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Consensus Evidence-Based Clinical Practice Recommendations for the Diagnosis and Treat-To-Target Management of Osteoporosis in Chronic Kidney Disease Stages G4-G5D and Post-transplantation: An Initiative of Egyptian Academy of Bone Health

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Keywords

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Abstract

Objective: The aim of this study was to reach a consensus on an updated version of the recommendations for the diagnosis and Treat-to-Target management of osteoporosis that is effective and safe for individuals with chronic kidney disease (CKD) G4-G5D/kidney transplant. ***Methods:*** Delphi process was implemented (3 rounds) to establish a consensus on 10 clinical domains: (1) study targets, (2) risk factors, (3) diagnosis, (4) case stratification, (5) treatment targets, (6) investigations, (7) medical management, (8) monitoring, (9) management of special groups, (10) fracture liaison service. After each round, statements were retired, modified, or added in view of the experts' suggestions, and the percent agreement was calculated. Statements receiving rates of 7–9 by more than 75% of experts' votes were considered as achieving consensus. ***Results:*** The surveys were sent to an expert panel (n = 26), of whom 23 participated in the three rounds (2 were international experts and 21 were national). Most of the

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participants were rheumatologists (87%), followed by nephrologists (8.7%), and geriatric physicians (4.3%). Eighteen recommendations, categorized into 10 domains, were obtained. Agreement with the recommendations (rank 7–9) ranged from 80 to 100%. Consensus was reached on the wording of all 10 clinical domains identified by the scientific committee. An algorithm for the management of osteoporosis in CKD has been suggested. ***Conclusion:*** A panel of international and national experts established a consensus regarding the management of osteoporosis in CKD patients. The developed recommendations provide a comprehensive approach to assessing and managing osteoporosis for all healthcare professionals involved in its management.

Introduction

While osteoporosis is a public health epidemic that has a significant health impact as well as economic burden, chronic kidney disease (CKD) represents a unique challenge to health care professionals dealing with bone health particularly. Osteoporosis and CKD are not only common conditions, which affect all ages, genders, races, and ethnicities, but are also known for their associated substantial morbidity and mortality [1]. Coupling mineral disorders to specific bone features reported in CKD patients resulted in the introduction of one joint entity called CKD-mineral bone disorder (CKD-MBD). This refers to clinical incidents linked to calcium and phosphate metabolism including fractures, biochemical abnormalities, and cardiovascular events such as vascular calcifications [2]. Alterations in mineral and bone metabolism occur early in the CKD course; hence, they become almost universal in patients with advanced disease [3].

Over years, in patients living with CKD, osteoporosis usually develops subclinically, with fracture(s), often being the first presenting symptom. Both osteoporosis and CKD are common disorders among older adults and often go in concordance. At late stages of CKD, G4 (GFR = 15–29 mL/min), and G5 (end-stage CKD, GFR <15 mL/min), osteoporosis represents a condition of impaired bone quantity [4–10] as well as quality [11] that associates with a state of high risk of sustaining a fracture [12]. This is evidenced by the higher fracture risk of nonvertebral fractures (4–6 folds higher) in CKD G5D, in contrast to age- and gender-matched controls [13, 14]. Although vertebral fractures' prevalence is similar to general population, their associations with vascular calcifications are very strong [15]. Short term after kidney transplantation patients are at greater risk of hip fracture compared with those with renal failure who continue with hemodialysis, while after 1–3 years, the risk among transplant recipients appears to be lower [16].

The biochemical and histologic changes that occur with progressive kidney disease mandate specific therapeutic interventions. While the approach to osteoporosis care in patients with CKD G1–G3 is similar to non-CKD patients with osteoporosis [17], so long as there are no biochemical changes suggestive of the development of CKD–MBD, osteoporosis care in patients with CKD G4–G5D remains a key challenge and represents a treatment gap. This has been attributed to the paucity of data on the efficacy and safety of osteoporosis therapies as well as the complexity of the bone fragility pathophysiology in the CKD G4–G5D patients. Similar experience was noted for patients who had kidney transplantation. In spite of the trials to give an impulse to such clinical inertia [18, 19], and bearing in mind the advances in osteoporosis management, there is a need for updated versions of these treatment recommendations and to develop management strategies for this cohort of patients.

This work was carried out to develop and seek consensus on an updated version of the recommendations for the diagnosis and management of osteoporosis and new avenues for osteoporosis treatment that may be effective and safe for individuals with CKD G4-G5D/renal transplant. This consensus work builds on guidance issued for the diagnosis and management of osteoporosis in postmenopausal women and men [20].

Methods

Design

The multistep process strategy was used in developing a consensus, evidence-based treatment recommendations for osteoporosis in CKD G4-G5D. The guideline follows the "clinical, evidence-based guidelines" initiative protocol aiming at setting up an actionable clinical gold standard for osteoporosis in CKD patients' Treat-to-Target (T2T) management. A qualitative synthesis of scientific evidence and consensus based on clinical experience and existing scientific evidence was used to formulate the study design. This work conforms to the preferred reporting items for systematic reviews and meta-analyses recommendations for reporting systematic reviews [21].

Development Stages

Core Team

It is formed of 4 experts with recognized experience in osteoporosis and CKD management. The core team supervised and coordinated the teamwork, assisted with developing the scope of the project and initial Patient/Population, Intervention, Comparison, and Outcomes (PICO) clinical questions, and reached a consensus on the key questions to include in the recommendations. The core

team prespecified outcomes as critical for each PICO question for the systematic literature review. The team also nominated the expert panel and drafted the manuscript.

Literature Review Team

Led by an experienced literature review consultant and based on specific research questions identified to focus on the management of osteoporosis associated with CKD, the literature review was conducted with the assistance of an expert in methodology. The team completed the literature search (the PubMed/MEDLINE, EMBASE, and Cochrane databases), data abstraction as well as the quality of evidence rating [22]. Following the revision, each of the experts responsible for the literature review provided recommendations regarding each section based on evidence, when that was available, or their own experience. The level of evidence was determined for each section using the Oxford Centre for Evidence-based Medicine system [23].

Inclusion Criteria

Articles included were systematic reviews, randomized controlled trials, uncontrolled trials, observational studies including cohort, case-control, and cross-sectional studies, or those where economic evaluation was made.

Exclusion Criteria

Editorials, commentaries, conference abstracts, and nonevidence-based narrative/personal reviews were excluded.

Expert Panel

Given the fact that the developed recommendations will be adopted across several medical specialties, therefore, it was vital that the participating expert panel involved in developing the recommendations would be multidisciplinary. The core leadership team nominated 23 participants. The criteria for their selection included having professional knowledge and experience (at least 8 years of experience) in the field of bone health and CKD, management of osteoporosis as well as active participation in scientific research on bone health disorders. The expert panel assisted with developing the scope of the project and refining the PICO questions. PICO questions were drafted into recommendation statements and were sent to the expert panel with the evidence report, who voted on the recommendations.

