidelines [8].

Recommended daily calcium intake in children and young adults with CKD

As with healthy children, children with CKD require adequate calcium for skeletal mineralization, particularly during periods of active growth. Mineralization defects are more commonly seen in children than adults with CKD and strongly correlate with the CKD grade and calcium status: by bone histology studies 90% of children on peritoneal dialysis have deficient bone mineralization [149], and mineralization defects are noted even in very early CKD G2 before changes in serum calcium, phosphate or PTH are detected [150]. On imaging studies, a lower tibial cortical BMD was associated with low serum calcium and high PTH level, particularly in growing children [151] and this correlated with a higher fracture risk. Conversely, vascular calcification, with its associated high cardiovascular morbidity and mortality, is also seen in children and young adults, and has been associated with a high calcium intake [152–155] as well as CKD grade [153, 154, 156]. In young adults on dialysis, the coronary artery calcification score was shown to double within 20 months [157], and worsening of the calcification score was associated with a higher serum calcium and prescription of calcium-containing phosphate binders [157, 158]. In a recent study including 100 children and young adults with CKD G4–5D, vascular calcification was noted even as BMD increased, although a presumed buffering capacity of the growing skeleton may offer some protection against extraosseous calcification [13].

There are no studies to indicate the appropriate amount of calcium for a child with CKD, and calcium requirements need to be individualized depending on the patient's age, growth and rate of bone turnover. Importantly, extrapolation of data from adult studies is not appropriate, as the growing skeleton of children has significantly higher calcium requirements than a mature, possibly osteoporotic, adult skeleton. In the absence of evidence-based studies, it would be reasonable to provide children with CKD a comparable calcium intake (including calcium from diet, phosphate binders and supplements) to their healthy peers. These concepts have been discussed at length by the Paediatric Renal Nutrition Taskforce [14].

Recommended dialysis fluid calcium concentrations

Clinical practice points

- We suggest using a dialysis fluid calcium concentration of 1.25–1.50 mmol/L (2.5–3.0 mEq/L) in peritoneal dialysis and hemodialysis to maintain a neutral calcium mass transfer during dialysis.
- We suggest that a dialysis fluid calcium concentration of 1.75 mmol/L (3.5 mEq/L) be restricted to situations where a positive calcium balance is intended.

Table 4: Risk associated with calcium *vs* non-calcium containing phosphate binders, by dose of elemental calcium supplemented (dietary calcium not included).

Study	Population	N	Follow-up	Intervention	Elemental calcium by supplement	Hypercalcemia	VC progression
2018 Kovesdy [122]	CKD 3–4	120	12 months	Lanthanum, Ca, control	336 mg/day	No difference	No increased risk of VC progression with Ca
2018 Fujii [123]	CKD 5D (HD)	105	18 months	Lanthanum vs Ca	Median 600 mg/day	Ca slightly higher	No increased risk of VC progression with Ca
2007 Russo [120]	CKD 3–5	90	24 months	Sevelamer, Ca, control	800 mg/day	Ca slightly higher	No increased risk with Ca, but decreased risk with sevelamer
2015 Wada [124]	CKD 5D (HD) + DM2	41	24 months	Lanthanum vs Ca	Mean 1050 mg/day	No difference	No increased risk of VC progression with Ca
2002 Chertow [134]	CKD 5D	200	12 months	Sevelamer vs Ca	Mean 1150 mg/day or 1500 mg/day	Higher risk; 16% vs 5%	Increased VC progression with Ca
2012 Di Iorio [253]	CKD 3–4 (INDEPENDENT)	212	36 months	Sevelamer vs Ca	Mean 1180 mg/day	Higher risk; 78% vs 5%	Increased VC progression with Ca
2008 Takei [254]	CKD 5D (HD)	42	6 months	Sevelamer vs Ca	Mean 1360 mg/day	No difference	Increased VC progression with Ca
2008 Qunibi [133]	CKD 5D (CARE-2)	203	12 months	Sevelamer vs Ca + statin	Mean 1375 mg/day	Higher risk; 31% vs 19%	No increased risk of VC progression with Ca
2011 Kakuta [255]	CKD 5D (HD)	183	12 months	Sevelamer vs Ca	Max 1500 mg/day	Ca levels higher	Increased VC progression with Ca
2013 Ohtake [256]	CKD 5D (HD)	42	6 months	Lanthanum vs Ca	Mean 1500 mg/day	Ca levels higher	Increased VC progression with Ca
2012 Block [121]	CKD 3B–4	148	9 months	Lanthanum, sevelamer, Ca, placebo	Mean 1500 mg/day	Higher risk; 17% vs 0%	Increased VC progression with Ca
2005 Asmus [135]	CKD 5D (HD)	72	24 months	Sevelamer vs Ca	Mean 1720 mg/day	Higher risk; 54% vs 26%	Increased VC progression with Ca
2005 Block [136]	CKD 5D (HD)	129	18 months	Sevelamer vs Ca	Mean 2300 mg/day	Higher risk; 54% vs 22%	Increased VC progression with Ca.
2011 Toussaint [148]	CKD 5D	30	18 months	Lanthanum vs Ca	Mean 2900 mg/day	Similar risk; 13% vs 9%	Increased VC progression with Ca
2021 Ogata [126]	CKD 5D (HD) (LANDMARK)	2374	36 months	Lanthanum vs Ca	Median 600 mg/day	Similar risk; 6% vs 4%	No increased risk of all-cause or CV mortality, or reduced risk of hip fracture with Ca
2007 Suki [125]	CKD 5D (HD) (DCOR)	2103	20 months	Sevelamer vs Ca	Mean 1500 mg/day or 2000 mg/day	Ca levels higher	No increased risk of all-cause or CV mortality with Ca