Key Questions Used to Develop the Guideline

This guideline was based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used, and the outcomes used to measure efficacy, effectiveness, or risk. The evidence to answer the clinical questions was collected according to the following steps: formulation of clinical questions, structuring of questions, search for evidence, critical evaluation and selection of evidence, presentation of results, and recommendations. These questions, shown in Table 1 form the basis of the systematic literature search and consequently the clinical care standards.

Developing the Clinical Care Standards Framework

Based on the answers to the structured key questions and the literature review, a structured template was developed to facilitate standardized identification of guideline components. For each guideline component, the format in which the recommendations/information was provided and extracted has been identified.

Delphi Process

The Delphi technique is a structured method widely used to gather important information on a specific topic. It relies on the key assumption that forecasts from a group are generally more accurate than those from individuals. Therefore, the aim of the Delphi method is to construct consensus forecasts from a group of experts in a structured iterative manner. Its methodology is based on a series of questionnaires or "rounds" addressed to experts. The Delphi method generally involves the following stages. (1) A panel of experts is assembled. (2) Forecasting tasks/challenges are set and distributed to the experts. (3) Experts return initial forecasts and justifications. These are compiled and summarized in order to provide feedback. (4) Feedback is provided to the experts, who reviewed their forecasts considering the feedback. This step may be iterated until a satisfactory level of consensus is reached. (5) Final forecasts are constructed by aggregating the experts' forecasts. The key features of this method are the anonymity of participants and the controlled feedback [24–26].

Consensus Process

Three Delphi rounds were carried out to establish consensus regarding the T2T strategy for osteoporosis management in CKD patients. Once the main aspects of this strategy were identified, a discussion group has defined the aspects to be included in the questionnaire with the scientific committee. The structured Delphi approach ensures that the opinions of participants are equally considered. The Delphi process was conducted through online questionnaires. The first round of the electronic questionnaire included 13 items involved in the T2T strategy of osteoporosis management in CKD patients.

Voting Process

Live online-delivered voting was carried out in 3 rounds that were strictly time limited. All members of the task force were invited to participate and were preinformed of the time of opening and closure of each round of votes. Unique access links were sent out, and anonymous votes were gathered and processed. Comments on re-phrasing, potential ambiguity, unidentified overlaps were gathered regarding each statement at the same time in the voting process. Only the members of the task force had the right to vote on the statements.

Rating

Each statement was rated between 1 and 9 with 1 being "complete disagreement" and 9 being "complete agreement." Generally, 1–3, 4–6, and 7–9 represent disagreement, uncertainty, and agreement, respectively. There is no requirement to vote on all statements, and the members were encouraged to abstain if they feel that a statement falls outside their area of expertise. Therefore, an "uncertainty" vote represents "inconvenience about the accuracy of the recommendation." All statements are allowed for the entry of comments which were reviewed by the core team after each round of voting. In all the voting rounds, the members were further urged to leave comments wherever they vote a disagreement. This will enable the panel to identify an instance of misinterpretation of statement and invalidate the vote on that statement.

Table 1. Key questions used to develop the guideline

Domain	Key questions
Study targets	
Patients	Who are the targeted patients in these guidelines?
Targeted healthcare professionals	Who should treat osteoporosis with G4, G5 CKD?
Risk factors	What are the fracture risk factors in CKD-MBD?
Diagnosis	How to assess the CKD patients to identify those with osteoporosis?
Case stratification	What are the fracture risk and intervention thresholds?
Treatment targets	What are the treatment targets?
Investigations	
Lab	How to assess for bone turnover state in patients with G4, G5, and G5D?
Radiology	How to assess CKD patients radiologically?
Medical management	
	What are the treatment strategies of bone disease in G4-5D CKD?
Monitoring	
	How to do patient monitoring of bone health status?
	What is the frequency and monitoring of CKD patients who receive osteoporosis management?
Management of special groups	
	How to manage osteoporosis in CKD patients on hemodialysis?
	What is the management of osteoporosis in post kidney transplantation?
Fracture liaison service	Is it important to set up FLS?

Definition of Consensus

Definition of consensus was established before data analyses. It was determined that consensus, consequently, to become a recommendation in this guideline, would be achieved if at least 75% of participants reached agreement (score 7–9) or disagreement (score 1–3) [21–24]. A statement was retired if it had a mean vote below 3 or a "low" level of agreement. Statements whose rate came in the uncertainty score (4–6) were revised in view of the comments. The levels of agreement on each statement of recommendation were defined as "high" if after the second round of votes, all votes on a statement fell into the agreement bracket (7–9) [26–28].

Chronogram of Delphi Rounds

The first round took place between 12th and 15th May 2021 (4 days). The aspects about which respondents did not reach consensus in this first round were revised in view of the comments and included in the second round. The second round took place (1 week after the first round) and remained for 4 days, between 22nd and 25th May 2021 (4 days). The third round took place (2 weeks after the second round) and remained for 4 days between 11th and 14th June 2021 (4 days).

Results

Literature Research and Evidence Selection

In the study selection process, we found 128 potentially relevant studies by search strategy. 80 were excluded by screening of title and abstracts (studies did not examine population or intervention of interest, did not match study design of interest, or did not report outcome measures of interest). Therefore, 48 relevant studies were included for full article review. Thirty-six studies were excluded as citations did not provide evidence matching a PICO. Therefore, we included 12 studies in this work (Fig. 1).

Expert Panel Characteristics

The Delphi form was sent to international expert panel (n = 2) and national expert panel (n = 21) who participated in the three rounds. International respondents were from the UK (n = 2, 100%). National respondents were drawn from different governorates and health centers across Egypt: Ain Shams university (n = 10, 43.5%), Cairo University (n = 2, 8.7%), Tanta university (n = 2, 8.7%), Benha university (n = 2, 8.7%), Alexandria university (n = 1, 4.3%), Suez Canal University (n = 1, 4.3%), Zagazig university (n = 1, 4.3%), Minia university (n = 1, 4.3%), Assiut university (n = 1, 4.3%). Two of all expert panel (8.7%) were nephrologists, 20 (87%) were osteoporosis specialists, and 1 (4.3%) was geriatric specialist.