Ca, calcium; CV, cardiovascular; DM2, type 2 diabetes mellitus; HD, hemodialysis; VC, vascular calcification.

Table 5: Systematic reviews and meta-analyses investigating survival benefit of non-calcium vs calcium containing phosphate binders.

Study	Population	Design	N	Interventions	Conclusions
2013 Jamal [127]	CKD 3–5D	Meta-analysis	15 trials, N = 4622	Ca vs non-Ca containing phosphate binders	Reduced risk of all-cause mortality with non-Ca vs Ca containing phosphate binders
2016 Palmer [128]	CKD 3–5D	Meta-analysis	77 trials, N = 12 562	Any phosphate binder	Reduced risk of all-cause mortality with Sevelamer, but not Lanthanum, compared with Ca containing phosphate binders
2016 Patel [129]	CKD 3–5D	Meta-analysis	25 trials, N = 4770	Sevelamer vs Ca containing phosphate binder	Reduced risk of all-cause, but not CV mortality with Sevelamer compared with Ca containing phosphate binders
2016 Sekercioglu [130]	CKD 3–5D	Meta-analysis	28 trials, N = 8335	Ca vs non-Ca containing phosphate binders	Reduced risk of all-cause mortality with non-Ca vs Ca containing phosphate binders (network analysis); no difference with conventional analysis
2018 Ruospo [131]	CKD 3–5D	Cochrane review	104 trials, N = 13 744	Any phosphate binder	Reduced risk of all-cause, but not CV, mortality with Sevelamer compared with Ca containing phosphate binders
2022 Lioufas [132]	CKD 3–5	Meta-analysis	20 trials, N = 2498	Ca vs non-Ca containing phosphate binders	No clear conclusions on risk of all-cause mortality or CV events

Ca, calcium; CV, cardiovascular.

Background and rationale

Calcium transfer during dialysis is an important contributor to overall calcium balance in CKD G5D (see Question 2). Originally, the standard dialysate calcium was designed to match patients' serum ionized calcium levels, i.e. a dialysate calcium concentration of 1.25 mmol/L (2.5 mEq/L) was preferred. Later, the use of higher dialysate calcium was advocated to control secondary hyperparathyroidism. Following the introduction of calcium-containing phosphate binders and active vitamin D derivatives, the combined use of these medical therapies and a high dialysate calcium often led to hypercalcemia. The KDOQI guidelines therefore recommended a dialysate calcium of 1.25 mmol/L as the "currently most convenient" standard, allowing for simultaneous use of the above-mentioned therapy. The KDOQI guidelines stressed that there were no data to document that any particular calcium dialysate was safer, more effective or associated with fewer complications. Though interventional studies investigating the effect of different dialysate calcium on outcomes existed at this time, it was considered impossible to draw firm conclusions from these data, due to the marked changes in the medical treatment of mineral metabolism that had occurred in this time period [7, 8, 11]. The later KDIGO guidelines also recommended a lower calcium concentration in the dialysate as standard, to avoid calcium loading [7].