Delphi Round 1

The key clinical question comprised 14 questions stratified under 10 domains (Table 1) including: study

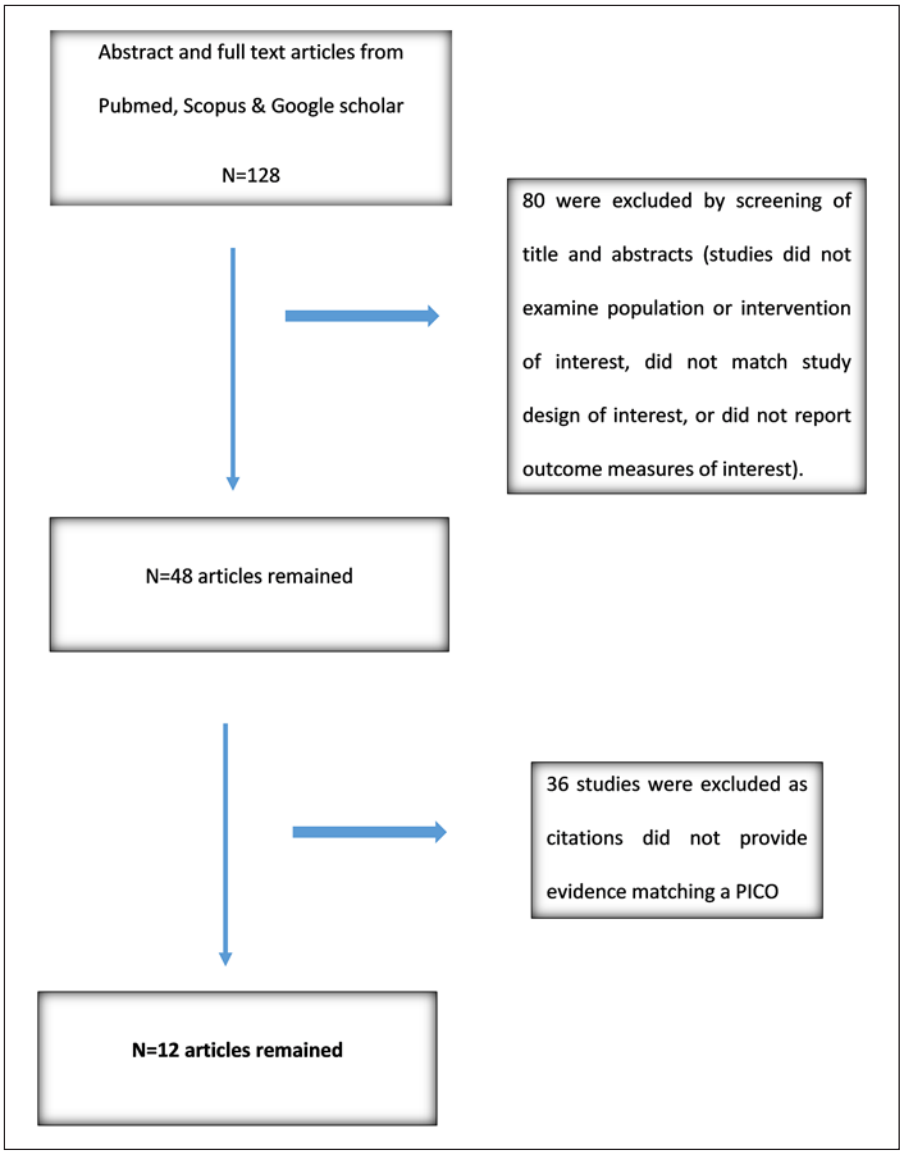

Fig. 1. Flow chart for the study selection process.

targets, risk factors, diagnosis, case stratification, treatment targets, investigations, management, monitoring, fracture liaison service (FLS), management of special groups. Each domain entails one or more elements. In this round, the participants were asked to rate the overall principles considered in the decision-making for T2T management of osteoporosis in patients living with CKD. The response rate for round 1 was 100% from both the international (4/4) and national groups (21/21). Consensus was reached on the domains (i.e., ≥75% of respondents strongly agreed or agreed); however, there were comments raised regarding the wording of 10 of the questions. Comments (excluding minor editing suggestions) were equally distributed over the 10 domains. Four of the edited questions were as follows: 1 in the study target domain, 1 in the risk factor domain, 1 in case stratification, and 1 in the management domain. The remaining 6 amended questions were from diagnosis, management, monitoring, and management of special group domains. According to the experts' advice, 2 questions were retired: one question in the study targets domain and the other one in the management domain. The question in the study targets domain was retired as it was repeated in another domain, whereas the second question in the management domain was added to another question in the same domain. Diversity of opinion was great-

Table 2. Breakdown of statements of recommendations and their individual level of agreement

No	Domain	Statement	LE	SoR	Mean rate	Sd	% of agreement	Level of agreement
1	Study targets	**Who are the targeted patients in these guidelines?**	2	B	8.6	0.8	100	H
		Postmenopausal women with CKD, women or men >50 years old with CKD						
		Women and men <50 years old should be assessed on individual basis and after considering their specific risk factors: G1-3 of CKD (eGFR>30 mL/min): receive the same management guidelines as osteoporotic patients without CKD						
		G4-5D of CKD (eGFR<30 mL/min) and post kidney transplant patients with low BMD: those who belong to these guidelines below						
2	Risk factors	**What are the fracture risk factors in CKD-MBD?**	2	C	8.5	0.8	100	H
		Higher CKD grades: G4-5D, BMD ≤ −2.5, previous fracture (hip, spine, wrist), postmenopausal women, age ≥65 years, BMI ≤20 kg/m^2, history of hip fracture in a first-degree relative, corticosteroid therapy (≥5 mg/day of prednisone or equivalent for ≥3 months), untreated premature ovarian failure, high falls risk in the previous year (≥2), hyperparathyroidism, eating disorder, chronic malnutrition or malabsorption syndromes, deficiency vitamin K (especially vitamin K1) [40], male gender, early menopause (40–45 years), current smoker, consumption of ≥3 units of alcohol/day, prolonged use of warfarin, PPI >1 year, type 1 diabetes mellitus, rheumatoid arthritis, and hyperthyroidism						
3	Diagnosis	**How to assess the CKD patients to identify those with osteoporosis?**	2	B	8.5	0.8	90	H
		Bone quantity: DXA/VFA (vertebral fracture assessment)						
		DXA: in patients with CKD G4–G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, BMD testing by DXA is suggested to assess fracture risk if results will impact treatment decisions [43]						
		VFA is indicated for all patients undergoing DXA scan						
		Limitations of spine DXA measurements due to aortic calcifications should be considered						
		Using plain radiographs to evaluate abdominal aortic calcification in selected patients in order to assist in personalized treatment advice						
		Bone quality: TBS						
		Fracture risk assessment: if no country-specific measures are available, the FRAX can be calculated according to regional validated measures, FRAX calculation using TBS is advisable						
4	Case stratification (G3-G5)	**What are the fracture risk and intervention thresholds?**	1	B	8.6	0.8	90	H
		Case stratification according to fracture risk and intervention thresholds: patients should be stratified according to their risk of fracture, low, moderate, high, and very high risk						
		Low risk includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −1.0, and 10-year hip fracture risk <1% and 10-year risk of major osteoporotic fractures <10%						
		Moderate risk includes no prior hip or spine fractures, a BMD T-score at the hip and spine is < − 1 and > − 2.5, or 10-year hip fracture risk <3% or risk of major osteoporotic fractures ≥10% and <20%						
		High risk includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of −2.5 or below, or 10-year hip fracture risk >3%, or risk of major osteoporotic fracture risk ≥20% and >30%, and CKD-associated high bone turnover (PTH >350 pg/mL and BALP>20 ng/mL)						
		Very high risk includes ROD (is a form of metabolic bone disease seen in patients with chronic renal insufficiency characterized by bone mineralization deficiency due to electrolyte and endocrine abnormalities. Patients present with osteomalacia, osteonecrosis, and pathologic fractures. Diagnosis is made based on a thorough evaluation of serum labs, clinical features, and radiographic findings) [29], recent fracture (e.g., within preceding 12 months), fracture while on anti-osteoporosis medication, multiple fractures, fractures while taking drugs that affect bone adversely (e.g., long-term glucocorticoid therapy: a corticosteroid dose of ≥5 mg/day, longer than 3 months), a BMD T-score ≤−3, high risk of falls or previous history of injurious falls, and a very high fracture probability (the example given is a FRAX score ≥30% for major osteoporotic fracture and >4.6% for hip fracture)						