A dialysis fluid calcium concentration of 1.25–1.50 mmol/L (2.5–3.0 mEq/L) should ensure a near-neutral calcium transfer during dialysis, as detailed in Question 2. A lower dialysis fluid calcium concentration (<1.25 mmol/L) may increase skeletal calcium efflux and also the risk of hemodynamic instability [159]. Two RCTs reported reduced progression of vascular calcification with dialysis fluid calcium 1.25 vs 1.50 mmol/L [160, 161], while others reported no difference when comparing these two calcium concentrations [162, 163]. No survival benefit was observed when dialysis fluid calcium was lowered from 1.50 to 1.25 mmol/L [164, 165]. A retrospective study comparing hemodialysis facilities that switched the standard dialysis fluid calcium concentration from 1.25 mmol/L to <1.25 mmol/L observed greater rates of intradialytic hypotension and hospitalization for heart failure with the lower dialysis fluid calcium [166]. Levels of PTH and phosphate increased, as did the use of phosphate binders, active vitamin D derivatives, and calcimimetics in centers converting to dialysis fluid calcium <1.25 mmol/L. There was no difference in all-cause mortality; thus, there seem to be little benefit in reducing dialysis fluid calcium concentrations below 1.25 mmol/L [166].

Use of a higher dialysis fluid calcium (1.75 mmol/L; 3.5 mEq/L) has been associated with increased all-cause mortality [167, 168] and progression of vascular calcification [169]. In an RCT by Ok *et al.*, 425 patients with PTH levels <300 pg/mL were randomized to dialysis fluid calcium 1.25 vs 1.75 mmol/L for 2 years. During this time, coronary artery calcification score by computed tomography increased in both groups, but the rate of progression was greater with use of dialysis fluid calcium of 1.75 mmol/L [169].

Altogether, it is reasonable to assume that a dialysis fluid calcium concentration of 1.75 mmol/L will lead to a positive calcium mass transfer during dialysis, which may contribute to progression of vascular calcification. A benefit of reducing calcium concentration in the dialysis fluid from 1.50 to 1.25 mmol/L seems uncertain, and dialysis fluid calcium <1.25 mmol/L may cause harm due to cardiovascular instability.

Theoretically, optimal dialysis fluid calcium concentration could contribute to better control of secondary hyperparathyroidism and to maintenance of bone health. Increased levels of PTH are a consistent finding when reducing calcium concentration in the dialysis fluid [107, 163, 166] and may be accompanied by increases in bone turnover markers [170, 171]. On the other hand, lowering dialysis fluid calcium decreases the prevalence of low bone turnover on bone biopsies [169]. Thus, it could be argued that dialysis fluid calcium concentration should be individualized for optimal calcium balance.

Assessing an individual's calcium requirements in clinical practice

Key evidence points

- A serum calcium level does not reflect calcium balance as it is tightly controlled through hormonal regulation.

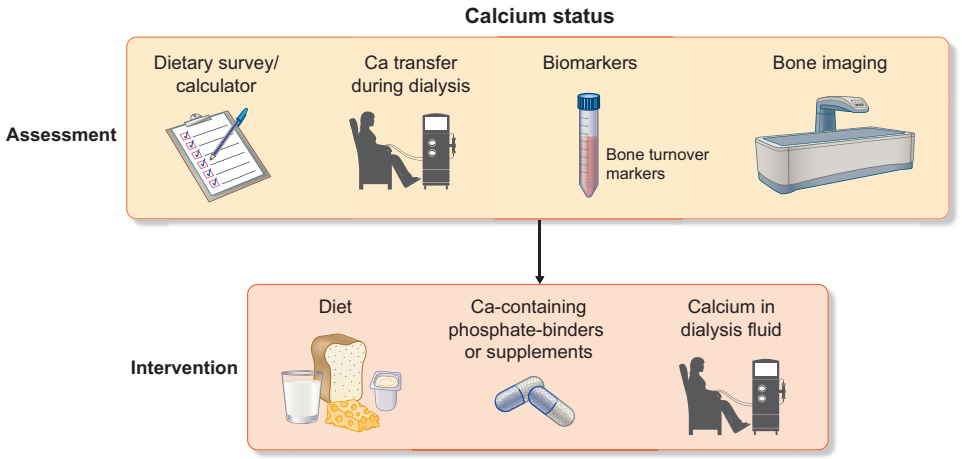


Figure 5: Assessment of calcium status in patients with CKD. Total calcium intake, including both dietary intake and contributions from medications or supplements, should be assessed. For patients on kidney replacement therapy, calcium mass transfer during dialysis must be considered. High bone biomarkers and low bone density may indicate calcium efflux from the skeleton, which should be addressed. If a calcium deficit is revealed, dietary intervention is preferred, and any supplementation should be by calcium-containing phosphate binders if phosphorus is high.