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Table 2 (continued)

No	Domain	Statement	LE	SoR	Mean rate	Sd	% of agreement	Level of agreement
5	Management							
	Healthcare professional	**Who should treat osteoporosis with G4, G5 CKD and post kidney transplant?**	2	B	8.3	0.9	95	H
		Treatment should adopt multidisciplinary approach						
		The nephrologist should liaise with the local osteoporosis specialist for the patient's bone health management						
		Specialists who have experience in managing osteoporosis, including rheumatology, orthogeriatric medicine, and endocrinology						
		Management should work in collaboration with the treating nephrologist: for a healthcare practitioner to be recognized as an osteoporosis specialist, he/she should be [30] (1) working in national/university hospital/ministry of health hospital with regular meetings and provided services, (2) in solo practice if less than 3 years; a logbook showing traceable management and outcome management over 3 years, and if practice more than 3 years; the specialist should provide an audit comparing his service with gold standards as national guidelines for the treatment of osteoporosis showing the outcome of his service, (3) preferable if healthcare professionals have publications in a peer-reviewed journal whether national or international						
	Treatment targets	**What are the treatment targets?**						
		Hip and spine T-score > – 2; "low fracture risk" (from clinical and/or screening tests) should be established particularly for post-fracture patients	2	A	8.6	0.7	80	H
	Investigations							
	Laboratory	**How to assess for bone turnover state in patients with G4, G5, G5D, and post kidney transplant?**	2	C	8.5	0.8	100	H
		a- Lab investigations:						
		Bone profile: calcium, ALP, phosphorus						
		25-hydroxyvitamin D						
		BALP						
		PTH						
		**Mineralization defect should be suspected when low vitamin D, low calcium, high PO, high PTH, and high BALP are found						
		b- Bone biopsy: may be considered if a mineralization defect is suspected, or if the exact diagnosis of ROD has influence on the treatment decision						
	Radiological	**How to assess CKD patients radiologically?**	2	C	8.5	0.8	100	H
		X-ray: for confirmation of fracture						
		DXA-based VFA, or						
		Other radiological investigations such as CT or MRI are of value particularly for vertebral fracture assessment						
		Plain X-ray abdomen lateral view (vascular calcifications) – echocardiography (valvular calcification)						
	Medical management	**What are the treatment strategies of bone disease in G4-5D CKD?**	2	C	8.5	0.8	100	H
		Treatment strategies of bone disease in G4-5D CKD						

Table 2 (continued)

No	Domain	Statement	LE	SoR	Mean rate	Sd	% of agreement	Level of agreement
		a Control of uremia (correct metabolic acidosis, to avoid chronic mild hyponatremia, to reduce CKD- and age-related inflammation, and to clear uremic toxins with proven or putative skeletal toxicity), CKD-BMD, and normalization of the serum levels of calcium and phosphorus by appropriate measures as well as maintain and control of BALP serum levels in the normal range [32]						
		b Nonpharmacological [32,38]:	1	B	8.5	0.8	100	H
		Exercise and physical therapy: type of exercise includes aerobic, weight-bearing, resistance, balance training, Tai-Chi, and flexibility exercise						
		Intensity and duration should be tailored according to patient's physical condition						
		Nutrition: according to serum levels; Adequate dietary intake of calcium and vitamin D, 1,000–1,200 mg of calcium and [600–800 IU] of vitamin D per day in men and women >50 years of age. Adequate dietary intake of vitamin k. Adequate protein intake after discussion with nutritionist. In patients with CKD G3a–G5D, lowering of hyperphosphatemia levels toward the normal range should be achieved. Phosphate load from phosphate-rich sources should be avoided, not graded						
		Lifestyle modifications: moderation of alcohol consumption, cessation of smoking, and fall prevention measures [39]						
		c Pharmacological	2	C	8.5	0.8	100	H
		Use of vitamin D and calcitriol predialysis: nonactive form of Vitamin D can be used in any stage of CKD according to guidelines of vitamin D when levels of serum vitamin D<30 ng/mL						
		In patients with serum vitamin D levels >30 ng/mL, maintenance dose of nonactive form of vitamin D is advised (600–800 IU/day)						
		In adult patients with CKD G3a–G5 not on dialysis, do not routinely use calcitriol (the active form of vitamin D) [38]						
		Systemic calcitriol is indicated for suppression of secondary hyperparathyroidism in patients with CKD [38]						
		d Pharmacological management of high-risk group according to bone turnover status which is estimated by BTMs	2	C	8.7	0.8	95	H
		High bone turnover (raised BALP >20 ng/mL and PTH >600 pg/mL): exclude other causes of raised bone markers before treating high bone turnover like vitamin D deficiency, hypocalcemia, and hyperphosphatemia. If any of these causes present, then correct and recheck BALP and PTH. If vitamin D sufficiency (≥75 nmol/L) with serum-adjusted calcium and serum phosphate levels within the reference range, administer Dmab 60 mg subcutaneous 6 monthly						
		Monitor Dmab therapy in CKD patients with high bone turnover (bearing in mind that DMab may produce a reversible increase in intact PTH with values greater than 1,000 pg/mL [18						
		Vitamin D supplementation is required to prevent hypocalcemia and ideally should be initiated prior to treatment with Dmab because of the decrease of serum calcium that occurs shortly after the injection of Dmab						
		Patients with severe renal impairment (eGFR <30 mL/min) or receiving hemodialysis are at greater risk of developing hypocalcaemia. Clinical monitoring of serum calcium levels is recommended for patients predisposed to hypocalcemia						
		0 (baseline): before starting Dmab						
		+2 weeks: serum calcium level (only in those with an eGFR of 15–30 mL/min) and creatinine						
		+4 weeks: serum calcium level (only in those with an eGFR of 15–30 mL/min) and creatinine						
		Normal bone turnover (between low and high values) (BALP 7–10 ng/mL and PTH 130–600 pg/mL): consider Dmab (60 mg subcutaneous 6 monthly) and consider HRT/raloxifene (60 mg once-daily long-term treatment >3 years) in postmenopausal women [10, 18]						
		Low bone turnover (PTH (130–300 pg/mL), BALP <7 ng/mL): consider teriparatide (20 μg subcutaneously once a day for 24 months) [46]						
		Treatment strategies of bone disease in G4-5D CKD						