- Serum PTH level is a poor biomarker of bone turnover status and calcium homeostasis as PTH lacks specificity and shows high biological and inter-assay variability.

Clinical practice points

- We recommend that patients with CKD receive individualized dietary counseling, preferably by a qualified dietitian.
- In children with CKD, we suggest that the diet is regularly assessed for total calcium content. The frequency of assessment is based on the child's age, CKD grade and trends in serum calcium, phosphorus and PTH.
- In adults with CKD, we suggest assessing calcium status routinely at first presentation, every 12 months, and when clinically indicated (unexplained hypo- and hypercalcemia, prior to initiating or adjusting therapy for secondary hyperparathyroidism or osteoporosis).
- The following groups of patients are at greater risk of calcium deficiency or reduced calcium absorption and require close monitoring of their calcium intake: children during periods of rapid growth, elderly patients, patients with specific dietary preferences (vegans, vegetarians), patients in CKD G5-5D, patients on phosphate-restricted diets, patients with malabsorption or on PPIs and patients with severe vitamin D deficiency.
- Treatment decisions should be based on trends in serum calcium, phosphate, PTH, alkaline phosphatase and 25 dihydroxy vitamin D, considered together.
- The whole-body calcium status of an individual may be estimated by evaluating the calcium intake (from diet and calcium-containing medications) and calcium mass transfer from dialysis, together with biomarkers of mineral metabolism and bone turnover, and bone imaging.

Background and rationale

In clinical practice, dietary surveys, biochemical parameters and imaging techniques, preferentially in concert, may help to estimate the calcium status and balance in the individual patient (Fig. 5). Given the complex inter-dependency of these CKD-MBD measures, it is important to consider trends in levels rather than a single value, as suggested in the KDIGO CKD-MBD recommendations [7]. Obviously, one size does not fit all also applies to calcium management of patients with CKD across stages of disease.

Daily calcium intake, both from diet and supplements can be estimated by means of formal dietary history/recall (see Question 1, Estimating an individual's calcium intake) or questionnaires, including user-friendly online calculators, simple validated score systems and more extensive food frequency questionnaires [172, 173]. The estimation of calcium intake should become common practice in the work-up of CKD-MBD at first presentation, and when indicated, e.g. in patients with unexplained hypo- or hypercalcemia, and prior to initiating or adjusting therapy in patients with secondary hyperparathyroidism and osteoporosis.

Serum calcium levels are strictly maintained through hormonal control. They do not reflect overall body calcium balance and may not be very informative except at extremes. Using serum calcium levels as a proxy of calcium balance may lead to inadequate, and sometimes deleterious, clinical decisions [174]. Furthermore, only the "free" or unbound calcium is biologically active, and so albumin-corrected calcium and total calcium levels do not necessarily reflect the correct serum calcium, particularly in CKD patients with alterations in pH, anion gap and circulating plasma proteins [175–177]. Not surprisingly, true hypo- and hypercalcemia (by ionized calcium levels) are associated with increased risk of all-cause mortality in patients with apparent normocalcemia based on total or albumin-corrected calcium levels [178, 179].

Exogenous calcium deprivation triggers PTH synthesis and secretion, rendering PTH a candidate biomarker of calcium balance. Circulating levels of biointact PTH in CKD, however, are determined by many factors beyond calcium status, most notably phosphate levels [180, 181]. Further, there is end-organ hyporesponsiveness to PTH in CKD, leading to a reduced calcemic response [182–184]. PTH as a biomarker is fraught with limitations, including high biological variability and variable retention of PTH fragments [185]. PTH, therefore, is a poor biomarker of calcium status.

Shifts of calcium from the skeletal store can be assessed by considering skeletal remodeling rates and bone demineralization. Skeletal remodeling can be determined by bone histomorphometry or estimated by circulating bone turnover markers. A high bone turnover assists in maintaining calcium levels by

Table 6: Elemental calcium content and phosphorus binding capacity of commonly used calcium salts.

		Dosage	Elemental calcium (%)	Phosphorus binding (mg/g)	Calcium absorption (%)	Comments
Phosphate binders	Calcium carbonate [199–201]	Tablets, 500 mg	40	19	39	Dependent on acidity for dissolution. Inexpensive.
	Calcium acetate [199–201]	Tablets, 667 mg	25	50	32	Less dependent on acidity. Inexpensive.
	Calcium ketoglutarate [257]	Tablets, 1000 mg	21	~CaCO	<CaCO	Less dependent on acidity. Gastro-intestinal side effects common.
	Calcium lactate [258]	Tablets. 325 mg	13	~CaCO	32	Rarely used
Supplements	Calcium citrate	Tablets, 1000 mg	21	poor	30	Increases absorption of trace elements, including aluminum
	Calcium gluconate	Tablets, 500, 648, 972 mg	9	poor	27	Rarely used

CaCO = calcium carbonate.

increasing skeletal calcium efflux in the event of low exogenous calcium supply. High levels of bone turnover markers are thus indicative of current skeletal calcium efflux. Low BMD by imaging techniques such as dual-energy X-ray absorptiometry or quantitative computed tomography reflect calcium drain from the skeleton over a longer time period (years). High levels of bone turnover markers associate with increased risk of fractures [186–188] and all-cause and cardiovascular mortality [188–190] in the short-term, and low BMD associates with poor overall long-term outcomes in CKD [187, 191–194].

Preferred calcium source and intake conditions

Clinical practice points

- In patients with CKD we recommend optimizing calcium intake through the diet, rather than with supplements.
- Advice on dietary calcium intake should consider calcium content and bioavailability, as well as adhering to dietary phosphate restrictions, if required, and ensuring an adequate protein intake. Adapt the dietary intake to respect planetary health whenever possible.
- Calcium supplementation should be individualized, with consideration of calcium content and bioavailability, phosphate binding capacity and personal preferences.
- In individuals who require a phosphate binder, consider using a calcium-based phosphate binder, as opposed to a calcium supplement, if dietary calcium intake is low.
- For efficient phosphate binding, calcium salts (and other phosphate binding medications) must be given with meals.
- Avoid combination of calcium citrate with aluminum containing medications.

Background and rationale

Dairy may be the preferred source of calcium. In addition to a high calcium content and bioavailability, dairy products are rich in high quality protein. Dairy products, however, are also rich in phosphate. The recommendation to increase the consumption of dairy may thus conflict with the recommendation to restrict dietary phosphate. It should, however, be acknowledged that the latter recommendation is increasingly debated and that recent studies have identified phosphate additives as the main contributor to hyperphosphatemia. Plant-based alternatives to dairy may be considered [195], not only because of their lower phosphate bioavailability, but also from a global "one health" perspective [34].

Calcium supplements, preferably given as a phosphate binder, may be necessary when the dietary phosphate intake exceeds recommended limits so that the dietary intake of calcium cannot be readily increased. Calcium supplements vary in calcium content and bioavailability and in their phosphorus-binding capacity (Table 6) [196, 197]. All calcium salts should be given with meals, if used as phosphate binders. Calcium carbonate should also preferentially be given with meals if used as a supplement, as dissolution is dependent on acidity [36], while calcium uptake of other calcium salts may be greater if given in-between meals [198]. Of the two most commonly used calcium-containing phosphate binders, calcium carbonate is less efficient in binding phosphorus compared with calcium acetate, thus requiring a higher dose and resulting in a greater elemental calcium load to achieve a similar phosphate control [199–201].

QUESTION 4: WHAT IS THE APPROACH TO HYPO- AND HYPERCALCEMIA?

Clinical practice points

- We recommend to avoid hypercalcemia in children and adults with CKD.
- In cases of hypercalcemia, investigate and treat iatrogenic causes first, by reducing calcium-containing medications, active vitamin D derivatives and/or dialysis fluid calcium.
- Once iatrogenic causes of hypercalcemia have been addressed, investigate and treat pathological conditions associated with hypercalcemia such as sarcoidosis or malignancy.
- We suggest treating acute, iatrogenic hypocalcemia (as seen after surgical parathyroidectomy, anti-resorptive therapies or calcimimetic use) with calcium supplementation, active vitamin D derivatives and/or temporary increase of dialysate calcium to 1.75 mmol/L, under careful monitoring.
- We suggest pre-treatment with calcium-containing medications and active vitamin D derivatives in situations where

Table 7: Observational studies on risk of hard endpoints with deviations in serum calcium.