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Table 2 (continued)

No	Domain	Statement	LE	SoR	Mean rate	Sd	% of agreement	Level of agreement
		ABD (PTH <150 pg/mL, with low BALP <12.9 ng/mL): prevention of CKD progression, management of ABD risk factors such as diabetes, decrease calcium and vitamin D load so as to relax PTH suppression, limiting the use of calcitriol can assist in alleviating PTH over suppression. The use of calcimimetics should be avoided, bisphosphonates are contraindicated. Low calcium dialysate should be used						
		Teriparatide may be used in patients with irreversible ABD (e.g., due to post-parathyroidectomy hypoparathyroidism)						
		e Pharmacological: osteomalacia (low vit. D, high ALP, high BSAP): using treatment strategies recommended for the general population for vitamin D deficiency and insufficiency. Taking in consideration using calcitriol or 1 alpha in ESRD patients, considering level of calcium pretreatment	5	C	8.6	0.7	95	H
6	Monitoring							
		How to do patient monitoring of bone health status?	2	C	8.4	0.9	90	H
		If T-score > −2.5 with low fracture risk: reassess DXA-BMD in 1–2 years						
		If T-score > −2.5 with intermediate fracture risk: reassess DXA-BMD in 1–2 years						
		If T-score ≤ −2.5 with high or very high fracture risk, or T-score > −2.5 with fracture: assess bone turnover by ALP every 12 months; calcium, phosphorus, PTH, and vit. D every 3–6 months; reassess DXA-BMD every 1–2 years						
		What is the frequency and monitoring of CKD patients who receive osteoporosis management?	1	B	8.4	0.9	95	H
		Adherence: could be achieved by patient education and counseling						
		Methods of monitoring of treatment: BMD as assessed by DXA. Treatment periods ≥2 years are necessary to show a measurable and reproducible BMD response to therapy. The target is a T-score > −2 at hip as well as spine						
		Non-kidney-retained markers of bone turnover (BALP and PTH)						
		The measurement of BTMs after withdrawal of osteoporosis therapy, bearing in mind the rebound effect after cessation of Dmab, is useful to evaluate patients who are pausing treatment. An increase in markers of bone turnover more than the LSCs reflects a loss of treatment effect and identifies patients who are likely to have a decrease in BMD. These changes could indicate a reintroduction of treatment						
7	Fracture liaison service	**Is it important to set up FLS?**	1	B	8.5	0.9	95	H
		FLSs: the majority of patients presenting with fragility fracture do not receive appropriate assessment and treatment; here comes the role of FLSs who address this need through a systematic approach to identify cases and assess the risk of further fractures (including falls risk) and the need for treatment						
8	Management of special groups	**How to manage CKD-MBD in CKD patients on hemodialysis?**	1	C	8.6	0.7	+998	H
		Maintain BALP levels in the normal range						
		Maintain the level of intact PTH in the range of 2–9 times upper normal limit: marked changes of PTH level in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside the range.						
		For those requiring PTH-lowering therapy, suggest calcimimetics, calcitriol, or vitamin D or combination of calcimimetics with calcitriol or vitamin D						
		In patients with severe hyperparathyroidism who fail to respond to medical/pharmacological therapy, suggest parathyroidectomy						
		What is the management of osteoporosis in post kidney transplantation?	1	B	8.7	0.7	100	H
		Management of kidney transplant						
		In patients in the immediate post-kidney-transplant period, serum calcium and phosphate should be measured at least weekly, until stable						

Table 2 (continued)

No	Domain	Statement	LE	SoR	Mean rate	Sd	% of agreement	Level of agreement
		In patients after the immediate post-kidney-transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH on the presence and magnitude of abnormalities and the rate of progression of CKD						
		Vitamin D deficiency and insufficiency can be corrected using treatment strategies recommended for the general population						
		In patients in the first 12 months after kidney transplant with an estimated GFR >∼30 mL/min and low BMD (defined by a T-score of ≤ −2.5)						
		a Encourage patients to follow the lifestyle changes. Consider treatment with vitamin D, calcitriol/alfacalcidol if there is no hypercalcemia. Recommend lowest possible dose of glucocorticoids to prevent rejection						
		b Persistent hyperparathyroidism and severe hypophosphatemia should be treated before considering additional medical therapies for osteoporosis, repeat BMD 12 months after treating these conditions						
		c Treatment choices should be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, bone alkaline phosphatases, and 25(OH)D						
		Vitamin K and osteocalcin can be used as biomarkers; however, consideration should be given to concurrent immunosuppressive therapy as it can influence both turnover directly as well as indirectly (vitamin K levels)						
		Patients who have osteoporosis and no evidence of low-turnover bone disease with antiresorptive therapies such as bisphosphonates						
		Dmab is an alternative option in patients with osteoporosis and low GFR who cannot receive bisphosphonates						
		For patients with low-turnover bone disease, teriparatide may be a potential option						
		Monitoring and frequency of monitoring						
		From G1T-G3T: assess serum calcium and phosphorus every 6–12 months; assess PTH once; and BALP every 12 months						
		G4T: assess serum calcium and phosphorus every 3–6 months; assess PTH every 6–12 months; assess BALP every 12 months						
		G5T: assess serum calcium and phosphorus every 1–3 months; assess PTH every 3–6 months; assess BALP every 12 months						
		From G1T to G5T: assess 25(OH)D levels and repeat it according to baseline values and therapeutic interventions						

LE, level of evidence according to the Oxford Centre for Evidence-Based Medicine (CEBM) criteria. H, high level of agreement. SoR, strength of recommendations; TBS, trabecular bone score; VFA, vertebral fracture assessment; ABD, adynamic bone disease; BTM, bone turnover marker; FLS, fracture liaison service; LCS, least significant change; BALP, bone-specific alkaline phosphatase; ROD, renal osteodystrophy.

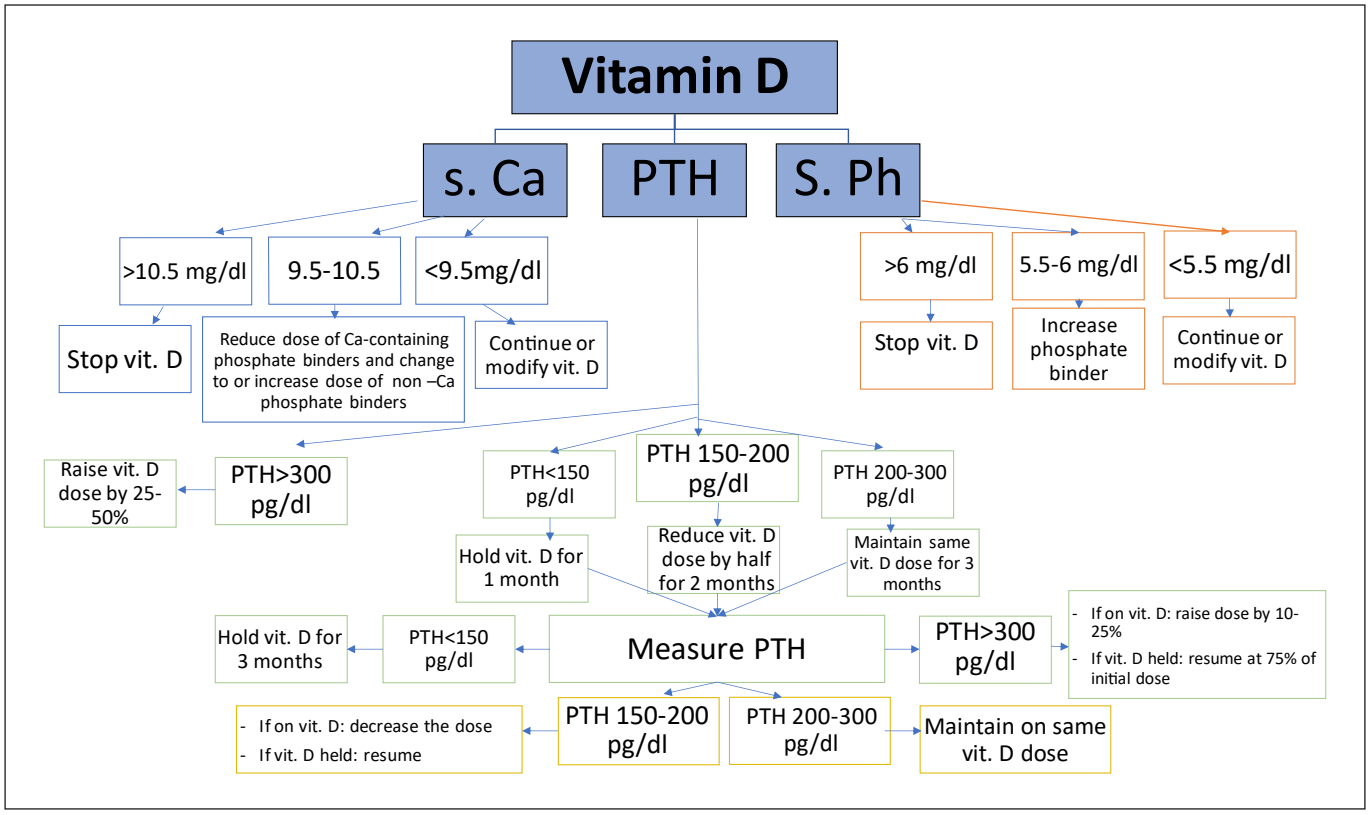

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Fig. 2. Management of vitamin D based on serum calcium, phosphorus, and PTH levels in CKD patients G4-5.

est for the question "What are the investigations to be done?"; this question was retired and rephrased to be "How to assess for bone turnover in patients with G4, G5 and G5D."

Delphi Round 2

Based on input from round 1, the experts were presented with 18 statements stratified under 10 domains. The response rate for round 2 was 100% from international (4/4) and national groups (21/21). Consensus was reached for 10 statements; hence, they were retained, whereas modifications were suggested for 8 statements. Comments (excluding minor editing suggestions) included modifying some statements (1 in the study targets, 1 in the risk factor, 1 in the investigations in the management, 3 in the treatment strategies, 1 in the monitoring, and 1 in the management of the special group domains). The statements were revised and amended. In addition, one statement was added in the investigations in the management section (radiological investigations of CKD-MBD). The separate statement about treatment of adynamic bone disease was retired and added to the statement above (Pharmacological Management of high-risk group according to Bone turnover status).

Delphi Round 3

Based on input from round 2, the experts were presented with 18 statements stratified under 10 domains. The response rate for round 3 was 100% from both the international (4/4) as well as national groups (21/21). The experts came to consensus on the 18 statements to retain in the T2Tt management recommendations. The core team reviewed and made minor revisions to one of the retained statements that reached consensus (in the pharmacological treatment strategies regarding denosumab [Dmab] and teriparatide therapies). Frequency of high-rate recommendation (rank 7–9) ranged from 80 to 100%. The experts were comfortable with the final list of the statements and with the Delphi process overall. Table 2 shows the level of evidence and grade of recommendation assigned to each statement, in accordance with the Oxford Centre for Evidence-based Medicine criteria as well as mean ± standard deviation and level of agreement.