Study	Population	N	Follow-up	Exposure	Cutoffs, mg/dL [mmol/L]	Risk	Outcome
2004 Block [202]	CKD5D (HD)	40 538	1–2 years	Alb.corr (Ionized)	8.0; 11.0 [2.00; 2.75]	Linear	All-cause and CV mortality
2005 Young [203]	CKD5D (HD)	17 236	?	Alb.corr	7.8; 11.4 [1.95; 2.84]	Linear	All-cause and CV mortality
2006 Kalantar-Zadeh [204]	CKD5D (HD)	58 058	2 years	Alb.corr	8.0; 11.0 [2.00; 2.75]	J-shaped	All-cause mortality
2008 Tentori [205]	CKD5D (HD)	25 588	10 years	Alb.corr	7.6; 12.0 [1.90;2.99]	U-shaped	All-cause mortality
2008 Wald [206]	CKD5D (HD)	1846	4.5 years	Alb.corr	8.0; 11.0 [2.00; 2.75]	Linear	All-cause mortality and CV hospitalization
2011 Floege [207]	CKD5D (HD)	7970	2 years	Total	8.4; 11.0 [2.10; 2.75]	U-shaped	All-cause mortality
2011 Naves-Diaz [208]	CKD5D (HD)	14 125	4.5 years	Alb.corr	8.5; 11.0 [2.14; 2.75]	U-shaped	All-cause and CV mortality
2013 Fouque [209]	CKD5D (HD)	7700	2.5 years	Total	6.0; 12.0 [1.50, 2.99]	U-shaped	All-cause mortality
2014 Fukagawa [210]	CKD5D (HD)	8229	3 years	Alb.corr	8.0; 11.0 [2.00; 2.75]	J-shaped	All-cause mortality
2015 Fernandez- Martin [211]	CKD5D (HD)	6797	3 years	Total	6.0; 12.0 [1.50; 2.99]	U-shaped	All-cause mortality
2015 Rivara [212]	CKD5D (HD + PD)	129 076	<5 years	Total, Alb.corr	7.5; 10.5 [1.87; 2.62]	J-shaped	All-cause mortality
2017 Liu [213]	CKD5D (PD)	12 116	8 years	Alb.corr	8.1; 10,5 [2.14; 2.62]	J-shaped	All-cause mortality
2017 Wang [259]	CKD5D (HD)	35 114	2 years	Alb.corr	8.4; 9.6 [2.10; 2.40]	Linear	All-cause mortality
2019 Wakasugi [214]	CKD5D (HD)	220 054	1 year	Alb.corr	8.4; 11.0 [2.10; 2.75]	Linear	All-cause mortality
2020 Lamina [215]	CKD5D (HD)	8817	3 years	Total	6.4; 14.0 [1.60; 3.50]	J-shaped	All-cause mortality
2023 Yoshida [216]	CKD5D (HD)	2135	3 years	Alb.corr	7.0; 11.0 [1.75; 2.75]	U-shaped	All-cause mortality

CV = cardiovascular, HD = hemodialysis, PD = peritoneal dialysis.

iatrogenic hypocalcemia can be anticipated (parathyroidectomy, anti-resorptive treatment and calcimimetics).

- We suggest assessing calcium status in CKD patients with chronic hypocalcemia.

Background and rationale

Serum calcium is under strict hormonal control, and deviations from normal should be a cause for concern. Epidemiological studies in CKD show survival benefit when calcium is in the normal range [202–216]. The evidence is strongest for hypercalcemia, with the risk curve often reported as linear or J-shaped; though the expected U-shape appears when a wider range of calcium is considered (Table 7). In addition, case-mix, assays used, variables accounted for in adjusted analyses and statistical modeling applied are likely sources of variability. For trends in serum calcium, changes out of the normal range, in either direction, increase mortality risk [215, 217].

Hypercalcemia should be considered a pathological condition. Common causes of hypercalcemia in CKD are iatrogenic (calcium supplements, calcium-containing phosphate binders, active vitamin D derivatives, high calcium in the dialysis fluid) and the development of tertiary hyperparathyroidism [218]. Additional causes of hypercalcemia include malignancy, granulomatous disease (e.g. sarcoidosis), thyroid disease and immobilization [219]. In cases of hypercalcemia, the underlying cause should always be investigated, with iatrogenic causes identified and corrected first. Development of tertiary hyperparathyroidism is suspected if hypercalcemia occurs concurrently with inappropriately elevated PTH levels. Further evaluations should be carried out as necessary to rule out other pathologies, particularly in cases of adequately suppressed PTH.

Hypocalcemia can be a life-threatening condition. Acute, severe and/or symptomatic hypocalcemia should be promptly corrected using calcium-supplementation (often intravenous), active vitamin D derivatives and, in patients with CKD G5D receiving dialysis, by temporarily increasing the calcium concentration in the dialysis fluid to 1.75 mmol/L.

Common iatrogenic causes if hypocalcemia in CKD are surgical parathyroidectomy, anti-resorptive therapy and calcimimetic use. In the "hungry bone syndrome" following parathyroidectomy, the sudden reduction in PTH levels leads to unopposed calcium influx into bone due to widespread bone (re-)mineralization [220]. This can cause severe and life-threatening hypocalcemia, requiring large amounts of calcium supplementation post-operatively [221]. Hungry bone syndrome occurs in approximately 25% of patients with CKD G5D after parathyroidectomy [222, 223]. Lower calcium levels, higher PTH levels and higher bone turnover markers prior to surgery predict the severity and duration of hypocalcemia [224]. As the risk of hungry bone is linked to the severity of hyperparathyroid bone disease, optimization of medical therapy seems a logical preventative strategy. Initiation of calcium supplementation and active vitamin D derivatives pre-operatively [225] or immediately post-operatively [226] may limit the risk of severe hypocalcemia. Treatment with the short-acting bisphosphonate pamidronate prior to surgery has also been shown to reduce the risk of hypocalcemia and shorten the duration of hospitalization compared with historical controls [227]. However, this strategy may seem counterintuitive as it would block (re-)mineralization of bone that is recovering from hyperparathyroid bone disease, and indeed, BMD increase was less marked in patients treated with pamidronate in the abovementioned study [227].

With potent anti-resorptives such as denosumab, calcium efflux from bone is abruptly reduced, due to osteoclast activity being completely blocked [228]. This hypocalcemia could be considered an unmasking of an ongoing negative calcium balance—a dependency on calcium efflux from the skeleton to maintain low-normal serum calcium levels. Skeletal calcium influx may also occur, similar to hungry bone syndrome after parathyroidectomy, explaining the substantial increases in BMD that can be seen in patients with CKD treated with denosumab. Consistent with this, high levels of bone turnover markers, indicative of hyperparathyroid bone disease, prior to denosumab treatment predict the risk and severity of hypocalcemia [113].

The risk of hypocalcemia after bisphosphonate use is low, but still substantially higher in patients with CKD when compared with others with normal kidney function. In a retrospective population-based cohort study from Canada, patients with CKD G5–5D had a 24% risk of mild (ionized calcium <1.0 mmol/L) and

15% risk of severe (ionized calcium <0.9 mmol/L) hypocalcemia in the 6 months following initiation of denosumab therapy, compared with <1% risk of both in those with an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2. For bisphosphonates, the risk was 2.4% for mild and 0.1% for severe hypocalcemia in patients with CKD G5–5D, compared with <0.1% for both in those with an eGFR >60 mL/min/1.73 m^2 [229].

Treatment with calcimimetics often results in a reduction in serum calcium levels. In the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial ($N = 3861$ patients with CKD G5D receiving hemodialysis), 58% of cinacalcet treated patients experienced hypocalcemia after treatment initiation, compared with 15% in the placebo arm. Severe hypocalcemia (<7.5 mg/dL or 1.87 mmol/L) was seen in 18% with cinacalcet treatment vs 4% of controls and associated with higher PTH, higher bone turnover markers and lower calcium levels at baseline, consistent with hypocalcemia resulting from reduced calcium efflux from the skeleton [230]. In a European hemodialysis cohort ($N = 905$), all normocalcemic at baseline, two-thirds developed hypocalcemia during 12 months of cinacalcet therapy—severe hypocalcemia was seen in 9% [231]. Of note, neither of these trials found an association between treatment-related hypocalcemia and risk of hard outcomes (cardiovascular events and/or all-cause mortality). In a comparative meta-analysis, hypocalcemia was more common with use of the intravenous etelcalcetide than cinacalcet or evocalcet—most likely due to a greater efficacy in lowering PTH levels [232]. Hypocalcemia related to the use of calcimimetics is often reported to be transient and self-limiting, and whether calcium supplementation would be indicated in this situation is debated [233]. In the trials already mentioned, hypocalcemic episodes lead to minimal changes in medical therapy [230, 231]. However, hypocalcemia-related symptoms such as muscle cramps and paresthesia are reported to be twice as common with calcimimetics compared with placebo [234]. One RCT in children with CKD was terminated early due to a fatality linked to severe hypocalcemia in the cinacalcet arm [235]. Thus, it seems prudent to evaluate calcium status, and consider the need for calcium supplementation, prior to initiating calcimimetics. Children can be more prone to life-threatening seizures or arrhythmias, and a higher threshold of serum calcium levels has been suggested before initiating cinacalcet treatment [236].