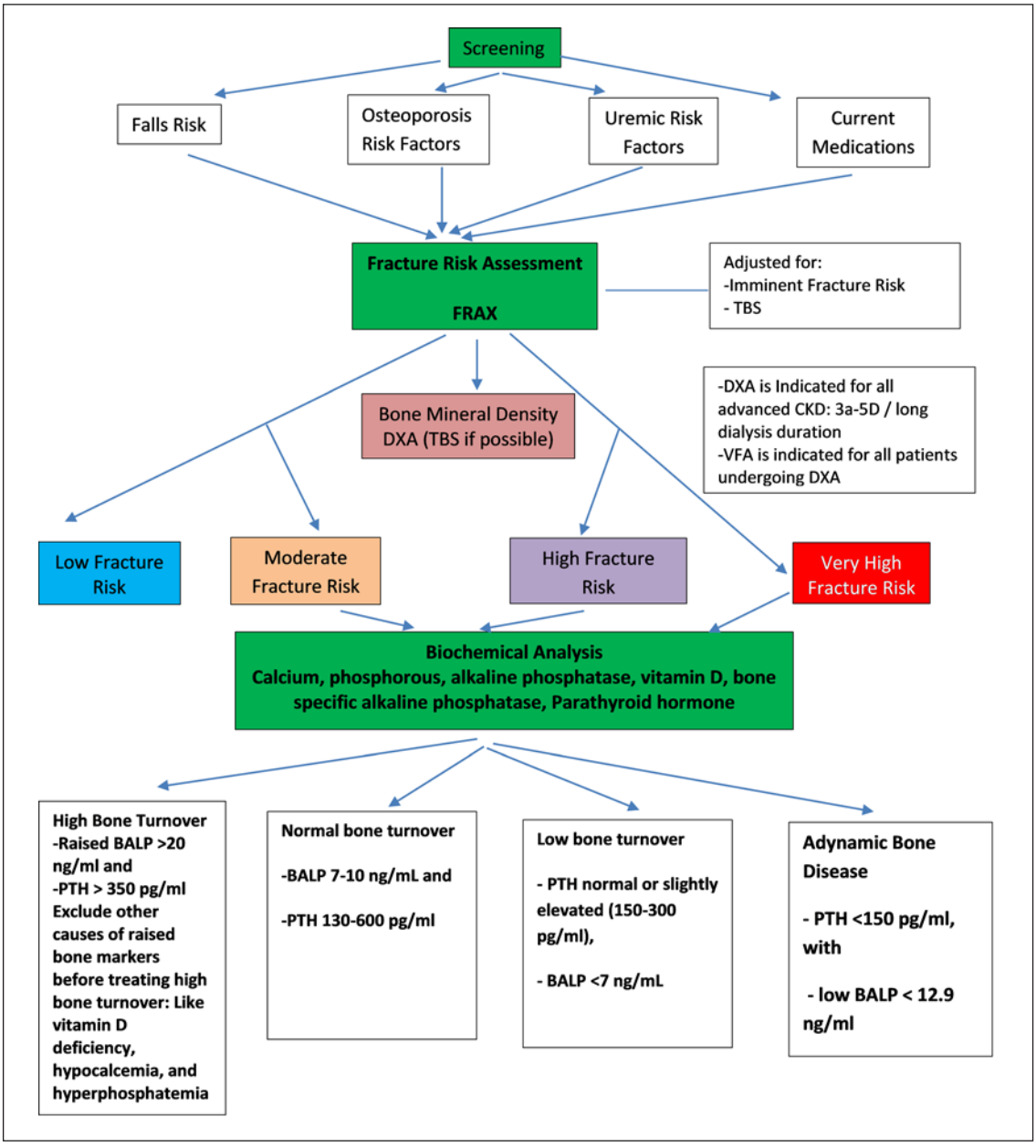

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Fig. 3. Algorithm for assessment of osteoporosis in CKD G4,5,5D and kidney transplant patients stratified according to their bone turnover.

Recommendations for Management Osteoporosis in CKD G4-5d

At the end of round 3, a total of 18 recommendation statements categorized into 10 domains were obtained as shown in Table 2. As clear, readily accessible as well as applicable treatment recommendations are highly required by the healthcare professionals as a guide in standard clinical practice; it was important to articulate the developed osteoporosis guideline for the day-to-day practice. Figure 2 shows an algorithm for the management of serum levels of 1, 25 (OH) vitamin D deficiency/insufficiency based on serum calcium, phosphorus, and parathyroid hormone (PTH) levels. An algorithm for assessment of osteoporosis in CKD patients stratified according to their bone turnover is shown in Figure 3.

Discussion

There is a wide treatment gap in the management of osteoporosis in CKD patients, particularly in patients with CKD stages 4–5D (eGFR below 30 mL/min 1.73 m^2), CKD patients on hemodialysis as well as those who had kidney transplantation. This work was carried out to formulate an updated clinical practice guideline for the pharmacological and nonpharmacological management of osteoporosis in CKD patients. This work was initiated in view of the recent developments in predicting those CKD patients at high risk of sustaining a fracture, the remaining unanswered questions about the optimal diagnostic and therapeutic approach of these patients as well as the existing treatment gap between those CKD patients at risk of fracture and those receiving treatment for the prevention of fragility fractures [20, 29]. This guideline was developed based on an evidence-based expert consensus on T2T strategy of osteoporosis in CKD. The study results reflect data not only from pivotal published treatment recommendations but also from postauthorization studies, in addition to the expert opinion.

The term CKD-MBD is currently used to describe a broader clinical syndrome that develops as a systemic disorder in CKD, manifested by abnormalities in bone and mineral metabolism and/or extra-skeletal calcifications. CKD-MBD associates with fractures as well as cardiovascular morbidity and mortality [30]. The term renal osteodystrophy specifically indicates changes in bone morphology associated with CKD; it is a form of metabolic bone disease seen in patients with chronic renal insufficiency characterized by bone mineralization deficiency due to electrolyte and endocrine abnormalities. Patients present with osteomalacia, osteonecrosis, and pathologic fractures. Diagnosis is made based on a thorough evaluation of serum labs, clinical features, and radiographic findings [29]. Osteoporosis was found to be twice as common in those with an eGFR<60 mL/min compared to those with an eGFR>60 mL/min, and compared with the general population, fracture incidence rates are more than fourfold higher [31]. Disturbances in mineral and bone metabolism occur early in the course of CKD, becoming almost universal in patients with advanced disease [29].

The management algorithm proposed in this work is based on setting a treatment plan tailored to the individual patient's bone turnover status using circulating levels of PTH and bone-specific alkaline phosphatase; this was in concordance with the American society guidelines for management of osteoporosis in CKD [32], whereas the European consensus and KDIGO guidelines [30, 33] adopted a bone mineral density (BMD)-centric approach in their treatment paradigm. Precise identification of the bone turnover status is of great value to predict classification and severity of bone affection in patients living with CKD. The KDIGO encourages the continued use of trends in PTH to guide therapy, and when trends in PTH are inconsistent, a bone biopsy should be considered [33].

The Delphi technique has proven to be a reliable measurement instrument in developing new concepts and setting the direction of future-oriented research [34]. The technique seeks the opinion of a group of experts in order to assess the extent of agreement and to resolve disagreement on an issue [35]. This consensus paper aimed to provide guidance on the T2T management of osteoporosis in patients with advanced CKD. In Delphi methodology, consensus usually arises when agreement or disagreement ranges from 50 to 80% [36]. In this work, the agreement ranged between 80 and 100%, indicating a building up experience as well as a strong trend among the health care professionals to have a T2T approach for osteoporosis management in CKD patients.

Treatment recommendations in this consensus paper have focused on postmenopausal women and men >50 years of age, with CKD stages G4-G5D (eGFR<30 mL/min). For patients living with CKD G1–G3, osteoporosis management remains similar to the general population, as long as there are no biochemical abnormalities suggesting the presence of CKD– MBD. Evaluation and treatment of younger patients with advanced CKD at increased fracture risk are complex and should be individualized. This agrees with KDIGO 2017 guidelines for treatment of CKD-MBD [35], as well as the European Consensus Statement on the diagnosis and management of osteoporosis in CKD stages G4–G5D [30], whereas the American society for management of osteoporosis in CKD targeted all CKD patients with eGFR<60 mL/min [32].