With persistent hypocalcemia, an assessment of calcium status should be performed, to address potential deficits, as detailed in Question 2. The total intake of calcium (diet + medications) should be assessed, and for patients on kidney replacement therapy, calcium mass transfer during dialysis also needs to be considered. Although the recommended intake of calcium is not affected by the presence or severity of vascular calcification or osteoporosis, a negative calcium balance will exacerbate secondary hyperparathyroidism, leading to bone resorption and demineralization. High levels of bone turnover markers, or decreases in bone mineral density on bone imaging, indicate shifts of calcium from the skeletal store, which may also need to be addressed (Fig. 5).

RESULTS OF THE DELPHI SURVEY

Of the 28 clinical practice points, all statements achieved an agreement higher than the pre-defined cut-off of 70% from the respondents, with over 90% agreement for all but one statement. Analyzing the level of agreement for each statement, an overall 83% consensus was achieved with a "strongly agree or agree" response and a 12% "neutral" response, largely reflecting the wide variations in practice in the absence of robust evidence. The highest "disagree or strongly disagree" rate (18%) was in response to a statement under Question 3, "Preferred calcium source and intake conditions" on the timing of administration of calcium containing medications with or without food. Given that the absorption of elemental calcium from different calcium salts varies widely, with some requiring an acidic pH for dissolution, and that the binding of calcium to dietary phosphate will reduce its absorption, we modified this statement and added further explanations for the rationale in the text. Based on comments from Delphi respondents, additional clarification to the text was also provided in some sections.

FUTURE RESEARCH

We recommend the following areas of research to provide further evidence for optimal calcium balance in adults and children with CKD G2–G5D:

(i) Data on habitual calcium intake in children and adults with CKD are sparse and fragmentary. Additional large epidemiological studies are required to define calcium intake across stages of CKD and to identify determinants.
(ii) Additional calcium balance studies across CKD G2–G5 should be performed to determine calcium requirements at different ages and stages of CKD.
(iii) Future calcium balance studies should include the evaluation of internal shifts in calcium, most notably skeletal calcium balance.
(iv) Calcium absorption in children and adults at different CKD grades should be determined, using double-tracer labeled calcium isotope studies.
(v) The interaction between common nutritional and pharmacological therapies (dietary fiber supplements, PPIs, etc.) and calcium absorption, and potential effects of such therapies on CKD-MBD-related outcomes, should be investigated.
(vi) Whole-body calcium balance studies at different ages and grades of CKD should be performed, including patients treated with dialysis, across modalities.
(vii) The effect of different dietary calcium intakes on bone turnover and mineralization should be investigated both in children and in adults, across different grades of CKD.
(viii) The evolution of bone demineralization and vascular calcification in CKD patients who are calcium and vitamin D deficient vs those with an adequate dietary calcium and vitamin D intake should be investigated.
(ix) The effect of calcium supplementation on relevant hard outcomes such as fractures, cardiovascular events and all-cause mortality, should be investigated by RCTs.

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AUTHORS' CONTRIBUTIONS

P.E. and R.S. were responsible for the conception and design of this work. P.E., R.S. and H.S.J. did the primary drafting of the manuscript. All authors contributed to the analysis and interpretation of data and gave their input to and helped revise the manuscript. All authors approved the final manuscript and accept accountability for the accuracy and integrity of this work.

CONFLICT OF INTEREST STATEMENT

P.E. reports research grant from Vifor CSL and Sanofi, and consultancy fees and speaker honoraria from Vifor CSL. J.B. declares receipt of advisory and/or lecture fees from Amgen, Abbvie, Sanofi, CSL-Vifor, AstraZeneca, Rubió and Bayer. R.S. reports research grants from Fresenius Medical Care and Vitaflo, and consultancy fees and speaker honoraria from Amgen, AstraZeneca, Fresenius Medical Care and Humacyte. The remaining authors report no conflicts of interest. All reported disclosures are unrelated to submitted work.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

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