Clinical risk factors for osteoporosis and fracture risk in CKD patients including traditional risk factors like older age ≥ 65 years, BMD ≤ −2.5, previous fracture (hip, spine, wrist), postmenopausal women, BMI ≤20 kg/m^2, history of hip fracture in a first-degree relative, corticosteroid therapy (≥5 mg/day of prednisone or equivalent for ≥3 months), untreated premature ovarian failure, high falls risk in the previous year (≥2), hyperparathyroidism, eating disorder, chronic malnutrition or malabsorption syndromes, deficiency of vitamin K (especially vitamin K1) [37], early menopause (40–45 years), current smoker, high phosphate intake,

consumption of ≥3 units of alcohol/day, prolonged use of warfarin, PPI >1 year, type 1 diabetes mellitus, rheumatoid arthritis, and hyperthyroidism, in addition to the CKD-specific risk factors such as higher CKD grades and long hemodialysis duration. These risk factors were collectively in agreement with the European consensus, American society, and KDIGO guidelines for management of osteoporosis in CKD [30, 32, 33] who classified them into traditional and CKD-specific risk factors, whereas Bover et al. [19], 2018 classified them into major and minor risk factors.

The scope of the present consensus recommendations is to review and update the assessment and diagnosis of osteoporosis in patients with CKD G4–G5D and post kidney transplantation. Screening the patients aiming at early osteoporosis diagnosis and a proper therapeutic approach are vital for bone health improvement. Diagnosis of osteoporosis is carried out by evaluating bone quantity (DXA & VFA) as well as bone quality (trabecular bone score). Reviewing guidelines for the general population, several bone societies recommend BMD screening in women and men >65 and >70 years, respectively. In CKD patients, BMD screening is recommended in younger ages, if either postmenopausal or >50 years considering those patients who might be at very high or high risk of sustaining a fracture [38, 39]. Using FRAX in stratification of CKD patients is controversial as neither CKD nor level of GFR are included in FRAX; however, Whitlock et al. [39], 2019 stated that the relationship between FRAX and major osteoporotic fracture was stronger in those with CKD compared to those with preserved eGFR. These findings support the use of FRAX to risk stratify patients with nondialysis CKD for major osteoporotic fractures and hip fractures.This guideline adopts the multidisciplinary approach in management of OP in CKD patients, with specialists [28] having experience in management of OP; however, and under circumstances of COVID-19 pandemic, if the specialist is not available, non-specialist should follow the recommendations, or there is an online teleclinic service provided in the tertiary care and the university hospitals.

The management of osteoporosis in patients with CKD G4–G5D is challenging. Efficacy and safety of the available nonpharmacological as well as pharmacological approaches in the setting of CKD G4–G5D should be taken in consideration [40]. The developed recommendations endorsed the concept that the choice of pharmacological osteoporosis therapy should be tailored according to individual patient's fracture risk level and that the future fracture risk is a continuum from low risk through high risk to very high risk. Also, evaluating the bone turnover status is vital to determine whether it is high, low, or adynamic bone state. This paves the way for using the safest pharmacological medications appropriate for each case (Dmab and teriparatide) side by side with nonpharmacological treatment, control of uremia, and vitamin D deficiency management. In stage 4 or more advanced CKD patients and CKD patients on hemodialysis with osteoporosis, bisphosphonates, if they are used (considering it off-label/zoledronic acid is contraindicated when GFR is less than 35 mL/min), must be used with caution, bearing in mind the potential development of such disorders as adynamic bone disease and its renal toxic effects [17]. Careful administration of teriparatide is suggested in patients with severe renal impairment due to an observed delay in elimination in these patients compared with healthy volunteers. In addition, PTH is secondarily upregulated in severe stages of CKD, which potentially reduces the response to teriparatide [41]. As regards to Dmab treatment, Bover et al. [18], 2019 documented that in CKD G4, there was no reduction in vertebral fractures and non-vertebral fractures but low statistical power due to the low sample size. Dmab may produce a reversible increase in intact PTH with values greater than 1,000 pg/mL [18], so cautions should be taken in monitoring PTH levels during treatment with Dmab. Moreover using Dmab in CKD patients with normal bone turnover can be considered as bone turnover in Dmab-treated patients shows an early profound decrease and thereafter partly recovers up to the next administration, whereas bone turnover is permanently suppressed for the duration of bisphosphonate therapy and even thereafter (long skeletal t1/2) [30].

To meet the T2T requirements, frequent monitoring of the efficacy of antifracture strategies in patients with CKD is highly recommended in these current recommendations. This emphasizes the role of the FLSs and gives attention to the management and monitoring of special groups (patients on dialysis and post kidney transplantation) who were considered here in this current work. These recommendations addressed the management of hemodialysis, as the continuous ambulatory peritoneal dialysis CAPD is rarely done and only performed in very few cases. These recommendations agree in general with those published recently by the European consensus, American society, and KDIGO recommendations for management of osteoporosis in CKD [30, 32, 33]. However, neither the European consensus nor the American society recommendations discussed the management of special groups.

The main strengths of the study are related to the diversity as well as the expertise of the participants (national and international), the high levels of consensus achieved, and the agreement with the most recently published osteoporosis in CKD treatment recommendations. Also, the adoption of the PICO methodology approach as well as the T2T outcome as the main pillars of this work.

The limitations of this study could be the two international experts, although these recommendations are an initiative of the Egyptian Academy of Bone Health. Also, the lower number of nephrologist participants in this study is considered a limitation.

Conclusion

A wide and representative panel of international and national experts established a consensus regarding the management of osteoporosis in CKD patients. The developed recommendations provide a comprehensive approach to the assessment and management of osteoporosis in CKD patients for all healthcare professionals who are involved in its management. This included who to treat, risk factors, case stratification, diagnosis, therapeutic objectives, patient monitoring. It also expanded to give guidance for the management of osteoporosis in special groups (patients on hemodialysis and post kidney transplantation) and highlighted the potential role of FLSs in standard practice. Prophylactic measures, early diagnosis, and a proper therapeutic approach were vital for bone health improvement in CKD patients.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature. Patient consent was not required as this study was based on publicly available data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Yasser El Miedany, Naglaa Ali Gadallah, Eman Sarhan, Mathias Toth, Mona Mansour Hasab El Naby, Mohamed Elwy, Sahar Ganeb, Maha El Gaafary, Mohamed Mortada, Samah Ismail Nasef, Nevine Mohannad, Safaa Ali Mahran, Mohammed Hassan, Mervat Eissa, Waleed Hassan, Basma M Medhat, Rasha Ghaleb, Samar Abdelhamed Tabra, Heba Gamal Saber, Rehab Ali, Sally Saber, and Salwa Galal. The first draft of the manuscript was written by Dr. Salwa Galal and Dr. Yasser El Miedany. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are openly available in [figshare] at http://doi.org/[10.6084/m9.figshare.19312589].

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